UDK 61(05)

ISSN 1330 -5301

R A D

HRVATSKE AKADEMIJE ZNANOSTI I UMJETNOSTI

497

MEDICINSKE ZNANOSTI

31

ZAGREB, 2007.

RAD HRVATSKE AKADEMIJE ZNANOSTI I UMJETNOSTI
KNJIGA 497

UDK 61(05)

ISSN 1330-5301

R A D

HRVATSKE AKADEMIJE ZNANOSTI I UMJETNOSTI

497

MEDICINSKE ZNANOSTI

31

ZAGREB, 2007.

CONTENTS / SADRŽAJ

EDITORIAL

It is my great pleasure to present the new issue of RAD, the first issue which is, in accordance with the new publishing policy of the journal, published entirely in English. It is also my great pleasure to confirm that we have kept most of our promises given when we formed the new Editorial Board and in the last year's issue (RAD, 30:7, 2006). So, we are being published in English, have become regular, are indexed in Biomedicina Croatica, are available on-line (http://hrcak.srce.hr), and will soon be available in other databases as well (like EBSCO Publishing's databases).

This issue of RAD, as we have already announced, introduces papers from the Fourth Scientific Meeting on Brain Disorders: "Scientific Basis of Diagnosis and Treatment of Vertigo" that was held on March 16th 2006 in Zagreb, preceded by the invited review for which we thank our scientists working in the USA. We primarily thank Prof. Ivan Damjanov, MD, PhD, a corresponding member of the Croatian Academy of Sciences and Arts, a worldwide known pathologist, as well as a well known patriot.

For the symposium papers we thank our guest editor Prof. Vida Demarin, MD, PhD, an associate member of the Department of Medical Sciences and a member of the RAD Editorial Board, for her great effort.

For the next issue of our journal we announce papers from the symposium "55 YEARS FROM ORGANIZING BEGINNING OF ALLERGOLOGY IN CROATIA: FUTURE WE BUILT ON THE PAST" which will be held in October 2007.

On behalf of the Editorial Board I guarantee that we will continue in our effort to introduce RAD to the most significant international databases, a process in which we expect a continued support of the members of the Department of Medical Sciences, as well as the entire biomedicine community.

Marko Pećina

UDK 618.11-006
Review
Received: 17 January 2007
Accepted: 25 April 2007

OVARIAN NEUROECTODERMAL TUMORS

Anamarija Morović i Ivan Damjanov

Department of Pathology Cincinnati, Cincinnati, Ohio and the Department of Pathology and Laboratory Medicine,The University of Kansas, School of Medicine, Kansas City, Kansas, USA

Summary

In this paper we have reviewed the publications dealing with primary neuroectodermal tumors of the ovary.These rare monophasic teratomas are composed exclusively or almost exclusively of neuroectodemal tissue and are thus an important paradigm of a type of malignancy that develops from ovarian germ cells. Approximately 60 neuroectodermal tumors of the ovary have been reported in the literature. Histologically, the tumors were classified as gliomas, such as ependymoma, ependymoblastoma, astrocytoma, glioblastoma multiforme, or as primitive neuroepithelial tumors such as medulloblastoma, medulloepithelioma, and neuroblastoma. Microscopically, they are identical to equivalent neuroectodermal tumors of the central nervous system. Most tumors were diagnosed in the third and fourth decades of life. Neuroectodermal tumors are rarely diagnosed in other age groups, although there are published reports of such tumors in children, adolescents or older women. The review of the litarature shows that most patients with clinical stage I and II were treated surgically, whereas those with stage III or IV tumors received additional radiation or chemotherapy, or both. The clinical stage at the time of diagnosis is the most important prognostic parameter of these tumors.Patients whose tumors were recognized early in the course of the neoplastic disease and treated appropriately had a good prognosis, but those with tumors in advanced stages advanced tumors had poor prognosis.

Key words: Ovary; Neuroectodermal tumor; Germ cell tumor

Correspondence to: Ivan Damjanov,Department of Pathology, The University of Kansas School of Medicine, 3901 Rainbow Blvd, Kansas City, KS, 66160, USA
email:idamjano@kumc.edu

INTRODUCTION

Teratomas of the ovary belong to the germ cell tumor and are thought to originate from activated germ cells, which have become activated in a process equivalent to parthenogenetic activation of germ cells in some animal species[1]. Benign teratomas account for over 90% of all ovarian germ cell tumors [2]. Also known as dermoid cysts, these teratomas are cystic and composed predominantly of skin and dermal appendages. Solid benign teratomas composed of numerous well differentiated somatic tissues are less common. The least common neoplasms in this histogenetical group are malignant germ cell tumors, such as embryonal carcinoma, yolk sac carcinoma, dysgerminoma and malignant mixed germ cell tumors corresoponding to testicular seminoma or malignant nonseminomatous germ cell tumors.

Teratomas that contain immature neural tissues are called immature and are considered potentially malignant.Immature teratomas that contain large amounts of immature neural tissue and those that have ruptured or disseminated through the abdominal cavity are treated as malignant. Tumors composed exclusively of immature neuroectodermal tissue have been separated from other teratomas and are treated as a distinct group of neoplasms [3]. These monophasic teratomas, collectively called neuroectodermal tumors of the ovary, are quite rare; our review of the literature disclosed approximately 60 primary ovarian tumors of this type [3-39].

During the last ten years we have encountered two neuroectodermal ovarian tumors: aprimitive neuroectodermal tumor in a 25 year-old woman and an ependymoma of the ovary in a 50 year old woman. We became interested in this form of tumors and thus decided to review the publications dealing with this problem.In this paper we have tabulated the published cases of ovarian neuroectodermal tumor and have reviewed the relevant data from the literature that are useful for the diagnosis of these tumors.

HISTOGENESIS

It has been generally accepted that teratomas of the ovary originate from parthenogenetically activated oocytes. Activated oocytes give rise to embryonic cells, which form early embyonic structures including the three germ layers: ectoderm, mesoderm and endoderm. In mature teratomas ectoderm differentiates, among others, into somatic tissues such as the epidermis and various cells of the central nervous system. The development of these tissues in benign teratomas occurs presumably the same way as in a developing embryo or fetus, and includes many intermediate stages of development. Thus, the central nervous system probably develops through several distinct stages, such as the formation of the neural plate and neural tube. In most teratomas, all neural tube cells

differentiate into glial and neuronal cells, but in some immature teratomas the neural tubes may persist. The immature precursors of neural and glial cells in these neural tubes may proliferate and even implant on the peritoneum and thus behave as malignant cells.

In some germ cell tumors the cells forming the neural tube do not differentiate the same way as they differentiate in the embyo. Instead, they may persist and continue forming neural tube like rosettes and medullary structures. These tumors will ultimately be composed of neural tube-like tissues and are then classified as medulloblastomas aor medulloepitheliomas. If the immature neural cells continue developing along the neural cell lines and also acquire some malignant properties, the tumor composed of such cells will be a neuroblastoma. Monophasic teratomas composed of cells that have become malignant astrocytes will be classified as glioblastoma multiforme or astrocytoma, ependymoblastoma or ependymomoma. Since all these monophasic teratomas stem from putative precursors in the embryonic neuroectoderm, all of them are collectively called neuroectodermal tumors of the ovary.

CLASSIFICATION

The neuroectodermal tumors of the ovary are microscopically identical to their neoplastic counterparts in the nervous system. For clinical-pathologic purposes they can be divided into three groups: (a) well differentiated, (b) anaplastic and (c) poorly differentiated (primitive) tumors [2].

The group of well differentiated tumors comprises ependymomas and astrocytomas. Ependymomas are apparently more common than astrocytomas, and are the most common neuroectodermal tumors of the ovary [3-9].

Anaplastic neuroectodermal tumor are relatively rare .Most of these tumors were classified as glioblastoma multiforme [18,19].

Poorly differented (primitive) neuroectodermal form a group that includes medulloblastoma, medulloepithelioma, neuroblastoma and ependymoblastoma[3]. Tumors composed of small cells that show only rudimentary signs of differentiation are called primitive neuroectodermal tumors.

REVIEW OF PUBLISHED CASES

Our review of the literture on PubMed revealed that thereare approximately 60 published ovarian neuroectodermal tumor.These cases have been tabulated to present all the relevant data and are presented in three tables: Table 1 dealing with well differentiated neuroectodermal tumors, Table 2 dealing with poorly differentiated (primitive

neuroectodermal tumors, and Table 3 dealing with anaplastic neuroectodermal tumors..

Table 1 - Well differentiated neuroectodermal ovarian tumors reported in the literature

Cases of well differentiated neuroectodermal ovarian tumors reported in the literature						
Case reports (age, y)	FIGO Stage	Therapy	Reccurence +/–	Outcome (y)	Diagnosis	Source,y
25	IA	OP	–	NED (5)	EPEND	Kleinmann et al.,1993
16	IA	OP	–	NA	EPEND	Kleinmann et al.,1993
49	IA	OP	–	NED (4)	EPEND+ASTRO	Kleinmann et al.,1993
36	IIA	OP	–	NED (3)	EPEND	Kleinmann et al.,1993
35	III	OP+CHEM	+	AWD (5)	EPEND	Kleinmann et al.,1993
30	III	OP+CHEM+RAD	+	DOD (5)	EPEND	Kleinmann et al.,1993
39	III	OP+CHEM	+	AWD (5)	EPEND	Auerbach et al., 1988
16	I	OP	+	NED (51)	EPEND	Carlsson et al. 1989
25	IV	OP+CHEM+RAD	–	NED (1)	EPEND	Carr et al., 1992
68	IA	OP	–	NED (1)	EPEND	Guerrieri et al., 1993
19	I	OP	+	DOD (9)	EPEND	Hirahara et al., 1997
41	IIIA	OP+CHEM	–	NED (4)	EPEND	Okazaki, 1997
30	III	OP+CHEM	–	NED (2)	EPEND	Garcia-Barriola et al.,2000
26	III	COP+CHEM+RAD	+	AWD (8)	EPEND	Mikami et al., 2001
23	IIIC	OP+CHEM	–	NED (1)	EPEND	Takano et al., 2005
76	IIB	OP	–	NA	EPEND	Erdogan et al., 2005
NA	NA	NA	NA	NA	EPEND	Fan et al., 2006
NA	NA	NA	NA	NA	ASTRO	Elesha SO, 1983
22	NA	OP	–	NED (8mo)	ASTRO	Skopelitou et al., 2002
NA	NA	NA	NA	NA	ASTRO	Berger et al., 1969

OP – operation, CHEM – chemotherapy, RAD – radiation, NED – no evidence of disease, NA – not available, AWD – alive with disease, DOD – died of disease, EPEND – ependymoma, ASTRO – astrocytoma

EPIDEMIOLOGY

Most women diagnosed with neuroectodermal tumor of the ovary are in their third or fourth decade of life. Occasionally these tumors may be diagnosed in younger or older women and there are reports of neuroectodermal tumors in young children, adolescents, as well as older women [2, 4, 6, 7, 12, 18, 21, 24]. In the largest published series based on the material from the Massacchussetts General Hospital, which also included the consultation materials of Drs. R.E.Scully and R.H. Young, the age range of the patients was 6 to 69 years (average 23 years) [3]. Anaplastic and primitive tumors tend to occur in younger patients than well differentiated tumors.

Table 2 – Primitive neuroectodermal ovarian tumors reported in the literature

Cases of primitive neuroectodermal ovarian tumors reported in the literature						
Case reports (age, y)	FIGO Stage	Therapy	Reccurence +/-	Outcome (y)	Diagnosis	Source,y
24	IA	OP	NA	NA	MEDBL	Kleinmann et al.,1993
20	IA	OP+CHEM	–	NED (9)	MEDEP	Kleinmann et al.,1993
32	I A	OP+CHEM	–	NED (3)	MEDEP	Kleinmann et al.,1993
16	IC	OP+CHEM	–	NED (7mo)	NEUBL	Kleinmann et al.,1993
13	III	OP	+	DOD (20mo)	MEDEP	Kleinmann et al.,1993
18	III	OP+RAD	+	DOD (3mo)	EPENBL	Kleinmann et al.,1993
18	III	OP+RAD	+	DOD (7mo)	NEUBL	Kleinmann et al., 1993
18	III	OP+CHEM	+	DOD (6mo)	EPENBL	Kleinmann et al., 1993
26	III	OP+CHEM	+	AWD (1)	EPENBL	Kleinmann et al., 1993
69	III	OP+CHEM+RAD	+	DOD (6mo)	MEDBL	Kleinmann et al., 1993
23	III	OP+CHEM+RAD	+	DOD (2mo)	MEDEP	Kleinmann et al., 1993
16	NA	NA	NA	NA	NEUBL	Kleinmann et al., 1993
NA	NA	NA	NA	NA	PNET	Boor et al., 1975
22	NA	OP	+	NED (4)	NEUBL	Block et al., 1984
NA	NA	NA	NA	NA	NEUBL	Reid et al., 1983
NA	NA	NA	NA	NA	PNET	Shuangshoti et al., 1987
NA	NA	NA	NA	NA	NEUBL	Theppisai et al., 1977
25	IC	OP+CHEM	+	NED (4)	PNET	Demitras et al., 2003
NA	NA	NA	NA	NA	PNET	Rangan et al., 2003
13	NA	OP+CHEM+RAD	+	DOD (17mo)	PNET	Chow et al., 2004
15	NA	CHEM+OP	+	DOD	NEUBL	Somjee et al., 1999
29	NA	OP+CHEM	+	DOD (11mo)	PNET	Kawauchi et al., 1998
13	NA	OP+CHEM	–	NED (18mo)	PNET	Lawlor et al., 1997
35	NA	OP+CHEM	–	NED (3.5)	PNET	Kanbour-Shakir et al., 1993
78	NA	OP+CHEM	–	NED (6mo)	PNET	Fischer et al., 2006
NA	NA	CHEM	+	DOD (13mo)	PNET	Ateser et al., 2007

MEDBL – medulloblastoma, MEDEP – medulloepithelioma, NEUBL – neuroblastoma, EPENBL – ependymoblastoma, PNET – primitive neuroectodermal tumor

CLINICAL FEATURES

Most of the patients presented with symptoms of abdominal and pelvic pain accompanied by abdominal fullness or obvious swelling. Other presenting symptoms were weight loss and deepening of the voice with hirsutism [2, 11]. There is also one report of a pregnant woman with bilateral ovarian ependymomas, which were diagnosed at the end of the pregnancy [5]. This paper is the only record of a bilateral neuroectodermal ovarian tumor in the literature; all other reported tumors were unilateral.

Table 3 - Anaplastic neuroectodermal ovarian tumors reported in the literature

Cases of anaplastic neuroectodermal ovarian tumors reported in the literature						
Case reports (age, y)	FIGO Stage	Reccurence Therapy	+/–	Outcome (y)	Diagnosis	Source,y
6	IA	OP	+	DOD (2)	GBM	Kleinmann et al.,1993
17	IA	OP	-	NED (4)	GBM	Kleinmann et al.,1993
15	IA	OP	-	NED (3)	GBM	Kleinmann et al.,1993
16	IIA	OP	+	DOD (5)	GBM	Kleinmann et al.,1993
15	IIA	OP	+	AWD (1)	GBM	Kleinmann et al.,1993
22	IIB	OP	NA	NA	GBM	Kleinmann et al.,1993
22	III	OP+CHEM+RAD	+	DOD (4mo)	GBM	Kleinmann et al., 1993
41	NA	OP	-	NED (3.5)	GBM	den Boon et al., 1999
34	NA	OP	-	NED (3)	GBM	Bjersing et al., 1989
16	NA	OP+CHEM	-	AWD	GBM	Yadav et al., 1999
NA	NA	CHEM	+	DOD	GBM	Nishida et al., 1984

GBM – glioblastoma

GROSS PATHOLOGY

Most tumors are large and the average size of tumors is 10-14 cm [3,13]. Grossly, most neuroectodermal ovarian tumors are solid but may be partially cystic. Cysts are lined by gray-tan tissue and may contain papillary structures protruding into the lumen. The solid parts of the tumor are composed of grayish white soft tissue. Areas of necrosis or hemorrhage may be prominent, especially in large tumors. The external surface is mostly smooth and glistening. Tumors with external nodules and surface papillary components have also been reported [3,13,14].

HISTOPATHOLOGY

Morphologically, neuroectodermal tumors of the ovary are identical to their counterparts in the central nervous system. Tumor cells show either glial or neural differentiation, or correspond to developmentally unclassifiable nervous system precursors. Histologically, neuroectodermal tumors of the ovary are classified as ependymoma, astrocytoma, glioblastoma multiforme, medulloblastoma, medulloepithelioma, ependymoblastoma, neuroblastoma and primitive neuroectodermal tumor. Different variants have been described in some of these tumors, especially ependymoma, but given the small number of reported cases the classification that is used for their counterparts in the central nervous system is probably not applicable to neuroectodermal ovarian tumors.

All reported ependymomas, except one occured as pure tumors. That case was classified as ependymoma with an astrocytoma component [3]. Like their central nervous system equivalents, ovarian ependymomas can be further classified as cellular, papillary or myxopapillary, but the patterns of growth are often intermixed one with another.. Tumors are composed of small cells with hypechromatic, round-to-oval nuclei, and scanty cytoplasm. Nuclei show remarkable uniformity and mitotic figures are not numerous. Tumor cells are arranged in lobules separated by fibrovascular septa or form patternless sheets. Perivascular pseudorosettes formed by tumor cells radially surrounding blood vessels can be observed as well as ependymal rosettes composed of tumor cells surrounding a lumen. Psammoma bodies can be seen [13,14]. Some tumors are more cellular, contain more mitoses and show signs of nuclear anaplasia. Atypical mitotic figures in tumor cells are also reported [13,14]. These tumors are appropriately classified as anaplastic ependymoma.

Astrocytomas are composed of cells resembling adult or fetal astrocytes. The tumors may also have the features of pilocytic or gemistocytic astrocytomas, and in some instances be admixed to typical ependymoma [3,15-16]. Glioblastomas are composed of neoplastic astrocytes arranged in sheets or lobules. They contain varying amounts of cytoplasm and may form eosinophilic fibrillary processes. The nuclei are round-to-oval, with some having irregular contours; nucleoli are occasionally prominent. Areas of necrosis are prominent , and sometimes surrounded by palisading tumor cells. Mitotic figures, as well as abnormal mitotic figures are prominent. Multinucleate giant cells are often present [3].

Medulloepithelioma, medulloblastoma, ependymoblastoma, neuroblastoma and primitive neuroectodermal tumors are closely related tumors, which are all composed of primitive neuroblastic or primitive, developmentally uncommitted precursors of neural and glial cells. Medulloblastomas have a most distinctive appearance and are characterized by papillary, tubular or trabecular arrangements of neoplastic neuroepithelium mimicking the embryonic neural tube. Medulloepitheliomas are characterized by elongated glands and canals composed of cytologically malignant, mitotically active epithelium with numerous mitoses. Neuroblastomas are usually higly cellular tumors arranged in lobules with varying quantities of connective tissue. Other features of neuroblastomas are fibrillary neuropil, Homer Wright rosettes, palisading cells and scattered ganglion cells. Ependymoblastomas are highly cellular tumors containing true rossettes and canals lined by multiple layers of markedly atypical, mitotically active cells [28]. Primitive neuroectodermal tumors are highly cellular and composed of small cells with hyperchromatic, round to oval nuclei and scanty cytoplasm

These cells are arranged into lobules separated by fibrovascular septa, but also may form patternless sheets. Varying amounts of finely fibrillar cell processes are present in the tumor. Areas of necrosis can be prominent [3].

ANCILLARY STUDIES

Immunohistochemistry

Ependymomas, astrocytomas and glioblastomas of the ovary react with antibodies to glial fibrillary acidic protein (GFAP). Ependymomas also show positivity for for vimentin [6,11,12], S-100 [6,7,11,12], epithelial membrane antigen (EMA) [6,7,11,12], neuron-specific enolase (NSE) [6,7,11], estrogen and progesterone receptors [3,5,11], CEA [12] and cytokeratin [6,7].

Primitive neuroectodermal tumors, medulloblastoma, and neuroblastoma show variable reactivity with antibodies to CD99, NSE and vimentin. Most cells are negative for, but scattered cells showing neural or glial differentiation will be positive for neurofilaments and synaptophysin, or GFAP and S-100. No cells react with antibodies for cytokeratin, desmin, chromogranin or inhibin [2, 22].

Molecular markers

Two papers report chromosomal abnormalities in primitive neuroectodermal tumors of the ovary. In the first paper the authors report the results of comparative genomic hybridization that revealed multiple chromosomal abnormalities including losses of chromosomes in 1p, 1q, 4q, 6p, 6q, 7q, 8q, 13q and 19q; as well as gains of chromosomes 1q, 2p, 7p, 9q, 18q and Xq. Loses of 13q14.1-q14.2, 1 p31, and 4q34-q35 indicated that Rb gene, ARHI, and FAT were deleted. Gains of 2p24.1, 1q23 and 7p12.3-p12.1 demonstrated that N-myc oncogene, FASL GITL, and EGFR were amplified. RT-PCR analysis showed that N-myc and EGFR were overexpressed, while Rb and ARHI were underexpressed [21].

In the second paper, the authors report a case of a primitive neuroectodermal tumor that possesed balanced chromosomal translocation t(11;22)(q24;q12), that is highly specific for tumors of the PNET/Ewing's sarcoma family. EWS/FLI-1 chimeric mRNA that originated from the characteristic chromosomal translocation was detected by reverse transcription-polymerase chain reaction [24].

DIFFERENTIAL DIAGNOSIS

Ovarian ependymomas may contain large gland-like spaces, which superficially resemble neoplastic glands in endometrioid adenocarcinomas. Papillary ependymomas may be confused with serous ovarian carcinomas. Both tumors may show complex papillary pattern of growth and contain calcifications or psammoma bodies. Sometimes, ependymal rosettes may resemble Call-Exner bodies of granulosa cell tumors, but in

general the ependymal cells have long, fibrillary, cytoplasmic processes and lack the characteristic nuclear grooves of granulosa cells. Sertoli-Leydig cell tumors may be in the differential diagnosis of ependymomas when the ribbons of cells or tubules in an ependymoma mimic the sex cords or tubules of a typical or retiform variant of the Sertoli-Leydig cell tumor. Gland-like spaces lined by cells with fibrillary cytoplasmic processes, perivascular pseudorosettes and positivity for GFAP confirm the diagnosis of ovarian ependymoma [3,11,30].

Immature teratomas can closely resemble primitive and anaplastic neuroectodermal tumors because they can contain immature neuroectodermal cells. Immature teratomas show greater diversity of neuroepithelial differentiation as well as a more extensive and varied admixture of endodermal, mesodermal and other ectodermal tissues.

Various malignant "small blue-cell tumors" must also be distinghished from primitive neuroecotdermal tumors and neuroblastomas. This group of tumors includes small cell carcinomas (primary and metastatic), malignant lymphoma and leukemia, metastatic melanoma, metastatic round cell sarcomas, and the intra-abdominal desmoplastic small round cell tumor. Immunohistochemistry may be useful in such cases.

TREATMENT AND PROGNOSIS

Most patients with clinical stage I and II of the disease received operation as the only treatment, while most patients with clinical stages III and IV were treated with operation and subsequent radiation or chemotherapy, or combination of both. Clinical stage seems to be the most important prognostic parameter of survival and patients with clinical stages I and II, have less reccurences of tumor and overall longer survival. Therefore, if the tumor is limited to one ovary and the patient wants to preserve fertility, simple oophorectomy or conservative treatment with chemotherapy is probably sufficient treatment [3,17,20]. Ovarian ependymomas sometimes express estrogen and progestin receptors and this finding can suggest that hormonal responsiveness of this tumor can be used as a treatment modality[4,6]. Mega-dose chemotherapy followed by peripheral progenitor cell rescue was reported in the literature as the treatment modality for metastatic primitive neuroectodermal ovarian tumor [25].

References

[1] *Damjanov I.* Teratocarcinoma: neoplastic lessons about normal embryogenesis. Int J Dev. Biol. 1993;37:39-46.

[2] *Tavassoli FA, Devilee P.* World Health Organization Classification of Tumors. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon: IARC Press, 2003.

[3] *Kleinmann GM, Young RH, Scully RE.* Primary neuroectodermal tumors of the ovary. A report of 25 cases. Am J Surg Pathol. 1993;17:764-78.

[4] *Auerbach R, Mittal K, Schwartz PE.* Estrogen and progestin receptors in an ovarian ependymoma. Obstet Gynecol 1988;71:1043-5.

[5] *Carlsson B, Havel G, Kindblom LG, Knutson F, Mark J.* Ependymoma of the ovary. A clinico-pathologic, ultrastructural and immunohistochemical investigation. A case report. APMIS 1989;97:1007-12.

[6] *Carr KA, Roberts JA, Frank TS.* Progesterone receptors in bilateral ovarian ependymoma presenting in pregnancy. Hum Pathol 1992;23:962-5.

[7] *Guerrieri C, Jarlsfelt I.* Ependymoma of the ovary. A case report with immunohistochemical, ultrastructural, and DNA cytometric findings, as well as histogenetic considerations. Am J Surg Pathol. 1993;17:623-32.

[8] *Hirahara F, Yamanaka M, Miyagia E, Nakazawa T, Gorai I, Minaguchi H, Kakei M, Yamamoto M, Kitamura H.* Pure ovarian ependymoma: report of a case treated with surgery, chemotherapy, irradiation and hyperthermotherapy. Eur J Obstet Gynecol Reprod Biol. 1997;75:221-3.

[9] *Okazaki H.* A case of ependymoma ovarii. Acta Obstet Gynecol Jpn. 1997;49:815-7.

[10] *Mikami M, Komuro Y, Sakaiya N, Tei C, Kurahashi T, Komiyama S, Hirose T.* Primary ependymoma of the ovary, in which long-term oral etoposide (VP-16) was effective in prolonging disease-free survival. Gynecol Oncol. 2001;83:149-52.

[11] *Garcia-Barriola V, De Gomez MN, Suarez JA, Lara C, Gonzalez JE, Garcia-Tamayo J.* Ovarian ependymoma. A case report. Pathol Res Pract. 2000;196 :595-9.

[12] *Takano T, Akahira J, Moriya T, Murakami T, Tanaka M, Goto M, Niikura H, Ito K, Mikami Y, Okamura K, Yaegashi N.* Primary ependymoma of the ovary: a case report and literature review. Int J Gynecol Cancer. 2005;15:1138-41.

[13] *Erdogan G, Ozel E, Pestereli HE, Salar Z, Tirak B, Karaveli S.* Ovarian ependymoma. APMIS. 2005;113:301-3.

[14] *Skopelitou A, Mitselou A, Michail M, Mitselos V, Stefanou D.* Pilocytic astrocytoma arising in a dermoid cyst of the ovary: a case presentation. Virchows Arch. 2002;440:105-6.

[15] *Elesha SO.* Malignant astrocytoma in an immature (malignant) ovarian teratoma. East Afr Med J. 1983;60:501-5.

[16] *Trabelsi A, Conan-Charlet V, Lhomme C, Morice P, Duvillard P, Sabourin JC.* Peritoneal glioblastoma: reccurence of ovarian immature teratoma (report of a case). Ann Pathol. 2002;22 :130-3.(In French)

[17] *den Boon J, van Dijk CM, Helfferich M, Peterse HL.* Glioblastoma multiforme in a dermoid cyst of the ovary. A case report. Eur J Gynecol Oncol. 1999;20:187-8.

[18] *Bjersing L, Cajander S, Rogo K, Ottosson UB. Stendahl U.* Glioblastoma multiforme in a dermoid cyst of the ovary. Eur J Gynaecol Oncol. 1989;10:389-92.

[19] *Yadav A, Lellouch-Tubiana A, Fournet JC, Quazza JE, Kalifa C, Sainte-Rose C, Jaubert F.* Glioblastoma multiforme in a mature ovarian teratoma with reccuring brain tumors. Histopathology. 1999;35:170-3.

[20] *Demirtas E, Guven S, Guven ES, Baykal C, Ayhan A.* Two successful spontaneous pregnancies in a patient with a primary primitive neuroectodermal tumor of the ovary. Fertil Steril. 2004;81:679-81.

[21] *Rangan A, Lobo FD, Rao AA.* Primary primitive neuroectodermal tumor of the ovary: a case report. Indian J Pathol Microbiol. 2003;46:58-9.

[22] *Chow SN, Lin MC, Shen J, Wang S, Jong YJ, Chien CH.* Analysis of chromosome abnormalities by comparative genomic hybridization in malignant peripheral primitive neuroectodermal tumor of the ovary. Gynecol Oncol. 2004;92:752-60.

[23] *Somjee S, Kurkure PA, Chinoy RF, Deshpande RK, Advani SH.* Metastatic ovarian neuroblastoma: a case report. Pediatr Hematol Oncol. 1999;16:459-62.

[24] *Kawauchi S, Fukuda T, Miyamoto S, Yoshioka J, Shirahama S, Saito T, Tsukamoto N.* Peripheral primitive neuroectodermal tumor of the ovary confirmed by CD99 immunostaining, karytypic analysis, and RT-PCR for ESW/FLI-1 chimeric mRNA. Am J Surg Pathol. 1998;22:1417-22.

[25] *Lawlor ER, Murphy JI, Sorensen PH, Fryer CJ.* Metastatic primitive neuroectodermal tumour of the ovary: successful treatment with mega-dose chemotherapy followed by peripheral blood progenitor cell rescue. Med Pediatr Oncol. 1997;29:308-12.

[26] *Yalcin S, Guler N, Soylemezoglu F.* Medulloblastoma in a patient successfully treated for immature teratoma of the ovary. Med Oncol. 1996;13:241-2.

[27] *Kanbour-Shakir A, Sawaday J, Kanbour AI, Kunschner A, Stock RJ.* Primitive neuroectodermal tumor arising in an ovarian mature cystic teratoma: immunohistochemical and electron microscopic studies. Int J Gynecol Pathol. 1993;12:270-5.

[28] *Reid H, Van der Walt JD, Fox H.* Neuroblastoma arising in a mature cystic teratoma of the ovary. J Clin Pathol. 1983;36:68-73.

[29] *Burger PC, Scheithauer BW, Vogel FS.* Surgical Pathology of the Nervous System and its Coverings, 4th edition. Philadelphia : Churchill Livingstone, 2002.

[30] *Mikami M, Sakaiya N, Kurahashi T, Komiyama S, Tei C, Mukai M, Hirose T.* Tumor imprint cytology of ovarian ependymoma. A case report. Cancer. 2001;92:3165-9.

[31] *Fan F, Hernandez-Rios P, Damjanov I, Dusing RW.* Metastasis of ovarian ependymoma to the liver diagnosed by fine needle aspiration cytology. Acta Cytol. 2006;50:709-10.

[32] *Berger N, Pochaczevsky R.* Astrocytoma-containing ovarian teratoma of childhood. Am J Roentgenol. 1969;107:647-51.

[33] *Boor PJ, Schoene WC.* Fetal cerebellar tissue associated with a primitive neuro-epithelial tumor in an ovarian teratoma. Can J Neurol Sci. 1975;2:139-41.

[34] *Block M, Gilbert E, Davis C.* Metastatic neuroblastoma arising in an ovarian teratoma with long-term survival. Case report and review of the literature. Cancer. 1984;54:590-5.

[35] *Shuangshoti S, Sindhavananda S, Kasantikul V, Nutakom T.* Primary primitive neuroectodermal (neuroepithelial) tumors of the ovary. J Med Assoc Thai. 1987;70:478-84.

[36] *Theppisai H, Shuangshoti S, Amatyakul A.* Nuroblastoma arising in metastizing ovarian teratoma. J Med Assoc Thai. 1977;60:396-404.

[37] *Fischer G, Odunsi K, Lele S, Mhawech P.* Ovarian primary primitive neuroectodermal tumor coexisting with endometrioid adenocarcinoma: a case report. Int J Gynecol Pathol. 2006;25:151-4.

[38] *Ateser G, Yildiz O, Leblebici C, Mandel NM, Unal F, Turna H, Arikan I, Colcaki D.* Metastatic primitive neuroectodermal tumor of the ovary in pregnancy. Int J Gynecol Cancer. 2007;17:266-9.

[39] *Nishida T, Sugiyama T, Oda T, Tazaki T, Yakushiji M, Kato T.* Prognostic significance of glioblastoma element in ovarian immature teratoma. Nippon Sanka Fujinka Gakkai Zasshi. 1984;36:1095-9.

Sažetak

Ovarijalni neuroektodermalni tumori

U ovom smo radu pregledali objavljenu literaturu o primarnim neuroektodermalnim tumorima jajnika. Ovi rijetki monofazični teratomi, sastavljeni isključivo ili gotovo isključivo od neuroektodermalnog tkiva, predstavljaju važnu paradigmu tumora koji se razvijaju iz zametnih stanica jajnika. Do sada je u literaturi opisano oko 60 slučajeva neuroektodermalnih tumora jajnika. Većinom se dijagnosticiraju u žena u trećem i četvrtom desetljeću života, a rijetko se pojavljuju u djece, adolecenata i starijih žena. Ovi se tumori dijele na gliome, kao što su ependimom, ependimoblastom, astrocitom, glioblastom, te na primitivne neuroepitelne tumore, kao što su meduloblastom, meduloepiteliom i neuroblastom. Histološka slika ovih tumora identična je tumorima koji se pojavljuju u središnjem živčanom sustavu. Većina bolesnica s niskim kliničkim stadijem bolesti (I i II) liječena je kirurški, dok su bolesnice s višim kliničkim stadijem (III i IV) dodatno liječene zračenjem, kemoterapijom, ili s oba modaliteta. Klinički stadij bolesti pri dijagnozi najznačajniji je prognostički pokazatelj kod ovih tumora. Bolesnice kod kojih je tumor dijagnosticiran i odstranjen u ranom kliničkom stadiju imaju dobru prognozu, dok je prognoza u uznapredovalim stadijima bolesti loša.

Ključne riječi: jajnik, neuroektodermalni tumori

The Fourth Scientific Meeting of Brain Disorders

SCIENTIFIC BASIS OF DIAGNOSIS AND TREATMENT OF VERTIGO

Guest Editor
VIDA DEMARIN

EDITORIAL

The position of the body in space is controlled by the ocular, vestibular and somatosensory systems. A mismatch of this sensory information causes vertigo. Vertigo is defined as a hallucination of movement or erroneous perception of self or object motion, i.e. vertigo is the illusion of motion, most often rotational motion. It is usually an unpleasant sensation due to the distortion of the static gravitational orientation perceived by the cortical spatial perceptional system. Vertigo is usually associated with difficulties in balance and gait, with nausea, vomiting, and nystagmus. However, patients with vertigo may also complain of dizziness, lightheadedness, unsteadiness, imbalance, spinning, floating, and swaying.

There are a variety of causes of vertigo: it can be caused by an inner ear disturbance producing peripheral vertigo, by a central disturbance producing central vertigo, by systemic diseases, or it can be psychogenic. The most common causes of vertigo include benign paroxysmal positional vertigo, acute vestibular neuronitis, Méniére's disease, migraine, anxiety disorders, vertebrobasilar ischemia and tumors of the pontocerebellar angle. It is important to distinct between peripheral, central and psychogenic vertigo in order to guide management decisions.

Vertigo is among the most common symptoms causing patients to visit a physician, almost as common as back pain and headache. As patients become older the incidence of vertigo increases. Today, as the average lifespan increases and there is an ever growing proportion of elderly patients who are more prone to vertiginous symptoms, it is expected that the incidence of vertigo will continuously increase in the everyday medical practice.

Because vertigo is so common and there are so many causes of vertigo from the benign to severe ones, the Department of Medical Sciences of the Croatian Academy of Sciences and Arts had decided to organize the Fourth Scientific Meeting on Brain Disorders: Scientific Basis of Diagnosis and Treatment of Vertigo that was held on Thursday, March 16, 2006, in the Illyrian Hall of the National House, Zagreb, Croatia. Many recognized practitioners and scientists delivered lectures on the diagnosis and treatment of different forms of vertigo, presenting a comprehensive interdisciplinary overview of vertigo.

This meeting was so well attended that it was decided to publish lectures held on the meeting, as well as some additional scientific results of work recently done on vertigo diagnosis at the University Department of Neurology, Sestre Milosrdnice University Hospital.

Therefore, this issue presents the most important lectures from this meeting and some recently finished scientific papers about vertigo. We hope that in this issue of the journal every physician who wants to know more and is interested to find additional information about the diagnosis and treatment of vertigo will find some valuable information about this common symptom and its diagnosis.

Vida Demarin

UDK 616.28-008.5-07
Review
Received: 17 January 2007
Accepted: 25 April 2007

DIFFERENTIAL DIAGNOSIS OF VERTIGO

Vida Demarin, Zlatko Trkanjec, Anka Aleksić-Shibabi[1], Melita Uremović[2]

University Department of Neurology, Sestre Milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
[1]Department of Neurology, Šibenik General Hospital, Šibenik, Croatia
[2]Zagreb Insurance Company, Zagreb

Summary

Vertigo is the illusion of motion, usually rotational motion. Vertigo is among the most common symptoms causing patients to visit a physician, and as patients become older the incidence of vertigo increases. Vertigo can be caused by an inner ear disturbance – peripheral vertigo, by a central disturbance – central vertigo, by systemic diseases, or it can be psychogenic. The most common causes of vertigo are benign paroxysmal positional vertigo, acute vestibular neuronitis, Méniére's disease, migraine, anxiety disorders, vertebrobasilar ischemia and tumors of the pontocerebellar angle. It is important to distinct between peripheral and central vertigo in order to guide management decisions. In this article a differential diagnosis of vertigo is presented.

Key words: vertigo, peripheral vertigo, central vertigo, benign paroxysmal positional vertigo, acute vestibular neuronitis, Méniére's disease, migraine, vertebrobasilar ischemia, tumor of pontocerebellar angle

INTRODUCTION

Body position in space is controlled by the ocular, vestibular and somatosensory systems. The somatosensory system provides information from the skin, muscles and joints, the most important being the proprioceptive system located in the neck muscles and joints. Information from these three systems is processed in the brain stem, and,

Correspondence to: Vida Demarin, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: vida.demarin@zg.t-com.hr

finally, integrated into the cortical perception system enabling postural reflexes that maintain the body position in space and conscious perception of spatial orientation [1].

A mismatch of this sensory information causes vertigo. Vertigo is defined as a hallucination of movement or erroneous perception of self or object motion. It is usually an unpleasant sensation due to the distortion of the static gravitational orientation perceived by the cortical spatial perceptional system, associated with difficulties in balance and gait. This erroneous perception of motion of person or environment may be linear or angular (rotatory). Central compensatory mechanisms enable deficiencies in one area to be overcome by other intact sensory systems [1,2].

Vertigo is a symptom that is perceived at higher cortical levels. Vertigo may be due to excessive physiological stimulation or pathological dysfunction. Symptoms that most often accompany vertigo include nausea, vomiting, nystagmus, and imbalance in standing and walking. Patients with vertigo may also complain of dizziness, lightheadedness, unsteadiness, imbalance, spinning, floating, and swaying. Gait imbalance or ataxia results from inappropriate or abnormal signals from the vestibulospinal system. Nausea and vomiting may occur from the activation of the chemoreceptor trigger zone in the medullar vomiting center. Nystagmus may be observed as a result of the dysfunction of the vestibulo-ocular system [1,2,3].

Vertigo is among the most common symptoms causing patients to visit a physician, almost as common as back pain and headache. The overall incidence of vertigo is 20-30% [4], reaching 50% in older patients and it is the most frequent symptom in patients older than 75 years [5]. Vertigo was the cause for 2% of consultations in general practice in the United Kingdom [6].

Vertigo can be caused by an inner ear disturbance – peripheral vertigo, by a central (brain) disturbance – central vertigo, by systemic diseases, or it can be psychogenic. Most authors take vestibular nuclei in the brainstem as the point differencing peripheral (before the vestibular nuclei) and central vertigo (after the vestibular nuclei). As a result, central compensatory mechanisms, symptoms of peripheral labyrinth dysfunction, will eventually recover. Symptoms of central nervous dysfunction, although usually milder, tend to persist over time [1,2,7].

The most common causes of peripheral vertigo include benign paroxysmal positional vertigo (BPPV), vestibular neuronitis and Méniére's disease. The most common cause of central dizziness is migraine, frequently referred to as vestibular migraine or migraine-associated dizziness, while other central causes include vertebrobasilar insufficiency, cerebellar and brainstem lesions, acoustic tumors, and demyelination [2, 9].

Vertigo can be induced by physiological and pathological causes. In physiological vertigo the sense of disequilibrium is due to the physiological excess of visual, vestibular, or somatosensory signals which cannot be compensated by other systems. In path-

ological vertigo there is an abnormal sensory signal (from the sensors) or abnormal signal processing (by the central nervous system) [10,11].

Physiological vertigo

Physiological vertigo occurs in normal individuals when the brain is confronted with a mismatch among the three stabilizing sensory systems when the vestibular system is subjected to unfamiliar head movements to which it is un-adapted, such as in seasickness; unusual head/neck positions, like in extreme head extension (e.g. painting a ceiling); or following a spin. The intersensory mismatch also explains carsickness, height vertigo, and the visual vertigo most commonly experienced during motion picture chase scenes where the visual sensation of environmental movement is unaccompanied by concomitant vestibular and somatosensory movement information, or when inadequate spectacles are worn. Space sickness, a frequent transient effect of active head movement in the weightless zero-gravity environment, is another example of physiological vertigo [1,3,9,11,12].

Pathological vertigo

Pathological vertigo results from lesions of the visual, somatosensory, or vestibular systems. Visual pathological vertigo occurs due to a sudden onset of an extra-ocular muscle paresis usually accompanied with diplopia. Somatosensory vertigo, rare in isolation, is usually due to a peripheral neuropathy or myelopathy especially of dorsal columns that reduces the sensory input necessary for central compensation when there is a dysfunction of the vestibular or visual systems. In the past the most often cause was tabes dorsalis [2,3,10].

However, the most common cause of pathological vertigo is the vestibular dysfunction. Pathological vestibular vertigo can be due to either the peripheral labyrinth dysfunction, systemic derangement (such as metabolic, endocrine, or circulatory abnormalities), or central vestibular dysfunction. This type of vertigo is frequently accompanied by nausea, nystagmus, postural unsteadiness, and gait ataxia. Psychogenic vertigo results from hyperventilation in a patient with a known psychiatric disease who can complain of severe vertigo without the associated nystagmus or other physical findings. Severely incapacitating vertigo may be seen in anxiety attacks [2,5,9].

Sudden onset and vivid memory of vertiginous episodes are often due to an inner-ear disease, especially if a hearing loss, ear pressure, or tinnitus are also present. Gradual and ill-defined symptoms are most common in central nervous system (CNS), cardiac, and systemic diseases. The time course of vertigo is also important. Episodic true vertigo that lasts for seconds and is associated with head or body position changes is probably due to BPPV. Vertigo that lasts for hours or days is probably caused by Ménière's disease

or vestibular neuronitis. Patients with peripheral vertigo can usually ambulate during episodes and are consciously aware of their environment [3,5,7,8,13].

A sudden onset vertigo that lasts for minutes can be due to a brain or vascular disease, especially if cerebrovascular risk factors are present. Central vertigo secondary to brainstem or cerebellar ischemia is often associated with other brainstem characteristics, including diplopia, autonomic symptoms, nausea, dysarthria, dysphagia, or focal weakness. Patients with cerebellar disease are frequently unable to ambulate during acute episodes of vertigo. Dysdiadochokinesis and gait ataxia during episodes are more likely due to cerebellar diseases, especially in the elderly population. Sensory and motor symptoms and signs are usually associated with CNS diseases [10,11,13,14,15].

History

Patients should be thoroughly asked about the characteristics and pattern of the vertiginous sensation, the onset and duration of vertigo, factors intensifying vertigo, such as positional changes, or whether vertigo is worse with the eyes open or closed. Associated auditory symptoms such as tinnitus, ear fullness, pain, or hearing loss usually indicate peripheral vestibular dysfunction. Signs of central neurological dysfunction include diplopia, ataxia, dysphagia, dysphonia, or sensory and motor complaints. The history should include a review of systems (especially head trauma and/or ear diseases) and screening for anxiety and/or depression. A history of prescription medicines, over-the-counter medications, herbal medicines, and data about smoking, alcohol and illicit drugs intake can help to identify pharmacologically induced syndromes. A history of headaches, especially migraine headaches, can be associated with migraine-related dizziness. A previous viral illness, cold sores, or sensory changes in the cervical C2-C3 or trigeminal distributions usually indicate vestibular neuronitis or recurrent episodes of Ménière's disease [1,2,3,5].

Causes of vertigo

The most common systemic causes of vertigo include cardiac diseases, arterial hypertension and hypotension, hematological diseases (e.g. anemia, leukemia, lymphomas, polycytemia), hypoglycemia, hypoadrenalism, Cogan's syndrome (interstitial keratitis with vestibular symptoms) and cervical vertigo.

Psychogenic vertigo results most often from hyperventilation in a patient with a known psychiatric disease. A patient with psychogenic vertigo may have a subjective complaint of severe vertigo without the associated nystagmus or other physical findings. Severely incapacitating vertigo may be seen in anxiety attacks or in severe height vertigo (acrophobia). The treatment of psychogenic vertigo would be based on the underlying psychiatric diagnosis. Psychotherapy and desensitization procedures are of-

ten useful. A diagnosis of psychogenic vertigo presumes that no physical findings substantiate an organic cause for the vertigo symptoms [18].

The most common causes of peripheral vertigo

One of the most common peripheral vestibular syndromes is benign paroxysmal positional vertigo (BPPV), which may occur at any age. The characteristic history includes brief episodes of positionally induced vertigo, particularly in rapid changes in position such as getting out of bed. True vertigo or rotational sensation usually lasts less than one minute; however, a nonspecific dizziness, often described as a swimming sensation or disequilibrium, may last hours to days. BPPV has often been described as "self-limiting" because symptoms often subside or disappear within six months of the onset. Although BPPV usually remits spontaneously, one third of patients have recurrent symptoms for more than one year [19,20].

Acute unilateral labyrinth dysfunction (vestibular neuritis or neuronitis) manifests as an acute onset of severe vertigo with an associated positional imbalance, nausea, and nystagmus. This syndrome is different from benign paroxysmal vertigo because it has a much more prolonged course, is usually more severe, and is not positionally induced. Vestibular neuronitis often has viral etiology. In vestibular neuronitis, due to the reduced signal from the affected side, the nystagmus fast phase is directed away from the affected side. Three to five days after the onset of acute vertigo the patient will probably have spontaneous resolution of nausea and will be able to partially suppress nystagmus by fixation. Generally, within two to three weeks the vertigo ceases [21,22].

Méniére's disease (endolymphatic hydrops) is a common cause of recurrent vertigo and auditory symptoms. Méniére's disease is characterized by a fluctuating hearing loss in the low frequencies, a sensation of ear fullness or pressure and tinnitus, and prolonged vertigo reaching its maximum over minutes and resolving over hours with an associated postural imbalance and nausea. There is often a low tolerance for loud noises. During the vertigo attack, which usually lasts 30 to 60 minutes, a characteristic nystagmus is seen, with the fast phase away from the affected ear [23].

Toxic substances known to cause vertigo and auditory symptoms include alcohol, heavy metals and drugs. Aminoglycoside antibiotics, such as streptomycin and gentamicin, are known vestibular toxins, while neomycin and kanamycin are ototoxic. Other vestibulotoxic and ototoxic drugs include acetylsalycilic acid intoxication, chloroquine, furosemide, quinidine and quinine [24].

Central vertimgo

Central causes of vertigo are less common than peripheral. Causes of vestibular vertigo include migraine, cerebrovascular diseases of the posterior cerebral circulation

including transient ischemia attack (TIA) (vertebrobasilar insufficiency), epilepsy, demyelinating disease of the posterior fossa, congenital malformations such as Arnold-Chiari malformation, subdural hematoma, fractures, cysts, arachnoiditis, syringobulbia, platibasia, neoplastic diseases, degenerative diseases of the posterior fossa, infectious diseases, toxic lesions, lesions of the temporal lobe, and supratentorial lesions compressing the brainstem [1,2,14,15].

Lesions of the vestibular nuclei and the vestibular portion of the cerebellum may cause vertigo, nystagmus, disequilibrium, and nausea. There are usually other signs of central nervous system dysfunction. Symptoms result from the involvement of the brain stem structures responsible for eye movement, speech, sensation of the face, extremities, and trunk, and motor control of the facial muscles and extremities. Presence of other neurological signs helps distinguish central from peripheral vertigo. Central vertigo tends to be less severe with fewer autonomic symptoms such as nausea and vomiting. It tends to persist over longer periods of time and occur in less sudden or severe attacks, except in the case of migraine or vascular disease [1,2,15,25].

Due to the dysfunction of brain stem compensating structures in central vertigo syndromes, vertigo, as well as nystagmus, may persist over considerable periods of time. Central nystagmus looks more severe than the patient's corresponding symptoms of vertigo or nausea. Postural changes tend to stimulate peripheral vertigo more than the central one. Peripheral vertigo tends to be reduced with fixation with the eyes open. Central vertigo tends to be worse with the eyes open, because of the conflict of visual and vestibular information. With the eyes closed, visual information is reduced, which reduces the visual vestibular conflict and reduces the sense of vertigo. Peripheral vertigo tends to fatigue with repeated head movements because of the intact brainstem compensation mechanisms. In central vertigo the vertigo does not fatigue or habituate with repeated movements, however it may vary on a day to day basis [2,25,26,27].

Cerebrovascular diseases

Vertebrobasilar insufficiency (TIA of the posterior cerebral circulation) denotes reversible episodes of focal ischemic neurological deficit that most often last 2-15 minutes causing transient neurological symptoms. Vertebral-artery disease can cause transient attacks of vertigo that are usually accompanied by other brain-stem or cerebellar symptoms [25].

The most common causes of vertebrobasilar ischemia are embolism, large-artery atherosclerosis causing arterial stenosis and occlusion, penetrating small-artery disease, artery dissection and subclavian steal syndrome (narrowing of the subclavian artery proximally to the vertebral artery origin when blood flows around through the left and right vertebral arteries, and posterior parts of the brain receive insufficient blood supply

causing neurological symptoms). Stenosis and occlusion most often occur at or near the origin of the vertebral artery [26,27].

Posterior-circulation ischemia rarely causes only one symptom but rather produces a collection of symptoms and signs. Symptoms and signs depend on the affected part of the brain: brain stem (medulla, pons, midbrain), cerebellum, and posterior parts of brain [26].

Dizziness, vertigo, headache, vomiting, double vision, loss and blurring of vision, ataxia, numbness and/or weakness, gait and limb ataxia, oculomotor palsies, and oropharyngeal dysfunction are frequent symptoms in patients with vertebrobasilar artery disease [25,26,27].

TIA can occur after a patient has been standing or in situations that reduce blood pressure or blood flow. These symptoms are related to ischemia of vestibulocerebellar structures in the medulla and cerebellum, most often consisting of dizziness, difficulty focusing visually, vertigo, loss of balance, and spells of decreased vision and ataxia [25, 26,27].

Patients with cerebellar infarcts often report dizziness, occasionally in conjunction with frank vertigo, blurred vision, difficulty walking, and vomiting. They often veer to one side and cannot sit upright or maintain an erect posture without a support. Patients may have hypotonia of the arm on the side of the infarct.

Ischemic infarcts can involve one posterior cerebral artery, which most often leads to a hemianopia of the contralateral visual field. Hemisensory symptoms may be present on the same side of the body and face as the hemianopia. Difficulty reading and naming colors often accompanies large infarcts of the left posterior cerebral artery, whereas neglect of the left visual field and disorientation to place may accompany infarcts of the right posterior cerebral artery [25,26,27].

Stenosis and occlusion of the basilar artery usually cause bilateral symptoms or crossed findings: ipsilateral symptoms of cranial nerves and contraleral symptoms of the trunk and limbs. Embolic infarction of the rostral midbrain and thalamus leads to a top-of-the-basilar syndrome characterized by somnolence and sometimes stupor, inability to make new memories, small, poorly reactive pupils and defective vertical gaze, and when severe, can cause the locked-in syndrome [25,27,28].

Wallenberg, or lateral medullary, syndrome occlusion of the vertebral or posterior cerebellar artery causes vertigo, nausea, vomiting, facial pain, ataxia, nystagmus, diplopiae, ipsilateral decreased pain and temperature in face, Horner's syndrome, limb ataxia, laryngeal and pharyngeal paralysis causing hoarseness, dysphagia and contralateral decreased pain and temperature sensations in the trunk and limbs [1,2,3,25].

Occlusion of the superior cerebellar artery causes vertigo, ipsilateral deafness, facial paresis and ipsilateral ataxia. Occlusion of the labyrinth artery causes infarction of thy labyrinth with vertigo, deafness and nystagmus. [1,2,25].

Vertebral artery dissection

Vertebral artery dissection may be caused by a trauma of the cervical spine such as whiplash injury, fierce rotational movements of the head, manipulative therapy of the neck, hyperextension of the neck, degenerative spondylotic changes of the cervical spine, hereditary connective tissue disorders and genetic disorders, migraine, high serum homocysteine level, infection, and use of oral contraceptives. The vertebral artery is most mobile and thus most vulnerable to mechanical injury at C1 to C2 as it leaves the transverse foramen of the axis vertebra and suddenly turns to enter the intracranial cavity. Women are 2.5 times more frequently affected by extracranial vertebral dissections. Intracranial vertebral artery dissections are more common in men [25,28].

The cardinal symptom in patients with a vertebral artery dissection is pain, most often in the posterior part of the neck or occiput, spreading into the shoulder. Diffuse, mostly occipital, headache, dizziness, or diplopia also occur. Intracranial vertebral artery dissections cause medullary, cerebellar, and pontine ischemia and can cause subarachnoidal hemorrhage [28,29,30].

Tumors of the pontocerebellar angle

Tumors of the pontocerebellar angle are most often benign. In younger patients the most frequent is acoustic neuroma, while in older patients meningeoma is more common.

The earliest symptoms of tumors of the pontocerebellar angle include unilateral sensorineural hearing loss/deafness, disturbed sense of balance and altered gait, vertigo with associated nausea and vomiting, and pressure in the ear, all of which can be attributed to the disruption of normal vestibulocochlear nerve function. Additionally, most patients reported tinnitus (most often a unilateral high-pitched ringing, sometimes a machinery-like roaring or hissing sound, like a steam kettle). Large tumors of the pontocerebellar angle may affect other local cranial nerves. Involvement of the facial nerve may lead to facial weakness and impairment of glandular secretions; involvement of the trigeminal nerve may lead to loss of taste and loss of sensation in the face and mouth, involvement of the glossopharyngeal and vagal nerves may lead to altered gag or swallowing reflexes. Even larger tumors may compress the adjacent brainstem and lead to increased intracranial pressure, with its associated symptoms, such as headache, vomiting, and altered consciousness [31,32].

Migraine and vertigo

Many patients with migraine have vertigo, between 26,5% - 42% of migraine patients experience vertigo. Almost one third of them have vertigo even without a head-

ache, while others experience vertigo during and after headache episodes. Patients having a migraine with aura have vertigo more often, probably because they can experience vertigo during aura [33,34,35]. On the other hand, 16-32% patients with vertigo have migraine [36,37]. These data suggest some connection between migraine and vertigo. Half of the patients with BPPV younger than 50 years fulfill diagnostic criteria for migraine [38,39]. Migraine is threefold more common in patients with BPPV than in the control group [40). Therefore, BPPV could be a form of migraine without a headache, or a migraine aura that does not evolve into a migraine headache attack. The other hypothesis suggests that the inner ear could be damaged with migraine associated vasospasm leading to symptoms of BPPV [40].

In basilar migraine vertigo is one of the symptoms lasting from 5 minutes to 1 hour, accompanied with tinnitus, hearing loss, ataxia, dysarthria, visual symptoms, diplopia, paresthesias, paresis, and consciousness disorders followed by a migraine headache. Most patients with basilar migraine have positive family history [41].

Cervical vertigo

Proprioceptive information from neck muscles and joints assists in the coordination of the eyes, head and body. Therefore, disorders of the proprioceptive information could cause vertigo named cervical vertigo. Symptoms accompanying cervical vertigo include disorientation, instability, gait ataxia, and gaze abnormalities that tend to worsen with head movements. Cervical vertigo is more common in elderly patients probably due to degenerative changes of the cervical spine and atherosclerosis [42, 43].

However, some authors do not consider cervical vertigo a distinct form of vertigo because the mechanisms of cervical vertigo are not fully understood, and in differential diagnosis it is difficult to exclude other forms of vertigo [44].

References

[1] *Victor M, Ropper AH.* Adams and Victor's principles of neurology. 7th ed. McGraw-Hill: New York, 2001: 301-28.

[2] *Storper IS.* Dizziness and hearing loss. In: Rowland LP (ed.). Meritt's Neurology. 11 th Ed. Lippincott, Williams&Wilkins: Philadelphia, 2005: 32-8.

[3] *Hain TC, Mico AG.* Cranial nerve VIII: Vestibular System. In: Goetz CG (ed.): Textbook of clinical neurology. 2nd Ed. Saunders: Philadelphia, 2003: 195-210.

[4] *Yardley L, Owen N, Nazareth I, Luxon L.* Prevalence and presentation of dizziness in a general practice community sample of working age people. Br J Gen Pract. 1998;48:1131-5.

[5] *Byrne M.* Assessment of the dizzy patient. Aust Fam Physician 2002;31:722-7.

[6] *Bird JC, Beynon GJ, Prevost AT, Baguley DM.* An analysis of referral patterns for dizziness in the primary care setting. Br J Gen Pract. 1998;48:1828-32.

[7] Disorders of equilibrium. In: Greenberg DA, Aminoff MJ, Simon RP. Clinical Neurology. 5th ed. New York: McGraw-Hill, 2002:95-126.

[8] American Academy of Otolaryngology-Head and Neck Surgery: Contemporary vestibular assessment. Otolaryngol Head Neck Surg 2000; 8: 391-7.

[9] *Brandt T, Daroff RB.* The multisensory physiological and pathological vertigo syndromes. Ann Neurol 1980; 7: 195-203.

[10] *Drachman DA, Hart CW.* An approach to the dizzy patient. Neurology 1972; 22: 323- 34.

[11] *Baloh RW.* Honrubia V, Jacobson K. Benign Positional Vertigo, Clinical and oculographic features in 240 cases. Neurology 1987; 37: 371-78.

[12] *Cawthorne T.* Positional nystagmus. Ann Otol Rhinol Laryngol 1954; 63: 481-90.

[13] *Halmagyi GM, Gresty MA.* Clinical signs of visual-vestibular interaction. J Neurol, Neurosurg, Psychiatry 1979; 42: 934-39.

[14] *Troost BT.* Dizziness and vertigo in vertebrobasilar disease. Part I. Peripheral and systemic causes. Curr Cone Cerebrovasc Dis 1979; 14: 21-4.

[15] *Troost BT.* Dizziness and vertigo in vertebrobasilar disease. Part II. Central causes and vertebrobasilar disease. Stroke 1980; 11: 413-5.

[16] *Hall SF, Ruby RR, McClure JA.* The mechanics of benign paroxysmal vertigo. J Otolaryngol 1979; 8: 151-8.

[17] *Brandt T, Daroff RB.* Physical therapy for benign paroxysmal positional vertigo. Arch Otolaryngol 1980;106:484-5.

[18] *Tiwari S, Bakris GL.* Psychogenic vertigo: a review. Postgrad Med. 1981;70:69-71.

[19] *Froehling DA, Silverstein MD, Mohr DN, Beatty CW, Offord KP, Ballard DJ.* Benign positional vertigo: incidence and prognosis in a population-based study in Olmsted County, Minnesota. Mayo Clin Proc 1991;66:596-601.

[20] *Lanska DJ, Remler B.* Benign paroxysmal positioning vertigo: classic descriptions, origins of the provocative positioning technique, and conceptual developments. Neurology 1997;48:1167-77.

[21] *Baloh RW.* Clinical practice. Vestibular neuritis. N Engl J Med 2003;348:1027-32.

[22] *Strupp M, Brandt T.* Vestibular neuritis. Adv Otorhinolaryngol 1999;55:111-36.

[23] *Wittner S.* Diagnosis and treatment Meniere's disease. JAAPA. 2006;19:34-9.

[24] *Lheureux P, Penaloza A.* Ototoxicity-related vertigo. Rev Med Brux 2002;23:A356-62.

[25] *Savitz SI, Caplan LR.* Current concepts - Vertebrobasilar Disease. N Engl J Med 2005;352:2618-26.

[26] *Caplan LR.* Posterior circulation ischemia: then, now, and tomorrow — the Thomas Willis Lecture-2000. Stroke 2000;31:2011-23.

[27] *Millikan CH, Siekert RG.* Studies in cerebrovascular disease: the syndrome of intermittent insufficiency of the basilar arterial system. Mayo Clin Proc 1955;30:61-8.

[28] *Rubinstein SM, Peerdeman SM, van Tulder MW, Riphagen I, Haldeman S.* A systematic review of the risk factors for cervical artery dissection. Stroke 2005;36;1575-80.

[29] *Wityk RJ, Chang HM, Rosengart A, Han WC, DeWitt LD, Pessin MS, Caplan LR.* Proximal extracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. Arch Neurol 1998;55:470-8.

[30] *Caplan LR, Baquis GD, Pessin MS, D'Alton J, Adelman LS, DeWitt LD, Ho K, Izukawa D, Kwan ES.* Dissection of the intracranial vertebral artery. Neurology 1988;38:868-77.

[31] *Yoshimoto Y.* Systematic review of the natural history of vestibular schwannoma. J Neurosurg 2005;103:59-63.

[32] *Ho SY, Kveton JF.* Acoustic neuroma. Assessment and management. Otolaryngol Clin North Am 2002;35:393-404.

[33] *Kayan A, Hood JD.* Neuro-otological manifestations of migraine. Brain 1984;107 (Pt 4):1123-42.

[34] *Selby G, Lance JW.* Observations on 500 cases of migraine and allied vascular headache. J Neurol Neurosurg Psych 1960; 23:23-32.

[35] *Kuritzky A, Ziegler DK, Hassanein R.* Vertigo, motion sickness and migraine. Headache 1981;21:227-31.

[36] *Stewart WF, Shechter A, Rasmussen BK.* Migraine prevalence. A review of population-based studies. Neurology. 1994;44(Suppl 4):S17-23.

[37] *Stewart WF, Shechter A, Lipton RB.* Migraine heterogeneity. Disability, pain intensity, and attack frequency and duration. Neurology 1994;44(Suppl 4):S24-39.

[38] *Hain TC, Squires TM, Stone HA.* Clinical implications of a mathematical model of benign paroxysmal positional vertigo. Ann N Y Acad Sci. 2005;1039:384-94.

[39] *Uneri A.* Migraine and benign paroxysmal positional vertigo: an outcome study of 476 patients. Ear Nose Throat J. 2004;83:814-5.

[40] *Ishiyama A, Jacobson KM, Baloh RW.* Migraine and benign positional vertigo. Ann Otol Rhinol Laryngol. 2000;109:377-80.

[41] *Bickerstaff ER.* Impairment of consciousness in migraine. Lancet 1961;2:1057-9.

[42] *Brandt T, Bronstein AM.* Cervical vertigo. J Neurol Neurosurg Psychiatry 2001;71:8-12.

[43] *Bolton PS.* Assessment of cervicogenic vertigo. J Manipulative Physiol Ther 1991;14:487-8.

[44] *Brandt T.* Cervical vertigo – reality or fiction? Audiol Neurootol. 1996;1:187-96.

Sažetak

Diferencijalna dijagnoza vertiga

Vertigo je iluzija kretanja, najčešće rotacijskog kretanja. Vertigo je među najčešćim simptomima koji dovode bolesnike liječniku, a sa starenjem učestalost vertiga se povećava. Vertigo može biti uzrokovan poremećajima unutarnjeg uha – periferni vertigo, centralnim poremećajima – centralni vertigo, sustavnim bolestima, a može biti i psihogeni. Najčešći uzroci vertiga su benigni paroksizmalni pozicioni vertigo, akutni vestibularni neuronitis, Méniéreova bolest, migrena, anksiozni poremećaji, vertebrobazilarna ishemijaa i tumori pontocerebelarnog kuta. Važno je razlikovati periferni od centralnog vertigo kako bi se mogle donijeti odluke o liječenju. U ovom članku prikazana je diferencijalna dijagnostika vertiga.

Ključne riječi: vertigo, periferni vertigo, centralni vertigo, benigni paroksizmalni pozicioni vertigo, akutni vestibularni neuronitis, Méniéreova bolest, migrena, vertebrobasilarna ishemija, tumor pontocerebelarnog kuta

UDK 616.28-008.5+616.853
Review
Received: 17 January 2007
Accepted: 25 April 2007

THE DIFFERENTIAL DIAGNOSIS OF VERTIGO AND EPILEPSY

Snježana Miškov, Hrvoje Hećimović

Zagreb Epilepsy Center, University Department of Neurology, Sestre Milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia

Summary

Vertigo is most commonly a feeling of spinning, usually due to the disturbance in the balance (vestibular) system. It may result from a dysfunction of the vestibular system at any point from the ear to the cerebral cortex.

Epileptic vertigo is a rare form of partial seizures, due to epileptic activity in parts of the cortex that represent the vestibular system: the parietal, temporal and frontal cortex. The episodes usually last no more than seconds or minutes. Unconsciousness will follow only if the seizure becomes generalized.

Diagnostic tests include EEG and MRI scans of the head. Further diagnostic evaluation in the case of medical intractability would include: video EEG monitoring, intracarotid amytal testing, ictal SPECT, neurophysiogical evaluation and intracranial EEG monitoring. An abnormal EEG is a major criterion for diagnosis. In most patients the abnormality consists of temporal or bitemporal sharp or slow wave foci. In some cases there are associated generalized seizure discharges. Treatment of epileptic vertigo is usually successful with traditional anticonvulsants such as carbamazepine and its relatives. If, after a reasonable trial with appropriate antiepileptic drugs, seizures remain inadequately controlled, a surgery can be considered.

Differential diagnosis of epileptic vertigo includes: a basilar type migraine, confusional migraine, benign paroxysmal vertigo of childhood and an aura without a headache. The main differential diagnosis of neocortical temporal lobe seizures is a mesial temporal lobe seizure. Ictal SPECT scanning and MRI can provide diagnostic data not otherwise obtain-

Correspondence to: Snježana Miškov, Zagreb Epilepsy Center, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: snjezana.miskov@zg.t-com.hr

able. In addition, proton MR spectroscopy and PET studies can be helpful to distinguish the mesial from neocortical temporal lobe seizures.

Key words: epilepsy, epileptic vertigo, partial epilepsy, neocortical epilepsy

INTRODUCTION

Although dizziness as a manifestation of epilepsy was recognized 100 years ago by Hughlings Jackson and later by Gowers, the possibility that brief episodes of dizziness may be due to epilepsy was not recognized. Today it is well known that epilepsy is an important cause of transient dizziness [1].

True vertigo, from the Latin „vertere", to turn, is a distinct, often severe form of dizziness that is a movement hallucination. Vertigo is most commonly felt as a spinning, usually due to a disturbance in the balance (vestibular) system. The balance apparatus provides us with a sense of head position in the space and is linked via the nervous system to the eyes, spine and various parts of the brain. The connection between the balance system and the eyes serves to maintain visual stability during head movement, while connections with the spine assist in the maintenance of postural stability. Connections to other parts of the brain provide conscious awareness of head position and movement. A patient may experience severe vertigo for days or weeks. Nausea, vomiting and involuntary eye movements are common. The condition gradually improves, but symptoms can persist for weeks and months.

Epileptic vertigo is vertigo due to epileptic activity in parts of the cortex that represent the vestibular system: the parietal, temporal and frontal cortex. It is a rare form of partial seizures. Specific areas include the superior lip of the intraparietal sulcus, the posterior superior temporal lobe and the temporal parietal border regions [2] as well as the V5 area [3]. If there is full consciousness during the seizure, the clinical symptoms and signs are considered relatively simple and the seizure is termed a simple partial seizure. If consciousness is impaired, the seizure is more complex and is termed a complex partial seizure.

Pathophysiology

There is no unique pathophysiology of the neocortical temporal lobe. Any destructive, neoplastic, vascular, or congenital epileptogenic lesion can result in seizures from this region. Potential spread patterns may be mesial structures, producing seizures similar to mesial temporal lobe seizures. Other potential spread patterns have not been extensively studied [4]. A head trauma can produce focal lesions that involve the temporal or parietal association cortex which receives vestibular projections. These lesions can occasionally form seizure foci which can lead to a simple or partial complex sensory

manifestation in episodic vertigo. The episodes usually last no more than seconds or minutes. They can be associated with nausea, but not vomiting. Nystagmus can be seen due to stimulus of the contiguous cerebral oculomotor nerve. Tinnitus can be associated at times. Contralateral paresthesias and/or olfactory and gustatory symptoms are occasional. Unconsciousness will follow only if the seizure becomes generalized.

History

Although nonconvulsive seizures with complex behavior have been recognized since antiquity [5], their relationship to temporal lobe origin was more recently recognized, being first described in the late 1800s by Jackson [6,7]. Bladin wrote in 1998 [8]: «In the 19th century it was believed that epileptic vertigo could come over the affected person, changing that person into an uncontrollable psychopathic beast of lethal potential». Because of the lack of technology with which the various forms of vertigo could be differentiated, every onset of dizziness might have had potential to evolve into epileptic seizures. In stage one both disorders were attributed to different degrees of brain involvement [8]. Stage two started in 1861 with Menier's inner localization of vertigo, followed soon by the empathic recantations from Charcot, Jackson and Gowers, who realized that vertigo was essentially otic, and that they had overlooked ear diseases. Considerable evidence linking epilepsy, vertigo and the ear needs explanation [9]. Lehman wrote in 1999 [9]: «The Van Gogh shows how muddled this area still is. Many, including Gastaut, considered him to be epileptic, yet Arenberg, a Meniere disease expert, was convinced that Van Gogh had Menier's».

The psychic and motor characteristics of these seizures first prompted the designation of psychomotor seizures [10, 11]. With the advent of electroencephalography and the increased interest in surgical intervention, because of their anatomical location, they were later termed as temporal lobe seizures [12]. Vertigo has been associated with epilepsy since ancient times, but it was almost certainly over-interpreted. True vertigo (tornado seizures) as a seizure symptom does occur, but only rarely. Over the years this symptom has been equated with seizure origin in the posterior temporal neocortex or the temporoparietal junction, others have reported it with frontal seizure onset. There are, overall, few well-documented examples.

Diagnosis

Epileptic vertigo is a diagnostic problem only when the person does not have a full seizure, in other words they do not have convulsions, psychomotor symptoms and twitching characteristics of classic partial or generalized seizures. In most cases it presents as a "quick spin" type symptom. The person notes that the world makes a quick horizon-

tal movement, lasting roughly 1-2 seconds at most. The quick spin must be differentiated from a variety of other conditions including vestibular neuralgia, due to microvascular compression, Menier's syndrome and BPPV [13].

Diagnostic tests that are particularly helpful include EEG and MRI scans of the head. When these tests are normal, a response to an anticonvulsant medication is suggestive of vestibular neuralgia. Vestibular epilepsy is diagnosed when the EEG is abnormal. It should be emphasized that many otherwise normal persons can have mildly abnormal EEG tests. When there is no response to medication, the probability of one of the other disorders mentioned above is increased.

All patients developing seizures should have a complete general and neurological examination. Focal neurological defects (impairment of fine finger movements, evidence of hemiatrophy indicating a cerebral lesion occurring in early life) should be sought, as well as specific signs which include the presence of any coetaneous stigmata that may indicate the cause of the epilepsy (cafe au lait spots, adenoma sebaceum or trigeminal capillary haemangiomas, suggesting the possibility of neurofibromatosis, tuberous sclerosis and Sturge-Weber syndrome).

The diagnosis of epilepsy is essentially clinical and relies on the description of the seizure provided by the patient and an eyewitness.

In the case of a new onset seizure, patients should have MRI scans early in the course of evaluation to look for structural lesions as the cause of seizures. Structural lesions, depending on their location and appearance, can have a significant impact on the management and evaluation. If the MRI is normal or nonspecific, no further evaluation is required and medical management should be initiated or continued. In the case of a documented medical intractability, a possibility of surgical intervention should be considered [14]. In addition, a magnetic resonance spectroscopy might help differentiate mesial temporal seizures from neocortical temporal lobe seizures [15]. Further diagnostic evaluation in the case of medical intractability would include video EEG monitoring, intracarotid amytal testing, ictal SPECT, neurophysiogical evaluation and possible intracranial EEG monitoring. Most cases of temporal neocortical epilepsy are associated with cortical lesions such as cortical dysplasias, neoplasms or vascular malformations and do not represent a specific syndrome.

Electroencephalography- an abnormal EEG is a major criterion for diagnosis. In most patients the abnormality consists of temporal or bitemporal sharp or slow wave foci. In some cases there are associated generalized discharges.

Treatment

Depending on the results of the evaluation, the management can take one of several directions. If the MRI is normal and neocortical temporal lobe seizures are suspected,

medical management should be undertaken. If, after a reasonable trial with appropriate antiepileptic drugs, seizures remain inadequately controlled, a surgery can be considered, although seizure onset localization can limit possibility of surgical treatment, particularly on the language-dominant side. However, with careful presurgical evaluation through experienced epilepsy surgery programs, surgical therapy can be successful even in patients with no obvious MRI abnormalities [16,17].

Differential diagnosis

Differential diagnosis of epilepsy includes: a basilar type migraine, confusional migraine, benign paroxysmal vertigo of childhood and an aura without a headache. The main differential diagnosis of neocortical temporal lobe seizures are mesial temporal seizures. When the MRI reveals potentially epileptogenic structural lesions in the mesial or neocortical temporal regions, the differential diagnosis is greatly simplified. Patients with a normal MRI and suspected mesial or neocortical temporal origin are much more challenging. Ictal SPECT scanning [18] and MRI can provide diagnostic data not otherwise obtainable [19]. In addition, a proton MR spectroscopy and PET studies can be helpful to distinguish the mesial from neocortical temporal lobe seizures [20].

Spread patterns to mesial structures would produce seizures similar to those beginning medially. As the mesial temporal lobe seizures mainly occur in association with a mesial temporal sclerosis, the presence or absence of certain risk factors such as complicated febrile seizures can help differentiate the two conditions [21] as can the results of intracranial amytal testing [22]. A recent study suggested some of the lateralizing findings associated with the mesial temporal lobe seizures (contralateral dystonic posturing, ipsilateral automatisms, etc.) present in a mirror image fashion in aura of any type, complex visual auras, or complex memory flashbacks should suggest neocortical temporal seizure onset, but this needs better documentation [23]. Dizziness may also occur in patients with multiple sclerosis. Hyperventilation associated by anxiety or emotional distress may cause dizziness, with or without tetany, but in such patients EEG shows epileptic activity.

Conclusion

Dizziness is a common symptom, but its diagnosis is not always easy. It may result from a dysfunction of the vestibular system at any point from the ear to the cerebral cortex. In these disorders the onset occurs later than in patients with epileptic dizziness, where the mean age, according to the study of Kogeorgos et al. [1], is about 25 years. Epileptic dizziness may often appear as a part of an aura in generalized seizures, but is then usually poorly defined. It is more commonly a component of temporal lobe sei-

zures, in 19% of the patients [1]. In temporal lobe epilepsy dizziness is not simply an aura, but constitutes a part of the seizure, and may be its only manifestation. The dizziness itself is often characteristic, consisting of sudden very brief episodes followed by rapid recovery without sequelae. The person notes that the world makes a quick horizontal movement, lasting one to two seconds at most. These quick spins must be differentiated from a variety of other conditions including vestibular neuralgia, Menier's disease, BPPV, etc. Epileptic dizziness is caused by abnormal stimulation of the part of the cortex that represents the vestibular system: parietal, temporal and frontal. Specific areas include the superior lip of the intraparietal sulcus, the superior temporal lobe, and the temporal-parietal border regions [2]. These episodes usually occur without the associated symptoms of epilepsy, in other words, there are no convulsions, psychomotor symptoms or twitching characteristic of classic partial or generalized seizures. The diagnosis of epileptic dizziness is often suspected because of the occurrence of separate symptoms of temporal lobe epilepsy which can be found only by careful questioning [1]. Diagnostic tests that are particularly helpful include EEG and MRI. Treatment of epileptic vertigo is usually successful with traditional anticonvulsants such as carbamazepine and its relatives [24].

References

[1] *Kogeorgos J, Scott DF, Swash M.* Epileptic dizziness. British Medical Journal 1981;282(6265):687-9.

[2] *Penfield W, Jasper H.* Epilepsy and functional anatomy of the human brain. Boston Br J Surg.1954;41(168):337-43.

[3] *Laff R, Mesad S, Devinsky O.* Epileptic kinetopsia: ictal illusory motion perception. Neurology.2003;61(9):1262-4.

[4] *Williamson PD and Jobst BC.* Neocortical temporal lobe seizures, 2004, International league against epilepsy.

[5] *Temkin O.* The falling sickness. Baltimore: Johns Hopkins Press, 1945.

[6] *Jackson JH.* Case of epilepsy with tasting movements and «dreaming state»- very small patch of softening in the left uncinate gyrus. Brain. 1898;21:580-90.

[7] *Jackson JH.* Selected writings of John Huglings Jackson Volumes 1 and 2. Taylor J, editor. London, England: Staples Press, 1958.

[8] *Bladin PF.* History of „epileptic vertigo": its medical, social and forensic problems. Epilepsia. 1998;39(4):442-7.

[9] *Lehman RAW.* Letters to the editor. Epilepsia 1999;40(8):1168-1172.

[10] *Gibbs FA, Gibbs EL, Lennox WG.* Cerebral dysrhytmias of epilepsy. Arch Neurol Psychiatr. 1938;39:298-314.

[11] *Gibbs EL, Gibbs FA, Fuster B.* Psychomotor epilepsy. Arch Neurol Psychiatr. 1948;60:331-69.

[12.] *Williamson PD and Jobst BC.* Neocortical temporal lobe seizures. 2004: International league against epilepsy.

[13] *Tusa RJ, Kaplan PW, Hain TC, Naidu S.* Ipsiversive eye deviation and epileptic nystagmus. Neurology. 1990;40(4):662-5.

[14] *Williamson PD, Thadani VM, Siegel AM.* Nonlesional, medically intractable, localization-related epilepsy: a diagnostic challenge. Epilepsia. 1997;38(Suppl.8):65.

[15] *Vermathen P, Ende G, Laxer KD, Knowlton RC, Matson GB, Weiner MW.* Hippocampal N-acetylaspartate in neocortical epilepsy and mesial temporal lobe epilepsy. Ann Neurol.1997;42(2):194-9.

[16] *Friedman JM.* Posttraumatic vertigo. Med Health RI 2004, 87(10)296-300.

[17] *Schramm J, Kral T, Grunwald T, Bluncke I.* Surgical treatment for neocortical temporal lobe epilepsy: clinical and surgical aspects and seizure outcome. J Neurosurg. 2001;94(1):33-42.

[18] *Engel J Jr.* A Great Role for Surgical Treatment of Epilepsy: Why and When? Epilepsy Curr. 2003;3(2)37-40.

[19] *Aso K, Nakashima S, Watanabe K.* Neuronal migration disorders and epilepsy. No To Hattatsu. 1997;29(2):129-33.

[20] *Thadani U, Roden DM.* FDA Panel report: January 1998. Circulation. 1998;97(23):2295-6.

[21] *Hammen T, Stefan H, Pauli E, Schafer I, Huk W, Tomandl B.* 1H-MR spectroscopy: a promising method in distinguishing subgroups in temporal lobe epilepsy? J Neurol Sci. 2003;215(1-2):21-5.

[22] *O'Brien TJ, Kilpatrick C, Murrie V, Vogrin S, Morris K, Cook MJ.* Temporal lobe epilepsy caused by mesial temporal sclerosis and temporal neocortical lesions: A clinical and electroencephalographical study of 46 pathologically proven cases. Brain. 1996;119(Pt6):2133-41.

[23] *Hamberger MJ, Walczak TS, Goodman RR.* Intracarotid amobarbital procedure memory performance and age at first risk for seizures distinguish between lateral neocortical and mesial temporal lobe epilepsy. Epilepsia. 1996;37(11):1088-92.

[24] *Williamson PD and Jobst BC.* Neocortical temporal lobe seizures, 2004, International league against epilepsy.

[25] *Kluge M, Bayenburg S, Fernandez G, Elger CE.* Epileptic vertigo: evidence for vestibular representation in human frontal cortex. Neurology. 2000;55(12):1906-8.

Sažetak

Diferencijalna dijagnostika vertiga i epilepsije

Vertigo je najčešće osjećaj vrtnje, uobičajeno kao posljedica poremećaja osjetila ravnoteže (vestibularnog sustava). Može nastati zbog disfunkcije vestibularnog sustava na bilo kojem mejstu od unutarnjeg uha do kore mozga.

Epileptički vertigo je rijetki oblik parcijalnih napada koji nastaje zbog epileptičke aktivnosti u dijelovima korteksa koji predstavljaju vestibularni sustav: parijetalni, temporalni i frontalni korteks. Napadi obično traju nekoliko sekundi do nekoliko minuta, a gubitak svijesti nastaje samo kada se napad generalizira.

Dijagnostičke pretrage uključuju EEG i MRI glave. Daljnja dijagnostička obrada u rezistentnim slučajevima uključuje: video EEG monitoriranje, intrakarotidno primjenu amitala, SPECT tijekom napada, neurofiziološku procjenu i intrakranijsko EEG monitoriranje. Poremećeni EEG je glavni kriterij za dijagnozu. U većine bolesnika poremećaji EEG-a uključuju temporalna ili bitemporalna žarišta šiljastih i sporih valova. U nekih slučajeva pridružuju se generalizirana epileptička izbijanja. Terapija epileptičkog vertiga obično je uspješna primjenom tradicionalnih antiepileptika poput karbamazepina i njemu sličnih lijekova. Ukoliko, nakon razumnog roka primjene adekvatnih antiepileptičkih lijekova, napadi nisu adekvatno kontrolirani, mogu se razmotriti i kirurške metode.

Diferencijalna dijagnostika epileptičkog vertiga uključuje: bazilarnu migrenu, konfuzijsku migrenu, benigni paroksizmalni vertigo u djetinjstvu i auru bez glavobolje. Najznačajnija ke diferencijalna dijagnoza neokortikalnih temporalnih napada od mezijalnih temporalnih napada. Iktalni SPECT i MRI mogu pružiti dijagnostičke podatke koji se ne mogu dobiti na drugi način. Protonska MR spektroskopija i PET mogu biti od pomoći u razlikovanju mezijalnih od neokortikalnih temporalnih napada.

Ključne riječi: epilepsija, epileptički vertigo, parcijalna epilepsija, neokortikalna epilepsija

UDK 616.28-008.5-07
Review
Received: 17 January 2007
Accepted: 25 April 2007

ELECTROPHYSIOLOGICAL METHODS IN THE DIAGNOSTICS OF VERTIGO

Ivan Mikula

University Department of Neurology, Sestre Milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia

Summary

The *role of neurophysiologic tests in the diagnostics of vertigo* primarily consists of assessing the functional status of the sensory systems responsible for the concept of space. They also have a limited application in assessing the functional status of structures responsible for the integration of this information. The data obtained by neurophysiological testing are purely functional giving no information considering the etiology of the disturbance, and only point to the localization and type of the disturbance that lead to vertigo. That is why they always need to be combined with neuroradiologic, neurosonologic and laboratory tests. The brain relies on three sensory systems to maintain spatial orientation: the vestibular system (the inner ear), the visual system (the eyes), and the somatosensory system (which conveys information from the skin, joint, and muscle receptors). These three systems overlap, allowing the brain to assemble an accurate sense of spatial orientation. Information from these systems is integrated in the cerebrum and cerebellum. However, a compromised system or conflicting signals can cause vertigo

Key words: Neurophysiological diagnostic tests, vertigo, electromyography, evoked potentials

Considering the manner in which the concept of space is formed in the human brain, we might say that, under normal circumstances, the brain relies on three sensory systems to maintain spatial orientation: the vestibular system (the inner ear), the visual

Correspondence to: Ivan Mikula, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: ivan.mikula@zg.t-com.hr

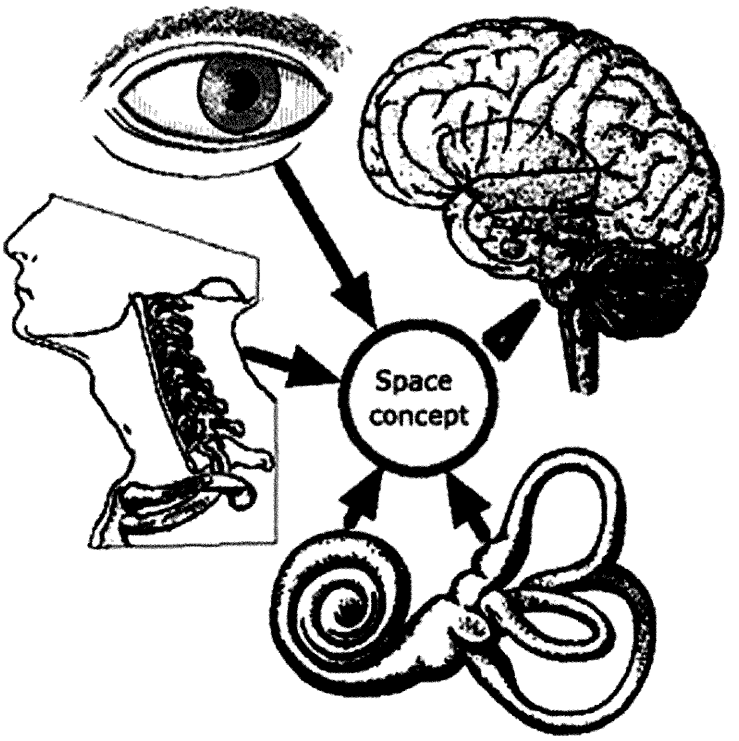


Figure 1. Space concept

system (the eyes), and the somatosensory system (which conveys information from the skin, joint, and muscle receptors). These three systems overlap, allowing the brain to assemble an accurate sense of spatial orientation [1]. Information from these systems is integrated in the cerebrum and cerebellum. However, a compromised system or conflicting signals can cause vertigo.

Among the proven causes of cervical vertigo, we count the vascular compression and the abnormal sensory input from the proprioceptive receptors. Vertebral arteries can be pressed by the nearby vertebrae or by local connective tissue structures. Other possible reasons include surgical procedures in the region and the chiropractic manipulation. The sensory information originating from cervical receptors can be absent or unreliable. Some individuals are more prone to this kind of damage, especially if there is any disturbance of function of other generators of information concerning the body position in space.

Electromyography (EMG) records the electric potential generated by muscle fibers in contraction or resting. It gives us indirect information about the state of cervical

receptors, by means of assessing the state of cervical nerve roots and the peripheral nerves originating from them. Combining EMG with measurement of the motor and sensory nerve conduction velocities, we also asses the function of the peripheral nerves [2].

For the orientation testing, we test the muscle activity at rest, during the maximum voluntary contraction and during moderate activity, from 10 needle positions in one muscle (2-3 needle placements, with rectangular needle movement). In special indications the exact analysis of motor unit action potentials is required (at least 20 potentials/muscle). We examine the number of phases and the duration of potentials.

Some significant pathologic changes that can be observed in a muscle at rest include: prolonged insertion activity, fasciculations, fibrillations, pseudo-myotonic discharges and positive sharp waves.

Insertion activity is the response of muscle fibers to a needle prick. It normally consists of short spike-shaped muscle potentials, which last a few seconds and promptly disappear after the needle is removed. It is shortened in fibrosis and fat degeneration, and prolonged in early denervation and myotonic disturbances.

Fibrillations are the earliest signs of neurogenic lesions. They appear 3-4 weeks after the neural damage, and disappear with the occurrence of re-innervation. They are short-lasting (<3 ms), of low amplitude (<300 μv), and appear in partly rhythmic intervals (<30/s), although sometimes it seems that the frequency of discharge is purely accidental. They may reappear with each new movement of the needle.

Positive sharp waves represent the most certain sign of neurogenic lesions. They look like very sharp positive deflections from the baseline, followed by a slower return to the baseline, often with a short negative phase before the return to the baseline. The amplitude of these waves may reach up to 1 mv, and their duration is about 50 ms. They appear in very regular intervals. They usually occur and disappear abruptly and the rhythm of their occurrence seldom varies.

Fasciculations are spontaneous discharges of entire motor units in irregular intervals and they appear as normal motor unit action potentials (MUP). We tell them apart from the normal MUP by their occurrence at rest and their irregular rhythm of firing. Many so called fasciculations are in fact a result of an inadequate relaxation of the muscle. The true fasciculation will always cause a visible movement of the needle, while that does not happen in a badly relaxed muscle.

Normal EMG pattern has the following features: no spontaneous activities, thick interference pattern during the maximum contraction, 2-3-phasic motor unit potentials, and medium duration of a single potential [3].

Myopathic EMG pattern has the following features: no spontaneous activities, early interference pattern development, inadequate development of strength due to the phenomenon of early recruitment of motor units, interference pattern of low-amplitude, motor-unit potentials are low, short and polyphasic. There is a characteristic de-synchronization of the muscle activity, resulting in the typical sound, which is often described as a "metal scratching" [4,5].

Neuropathic EMG pattern is characterized by positive sharp waves and biphasic fibrillations at rest and a reduced interference pattern with individual high-amplitude potentials, while motor unit potentials are prolonged and polyphasic. Prominent features are a temporal compensation ("central driving"), when the remaining PMU fire in higher frequency (25-40 Hz), and a spatial compensation, where the remaining potentials are high and wide (over 12 ms, over 15 mV). The sound of these gigantic potentials is often described as "banging, drumming, thunder".

Complex repetitive discharges, known also as the high-frequency or bizarre repetitive potentials, consist of long series of fast firing potentials, characterized by an abrupt beginning and ending. These potentials are of low-voltage and short duration, with a tendency of grouping, and they fire with frequency of 20-40 Hz. They are mostly of a constant amplitude and frequency. They can be seen in various myopathic and neuropathic diseases.

In diseases *where the transmission at neuromuscular junction is so impaired* that it results with errors in transmission or completely fails, some fibers get excluded from the motor unit that reacts to the stimulus. If the number of excluded fibers is big enough, this can be observed as a change of the potential morphology during the repetitive stimulation. The presence of such disturbances can be manifested as flickering (jitter) of the potential, or in more severely affected muscles, as a decrease of amplitude after the repetitive stimulation.

Myography is regularly combined with measurements of maximal sensory and motor *nerve conduction velocities*, which help determine the level of the neurogenic lesion. Normal values of nerve conduction velocities are different for different nerves, even for different segments of the same nerves. They also depend on the skin temperature - 1-2 m/s°C. Using a stimulus that exceeds the threshold, we trigger an action potential in the nerve, and it spreads antidromically and orthodromically. In axonal lesions, we find a slight reduction of conduction velocities, but a significant reduction of amplitudes. In demyelinating lesions, there is a significant reduction of nerve conduction velocities.

Apart from measuring nerve conduction velocities, we also make *reflexologic* tests. Their primary applications are in testing the proximal, inaccessible part of the nerve and in a better assessment of the function of the afferent segment of the reflex arc. These tests

are F-wave latencies and H-reflex on the extremities and blink reflex on the face. The blink reflex is obtained by means of stimulating the skin above the eye, where the afferents of the trigeminal nerve are located (ophthalmic branch, supraorbital nerve), and registering the electrical activity on both mm. orbiculares oculi (n. facialis).

In neurophysiology an *evoked potential* (or "evoked response") is an electric potential that is registered from a human or animal scalp after presentation of a certain kind of stimulus (as opposed to spontaneous electrical activities such as electromyography and electroencephalography) [6]. The amplitudes of evoked potentials are low, under few microvolts. To extract this low-amplitude signal from the surrounding noise and analyze it, it is necessary to average and amplify the signal. Early sensory evoked potentials were widely used in clinical medicine from 1970, namely SSEP (somatosensory), VEP (visual) and BAER (brainstem auditory evoked response), particularly in the diagnostics of demyelinating diseases. Nowadays, the late evoked potentials have also found their clinical application, particularly ERP (event-related, cognitive potentials), primarily in the diagnostics of dementias.

SSEP are elicited by applying a mild electrical shock to the peripheral nerve, **VEP** by watching the lighted checkerboard pattern (PSVEP, pattern shift visual evoked potential) or flash stimulation (LED or flashing lamp) and **BAER** by presenting the stimulus over light headphones.

Gustatory and olfactory evoked potentials are also used, although their clinical application is rather limited.

The importance of the clinical application of **cognitive and transcranial motor** potentials is increasing.

Indications for BAER testing are: suspected neurinomas of statoacustic nerve which could not with certainty be diagnosed using other diagnostic methods, follow-up of the recovery of brainstem functions after the compression or during some surgical procedures, localization of central nervous system lesions which are detectable by means of neurological examination, but not by neuroradiologic testing (CT or MRI scan), diagnosis of the demyelinating diseases which affect the brainstem, evaluation or screening for hearing impairment in newborns and infants. They are also used as an accessory diagnostic method for the verification of brain death [7,8].

Indications for SSEP testing are myelopathies of unknown etiology, spinocerebellar and olivocerebellar degenerations, localization of central nervous system lesions which are detectable by means of neurological examination, but not by neuroradiologic testing (CT or MRI scan), identification of clinically silent lesions in persons with suspected multiple sclerosis or Pelizaeus-Merzbacher's disease, for preoperative or intraoperative testing in persons due for surgical procedures on the spinal medulla. They are also used as an accessory diagnostic method for the verification of brain death.

The most common disturbances of vision that cause vertigo are abnormal movements of eyeballs, loss of vision acuity, differences of picture size, binocular conflicts and a reduction of visual field [9]. *Indications for VEP* are diagnostics of optical neuritis and multiple sclerosis, localization of visual system lesions which are detectable by means of neurological examination, but not by means of neuroradiologic testing (CT or MRI scan), and testing of vision in infants and newborns or persons unable to achieve verbal contact.

In the frame of diagnostics of cerebral functions, we can also test the *cognitive evoked potentials*. This test is mostly recommended for dementias and other disturbances of the higher brain functions. The most frequently tested component is P300 wave, which is registered above the frontal and parietal cortex as a response to target stimulus (10].

The *role of neurophysiologic tests in the diagnostics of vertigo* primarily consists of assessing the functional status of the sensory systems responsible for the concept of space, described earlier in the text. They also have a limited application for assessing the functional status of structures responsible for the integration of this information (11]. The data obtained by neurophysiological testing are purely functional and give no information considering the etiology of the disturbance, but only point to the localization and type of the disturbance that lead to vertigo. That is why they always need to be combined with neuroradiologic, neurosonologic and laboratory tests.

References

[1] *Loughran S, Tennant N, Kishore A and Swan IRC.* Interobserver reliability in evaluating postural stability between clinicians and posturography. Clinical Otolaryngology 2005;30:3,255-257

[2] *Binnie C, Cooper R, Mauguiere F, Osselton J, Prior P and Tedman B.* Clinical Neurophysiology, Volume 1:EMG, Nerve Conduction and Evoked Potentials. London: Elsevier; 2004, str. 100-453.

[3] *Chen CH, Young YH.* Vestibular evoked myogenic potentials in brainstem stroke. Laryngoscope 2003;113(6):990-3.

[4] *Cruccu G, Iannetti GD, Marx JJ, Thoemke F, Truini A, Fitzek S,* et al. Brainstem reflex circuits revisited. Brain 2005;128:386-394.

[5] *Ferber-Viart C, Dubreuil C., Duclaux R.* Vestibular Evoked Myogenic Potentials in Humans: a Review. Acta Otolaryngol 1999;119:6-15.

[6] *Itoh A, Kim YS, Yoshioka K, Kanaya M, Enomoto H, Hiraiwa F,* et al. Clinical Study of Vestibular-evoked Myogenic Potentials and Auditory Brainstem Responses in Patients with Brainstem Lesions. Acta Otolaryngol 2001;Suppl 545116-119.

[7] *Sartucci F, Logi F.* Vestibular-evoked myogenic potentials: A method to assess vestibulo-spinal conduction in multiple sclerosis patients. Brain Res Bul 2002;59:59-63.

[8] *Versino M. Colnaghi S, Callieco R, Bergamaschi R, Romani A, Cosi V.* Vestibular evoked myogenic potentials in multiple sclerosis patients. Clin Neurophysiol 2002;113:1464-1469.

[9] *Victor M, Ropper A.* Cerebrovascular diseases. In: Wonsiewicz M, Medina M, Navrozov M, editors. Principles of Neurology. 7th ed. International Edition. New York: McGraw-Hill; 2001,220-223.

[10] *Vila N, Valls-Sole J, Obach V, Saiz A, Alday M, Chamorro A.* Blink reflex in patients with Wallenberg's syndrome. J Neurol 1997;244:30–34.

[11] *Welgampola MS, Colebatch JG.* Vestibulocollic reflexes: normal values and the effect of age. Clin Neurophysiol. 2001;112(11):1971-9.

Sažetak

Elektrofiziološke metode u dijagnostici vrtoglavica

Uloga neurofizioloških pretraga u dijagnostici vrtoglavica primarno se sastoji u utvrđivanju funkcionalnog statusa senzornih sustava odgovornih za stvaranje koncepta prostora. Primjenjive su donekle i u određivanju stanja integrativnih neuralnih struktura, koji objedinjuju informacije dobivene iz istih senzornih sustava. Podaci dobiveni neurofiziološkim pretragama isključivo su funkcijskog karaktera i ne daju nikakvu informaciju o etiologiji poremećaja, već upućuju samo na lokalizaciju i vrstu poremećaja koji je doveo do vrtoglavice, te se uvijek moraju kombinirati s neuroradiološkim, neurosonološkim i laboratorijskim ispitivanjima. Obzirom na način stvaranja koncepta prostora u ljudskom mozgu, potencijalni generatori vrtoglavice su oči (koje prenose vidnu informaciju), unutarnje uho (koje prenosi slušnu i vestibularnu informaciju), cervikalni receptori (koji prenose proprioceptivnu informaciju), te mali i veliki mozak (čija je uloga u integraciji ovih informacija). Ovi sustavi se nadopunjavaju, omogućavajući mozgu da stvori točnu informaciju o položaju u prostoru. Neurofiziološka ispitivanja ovih struktura predstavljaju temelj neurofiziološke dijagnostike vertiginoznih smetnji.

Ključne riječi: Neurofiziološki dijagnostički testovi, vertigo, elektromiografija, evocirani potencijali

UDK 616.28-008.5-07
Review
Received: 17 January 2007
Accepted: 25 April 2007

THE ROLE OF NEUROSONOLOGY IN VERTIGO

Arijana Lovrenčić-Huzjan

University Department of Neurology, Sestre Milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia

Summary

Vertigo is a common symptom, and may represent a serious neurological disorder. If it develops suddenly, it may be a symptom of an acute stroke.

Neurosonology can be used in cerebrovascular disorders in order to asses the vessel patency, or to present different craniocervical artery diseases. Atherosclerotic changes may be seen, as well as inflammatory diseases, dissections, vasculopathies or vascular malformations. By means of a transcranial Doppler the intracranial hemodynamics can be assessed. A development of collateral pathways in extra- or intracranial occlusive diseases can be presumed, cerebral vasomotor reactivity can be tested, and, with the application of new softwares, microembolic signals can be detected.

Neurosonology can be used in a variety of neurological disorders presenting with vertigo.

Key words: Vertigo, Color Doppler, Transcranial Doppler, carotid artery, vertebral artery

INTRODUCTION

Vertigo is a common symptom. Since it may represent a neurological disorder, it is a frequent reason for neurological consultations. A sudden onset may be the symptom of an ischemic or hemorrhagic stroke, especially in the posterior circulation. It may represent different cerebrovascular disorders developing from vessel variability like hypo-

Correspondence to: Arijana Lovrenčić-Huzjan, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: arijana.lovrenčić@zg.t-com.hr

plasia, aplasia, vascular malformation, steno-occlusive changes in the vertebrobasilar circulation, or subclavian steal syndrome. A vessel inflammation or vasculopathies may lead to vertebrobasilar circulation disorders or can cause dissections. Besides vascular disorders, brain tumors in posterior fosse or demyelization, they may cause vertiginous symptoms.

Neurosonological studies are routinely performed in neurological clinics. Their greatest advantage is the real-time, bedside evaluation of the morphology and hemodynamics of brain vessels. The main goal is to identify large obstructive lesions in the extracranial and intracranial basal arteries and to monitor and facilitate spontaneous or drug-induced thrombolysis in the majority of patients. It also enables the identification of vascular lesions amenable for interventional treatment. The detection of rare causes of an ischemic stroke, such as dissections, vasculopathies and other less frequent etiologies is facilitated by a systematic use of ultrasound studies. Therefore, its usage is recommended as a part of comprehensive stroke treatment [1-7].

Vertigo in the emergency room

In acute vertigo a brain imaging study like CT scan is mostly used to exclude structural brain lesions that may imitate a stroke [1,2,3]. Rarely, in the first few hours, it will display ischemic changes. Therefore, neurosonological investigations may point at underlying stroke mechanisms. Also, in some centers, CT scan is not available on a 24-hour basis. Therefore, this useful test in clinicians' hands may help in patient management. Neurosonology has several advantages: it can be performed at the bedside and repeated as needed or applied for continuous monitoring; its usage is less expensive, and more available. It consists of extracranial color Doppler imaging of carotid and vertebral arteries and transcranial color Doppler sonography for intracranial evaluation. In acute vertigo, with an experienced clinician, it may help to distinguish an ischemic from hemorrhagic stroke by means of the underlining mechanism detection: macroangyopathic, cardioembolic, vasculopathy or dissection; or to raise the suspicion on the signs of vascular malformations. It may also point out the advantages of brain hemodynamic monitoring.

Extracranial evaluation of vertebral arteries

One fourth of ischemic strokes are related to the vertebrobasilar territory. Noninvasive investigations of vertebral arteries have become popular in the last decade with the invention of the color Doppler, so that vertebral occlusions have been seen more often, clinically presented with TIA or a mild stroke. Also, vertebral dissections have been recognized more often.

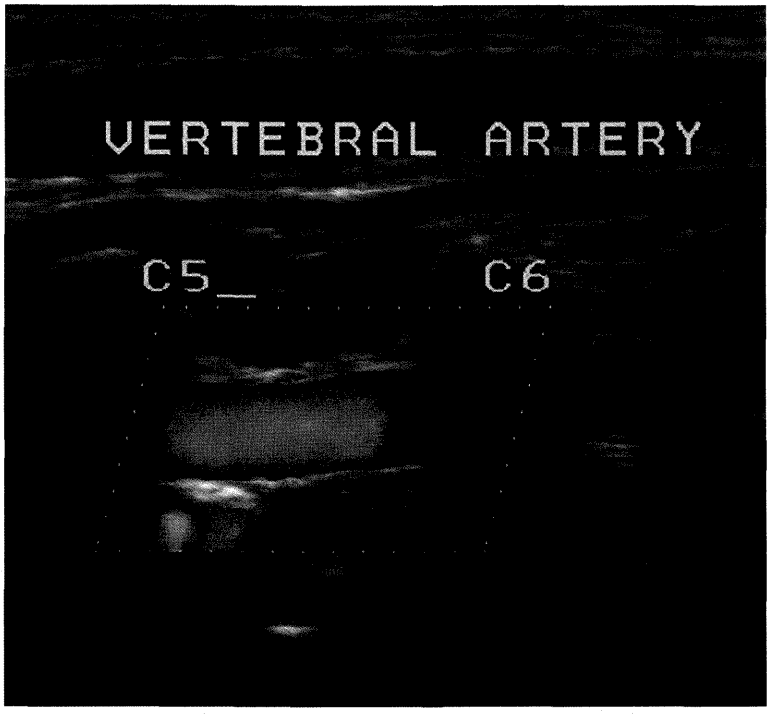


Figure 1. Normal vertebral artery

By means of vertebral artery color Doppler sonography (VCDS) normal vertebral arteries may be displayed (Fig. 1). Asymmetry of vertebral arteries may be found in up to 30% of healthy individuals, with the left vertebral artery wider, and more frequent as dominant [8,9,10,11]. Hypoplasia of a vertebral artery may be found in up to 10% of cases, slightly more often of the right than of the left vertebral artery [8,9,10,11]. Blood flow velocities and the mean diameter don't change with age. Females have higher blood flow velocities, and thinner vertebral arteries than males.

In hypoplasia [8,9,10] the findings may include poor color flow opacification, low flow velocities and increased resistance (Fig. 2). A hypoplasia in the vertebrobasilar system was found to predispose the adults to a posterior circulation ischemia [12].

VERTEBRAL artery occlusion and posterior circulation ischemia

The visualization of vertebral artery occlusion depends on the location, diameter and blood flow volume in the artery and collaterals [13]. The hemodynamic spectra may help in localizing the site of occlusion [13,14]. In patients with a distal occlusion, color

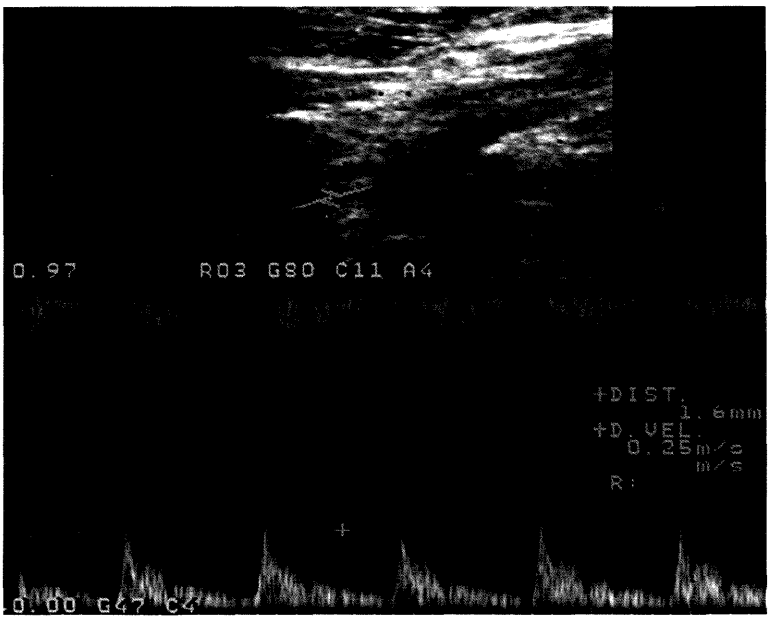


Figure 2. Hypoplastic vertebral artery

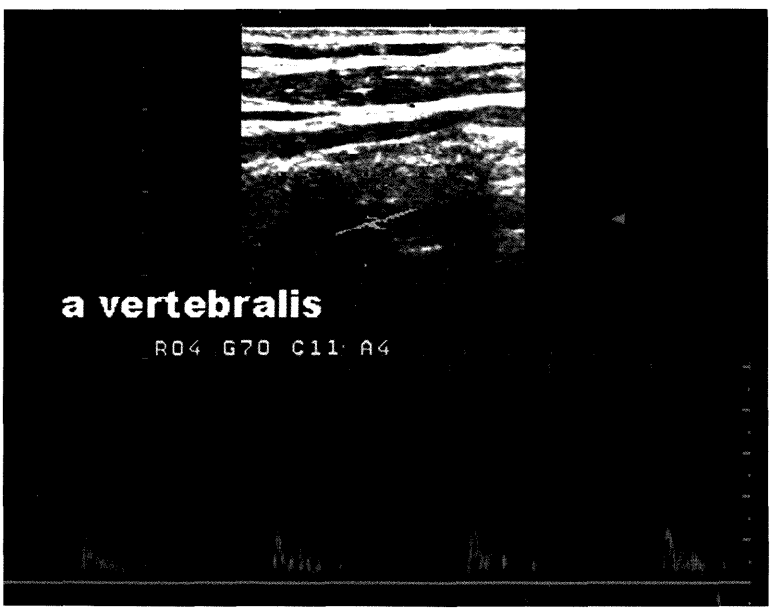


Figure 3. Vertebral artery occluded in the distal part, before the branching of the posterior inferior cerebellar artery

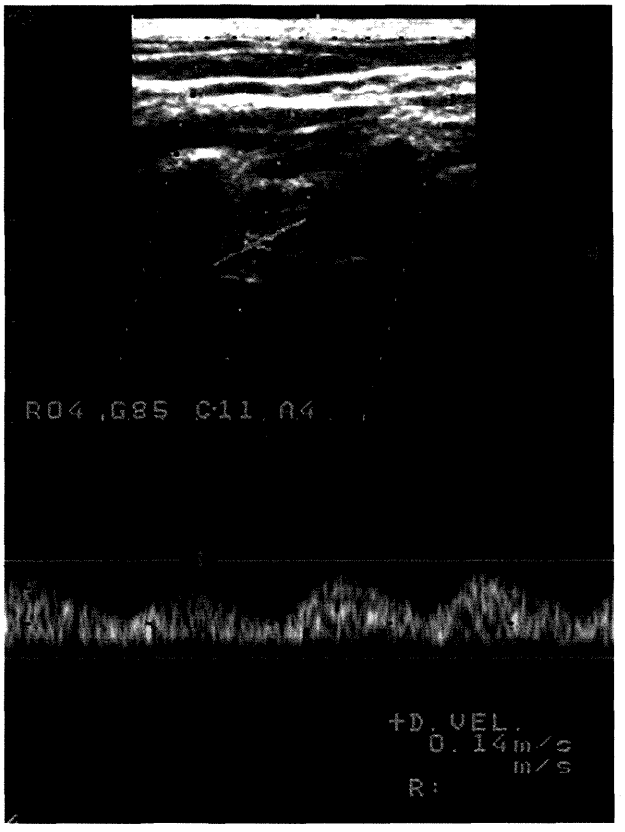


Figure 4. Vertebral artery occluded in the distal part, after the branching of the posterior inferior cerebellar artery

Doppler filling may be reduced due to similar hemodynamic changes as in the hypoplastic vertebral artery (Fig. 3). Difficulties in distinguishing the site of occlusion exist, since the collateral flow may resemble a vertebral artery. A power-enhancement Doppler enables visualization of a vessel with very low flow velocities, as in those vertebral arteries with a dampened flow due to distal or proximal occlusive lesions and a tortuous course [13,14,15]. VCDS can therefore distinguish the site of vertebral artery occlusion according to the following criteria. Vertebral artery occlusion at the origin (V1 occlusion) (Fig. 4): lumen filled with plaques, absence of directional or power Doppler flow within the lumen, presence of collateral flow [13,14,15,16]. Vertebral artery occlusion before the branching of the posterior inferior cerebellar artery (PICA): vertebral artery filled with color, absence of diastolic flow [13,14] (Fig. 4). Vertebral artery occlusion after the branching of the PICA: vertebral artery filled with color, damped flow (blood flow

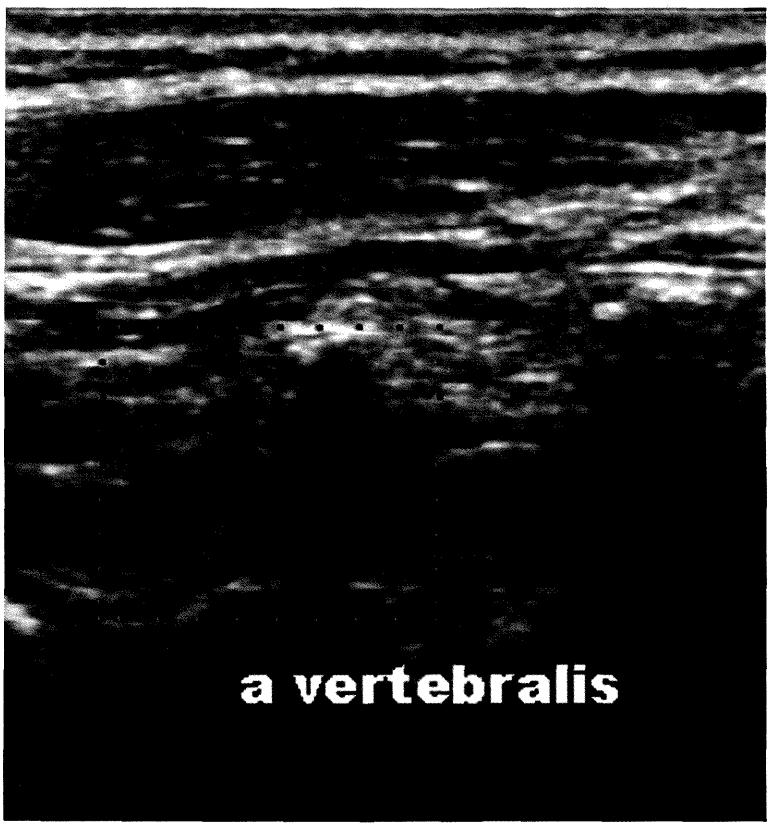


Figure 5. Vertebral artery occluded at the origin

velocities reduced more than 30% to contralateral side, presence of diastolic flow) (Fig. 3). The differences in end-diastolic flow velocities between the last two groups are thought to be based on the differences in the peripheral vascular resistance. In the group with occlusion after the branching of the PICA, blood can flow through the vertebral artery as far as the PICA. Therefore, the peripheral vascular resistance in this group is lower then in the previous group, before the branching of the PICA, thus resulting in higher end-diastolic flow velocities. If the occlusion is proximal of the branching of PICA, a higher resistance pattern with absent diastolic flow is expected. In patients with a basilar artery occlusion, in both vertebral arteries high resistance pattern would be found.

Most data on ischemia in the posterior circulation derive from the New England Medical Center Posterior Circulation Registry (NEMC PCR) [17,18], consisting of a consecutive series of 407 patients with signs and symptoms of posterior circulation ischemia seen during a 10-year period.

Clinical presentations in these 407 NEMC PCR patients [18] were as follows: 59% had strokes without transient ischemic attacks (TIAs), 24% had TIAs then strokes, and 16% had only TIAs. Embolism was the commonest stroke mechanism (40% of patients including 24% of cardiac origin, 14% intra-arterial, 2% cardiac and arterial). In 32% of patients large artery occlusive lesions caused a hemodynamic brain ischemia. Infarcts most often included the distal posterior circulation territory (rostral brainstem, superior cerebellum and occipital and temporal lobes); the proximal (medulla and posterior inferior cerebellum) and middle (pons and anterior inferior cerebellum) territories were equally involved. Severe occlusive lesions (>50% stenosis) involved more than one large artery in 148 patients; 134 had one artery site involved unilaterally or bilaterally. The most common occlusive sites were: extracranial vertebral artery (52 patients, 15 bilateral) intracranial vertebral artery (40 patients, 12 bilateral), basilar artery (46 patients). Intra-arterial embolism was the most common mechanism of brain infarction in patients with a vertebral artery occlusive disease. Thirty-day mortality was 3.6%. Embolic mechanism, distal territory location, and basilar artery occlusive disease carried the poorest prognosis. The best outcome was in patients who had multiple arterial occlusive sites; they had position-sensitive TIAs for months to years.

According to Wytick [17], out of 407 patients chosen for study from the NEMC PCR, 80 (20%) had V1 segment lesions, either higher-grade stenosis or occlusion. Patients were classified into 5 groups: 22 patients had V1 disease and a coexistent severe intracranial occlusive disease of the posterior circulation, 19 had V1 disease with an evidence of artery-to-artery embolism, 20 had a suspected V1 disease with an artery-to-artery embolism, but with other potential causes of the stroke or a less certain vascular diagnosis, 13 had V1 disease associated with hemodynamic transient ischemic attacks and 6 had proximal vertebral arterial dissection. Hypertension, cigarette smoking, and a coronary artery disease were common risk factors. Clinical features, the location of infarct and the outcome differed between the groups and reflected the presumed mechanisms of stroke.

The use of VCDS increases diagnostic confidence of the sonographic examination in patients with suspected vertebral artery disease, like stenosis, occlusion or dissection.

Vasculitis, vasculopathies, dissections

Vasculitis of the nervous system includes a group of disorders characterized by the histological feature of an inflammation of blood vessels. The diagnosis is suspected by a clinical presentation, and confirmed by signs of inflammation obtained with laboratory analysis, or biopsy. The use of CCDS may help in a noninvasive visualization of the disease [19]; by direct visualization if the location of the disease is present in a segment that is accessible to the ultrasound investigation, like the affection of the branches of the aortic arch [20], by indirect signs in the hemodynamics of the carotid or vertebral arter-

ies, like the subclavian steal syndrome in one of the vertebral arteries, or by visualizing dark halo around the pin like the color-coded flow in the temporal [21] or occipital artery [22]. In this way a hypoechoic vessel wall thickening of the temporal or occipital artery is described, most likely reflecting an inflammatory vessel wall edema. Fibrotic healing would increase the level or echogenicity of the vessel wall, and later on improve the flow. Color Doppler imaging enables differentiation between a spontaneous dissection and giant cell arteritis of the vertebral artery [23], which may have a similar clinical and sonographic appearance at first sight. Clinically, both diseases may be accompanied by an occipital headache and neck pain with an acute or subacute onset, with a later presentation of ischemic symptoms. Sonographicaly, both entities may display a hypoechoic vertebral artery with a residual channel of color flow. In dissection the intramural hematoma leads to a stenosis or occlusion of a vertebral artery, and a similar finding would be the result of an inflammatory hypoechoic vessel wall change in giant cell arteritis. The difference is that the hypoechogenicity in a dissection is extending along the extracranial vertebral artery, and is usually eccentric and crescent-shaped, often with a spiraling course. A concentric halo of a vertebral artery may have a good positive predictive value for the presence of vasculitis, especially if found in another vessel like the temporal artery. Vasculitis affecting smaller arteries may alter the intracranial hemodynamics, which can be measured as impaired vasoreactivity as a marker of smaller vessel involvement.

Between vasculopathies, Moyamoya disease [24] and fibromuscular dysplasia [25] can be displayed, and may predispose to a dissection. Dissections are lately more often recognized as relatively common causes of a stroke, particularly among young patients. Dissections lead to ischemic strokes through artery-to-artery embolism or by causing a significant stenosis and occlusion of the proximal vessel, and in some cases, dissections may lead to the formation of a pseudoaneurysm, which can also serve as a source of thrombus formation. Intracranial dissections in the vertebrobasilar territory have a higher risk of rupture, leading to a subarachnoidal hemorrhage (SAH). Dissections may appear as different findings in the color-coded Doppler mode [26-30]. When extending from the aortic arch, double lumens can be seen. Bifurcation stenosis may dissect leading to the formation of a color-coded flow in the plaque base. In younger persons dissections are usually affecting the distal parts of internal carotid or vertebral arteries. Hypoechoic stenosis of the vessels in distal parts can be seen, or, when located intracranially leading to a complete occlusion, the indirect signs of distal occlusions are present. Such signs include dampened flow, with a high resistance pattern, and possible inversed hemodynamics during the diastole. The goals of the therapy, when treating patients with dissections and an ischemic stroke, are to prevent further ischemic strokes and to promote healing of the dissected vessel. Carotid CDS may help in monitoring the vessel healing,

parallel with the emboli detection that may show a reduction in embolic signals [31-34]. One of the first neurosonological investigations of vertebral artery dissections [28] verified by angiography, magnetic resonance imaging or both, revealed that the most common dissected segments in 14 patients were as follows: atlantoaxial (V-3) in 6, V-3 and intertransverse (V-2) in 3, V-3 and intracranial (V-4) in 3, and V-2 in 2 patients. Extracranial and transcranial Doppler examination of the atlas loop, involving 12 patients, showed an absent flow signal in 5, low bidirectional flow signal in 1, and poststenotic low blood flow velocities in 3 patients. Seven of these patients had a high-grade stenosis or occlusion. The stenotic segment with an increased flow signal was identified directly in 2 patients. Duplex examination of the intertransverse segment confirmed an absent flow in 4 patients, making technically insufficient examination unlikely. In the 2 patients with directly detected stenosis, duplex examination showed low flow velocities before the stenosis. The combined use of extracranial and transcranial Doppler and duplex sonography increased the diagnostic yield to detect vertebral artery pathology. If abnormal sonographic findings were considered, the yield was 86%; relying only on the definitively abnormal findings (absent flow signal, severely reduced vertebral artery blood flow velocities, no diastolic flow, bidirectional flow, and a stenosis signal) the yield was 64%. Such results pointed out that there was no pathognomonic ultrasound finding for vertebral artery dissection. If a patient presents with suggestive symptoms, an ultrasound may corroborate the clinical suspicion and aid in the decision regarding an early anticoagulant treatment, and the definite diagnosis can be made with other imaging techniques demonstrating hematoma in the vessel wall.

In another series of vertebral artery dissections in 24 patients with 28 vertebral artery dissections in the neck (4 occurring bilaterally) [29], with 83% of dissections temporally related to trauma, and without an underlying vascular disease, the major initial manifestation was pain in the occipital or neck region. The next most common symptoms were vertigo and nausea in 17 patients. Clinical manifestations were: 5 patients with vertebrobasilar TIA (in 2 patients vestibulocerebellar TIA, in 1 patient visual TIA, in 1 patient motor TIA, and in 1 patient brain stem TIA with perioral paresthesia), 10 patients with a cerebellar infarction (in 4 patients bilateral), 5 patients with a brainstem infarction, in one a posterior cerebral artery territory infarction, and multiple vertebrobasilar ischemic lesions in 3 patients. Typical ultrasonographic findings were: irregular stenosis, dissecting membrane with a true and false lumen, localized increase in the diameter of the artery, pseudoaneurysm, intramural hematoma, and a tapering stenosis with a distal occlusion; while typical angiographic findings were irregular narrowing of the vessel lumen or a tapering stenosis with a distal occlusion. Magnetic resonance imaging showed a thickened vessel wall with a hematoma signal at the site of the dissection. Duplex color-flow imaging was valuable for the early diagnosis of an extracranial verte-

bral artery dissection and for follow-up examinations. In 43% of cases the most frequent localizations of dissections were the distal V1- and the proximal V2-segment (at the level of the C6 vertebra). The outcome was favorable, except for 2 patients with a basilar artery occlusion. In an earlier series by the same authors [35] in the follow-up examination a good regression of pathological findings was found in 70.8% dissections, with two occlusions completely reanalyzed.

Lately, the biggest series of 195 vertebral artery dissections in 169 patients were published [36]. Brain ischemia occurred in 131 patients (77%; ischemic stroke in 67% and TIA in 10%). Three patients with an ischemic stroke also showed signs of a subarachnoid hemorrhage (SAH) and 3 (2%) had SAH without ischemia. Head and/or neck pain was present in 118 out of 134 patients (88%) with brain ischemia or SAH, and pulsatile tinnitus in seven (5%) patients. The remaining 35 patients (21%) had an isolated head and/or neck pain in 21 (12%) cases, asymptomatic spontaneous vertebral artery dissection in 13 (8%), and cervical radiculopathy in one case (1%). Location of the spontaneous vertebral artery dissection was more often in the pars transversaria (V2; 35%) or atlas loop (V3; 34%) than in the prevertebral (V1; 20%) or intracranial (V4; 11%) segments (P=0.0001). A favorable outcome (mRA 0-1) was found in 82% of 107 ischemic stroke patients with follow up, and two (2%) patients died. Independent predictors of a favorable outcome were a low baseline National Institutes of Health Stroke Scale score and a younger age.

Transcranial evaluation of stroke, vessel occlusion or hemorrhage

Transcranial Doppler (TCD) measures the local blood flow velocity (BFV) and direction in the proximal portions of large intracranial arteries [6,7,37,38]. It is a "blind method", therefore operator dependent and requires training and expertise to perform and interpret the results. Several studies evaluated the ultrasound in comparison with neuroradiological imaging methods in the acute stroke setting [5,7]. Non–contrast-enhanced TCD was reported to have a sensitivity of 80% and a specificity of 90%, compared with digital subtraction angiography (DSA) in patients presenting within 5 hours of a middle cerebral artery (MCA) stroke [39], but the sensitivity for detecting internal carotid, basilar or vertebral artery occlusion is lower (SE 55-81%, SP 96%) [7]. By means of transcranial color coded Doppler (TCCD) flow imaging the sensitivity to detect advanced (greater than 50%) MCA, vertebral or basilar artery stenosis is higher (SE 100%, SP 100%) [40]. Therefore TCD or TCCD may be used as a screening test to determine the need for further angiographic studies. The bedside availability, convenience to the patient, and continuous monitoring possibility make TCD particularly suitable and practical for emergency evaluations. TCD also allows real-time assessment of the BFV, pulsatility, and microembolization, information which is not available with angiography.

Intracranial arterial occlusions detected by TCD are associated with poor neurological recovery, disability, or death after 90 days [41], whereas normal results predict early improvement [42]. In patients with an acute ICA territory stroke TCD findings, stroke severity at 24 hours, and CT lesion size were independent predictors of the outcome after 30 days [41]. When combined with the carotid duplex sonography, the presence and total number of arteries with suspected steno-occlusive lesions by TCD in TIA or stroke patients, were associated with a poor outcome (43,44], an increased risk of further vascular events and death within 6 months [45). Such a combined stroke patient evaluation can identify lesions amenable for interventional treatment (LAIT) in patients with an acute cerebral ischemia [46], achieving 100% accuracy.

Several TCCS studies have shown that the detection of a homogenously hyperechogenic area, sharply demarcated from the surrounding brain tissue, is diagnostic for an acute intracerebral hemorrhage (ICH) [47,48]. It is also possible to monitor the midline shift (MLS) in patients with space-occupying MCA infarcts, since MLS displacement may predict a fatal outcome in patients with malignant MCA infarcts [49]. TCCS can identify stroke complications like a hemorrhagic transformation, ventricular bleeding or MLS, and differentiate between an intracerebral hemorrhage and an ischemic stroke with a 95% sensitivity and 94% specificity [50]. Thus, if a CT scan is not readily available, TCCS may help in identifying patients with a primary brain hemorrhage or secondary hemorrhagic complications.

TCD in subarachnoidal hemorrhage (SAH)

Some patients with a subarachnoidal hemorrhage present with a headache and vertigo. In these patients TCD and TCCD is helpful for the assessment of cerebral vasospasm (VSP) and in differentiating a VSP from angiomas feeding vessels, or to directly visualize the vascular malformation.

Cerebral VSP is a delayed narrowing of the large capacity arteries at the base of the brain after SAH, often associated with the radiographic or cerebral blood flow evidence of diminished perfusion in the distal territory of the affected artery, and can be easily detected by means of TCD [51]. It has a typical temporal course with onset 3 to 5 days after the hemorrhage, reaching its maximal at 5 to 14 days, and gradually resolving over 2 to 4 weeks. In about one half of the cases a VSP is manifested by the occurrence of a delayed neurological ischemic deficit, which may resolve or progress to cerebral infarction [51].

Large and medium-sized cerebral aneurysms located in the proximal segments of the circle of Willis can be sometimes detected as colored oval structures of a pulsatile nature adjacent to large parent arteries [52,53]. Aneurysms located beyond the field of

scanning and those that are thrombosed cannot be detected. TCCS can detect 76 to 91% of nonthrombosed intracranial aneurysms of >6 mm in size (52,53], and the use of echo contrast agents or power Doppler may increase the rate of detection, including aneurysms >5 mm in size [52-54].

Arteriovenous malformations (AVMs) can be displayed as areas with a color mosaic, which is related to the focal accumulation of vascular convolutions and spectral hemodynamic abnormalities similar to those in the feeding vessels [55] TCD and TCCS can suggest the presence of AVMs by detecting abnormal increased systolic and especially end diastolic flow velocities and a decreased pulsatility in the feeding arteries [55,56).

CONCLUSION

Neurosonological investigations are useful in the evaluation of patients with vertigo. They can display the vertebrobasilar steno-occlusive disease, dissections, vasculitis or vasculopathies, and thus raise suspicion on acute ischemia. Noninvasive monitoring of the disease is possible. By means of TCCS, hyperdense signals may suggest a hemorrhage and vascular malformations can be seen.

References

[1] *Demarin V, Lovrenčić-Huzjan A, Trkanjec Z, Vuković V, Vargek-Solter V, Šerić V, Lušić I, Kadojić D, Bielen I, Tuškan-Mohar L, Aleksić-Shihabi A, Dikanović M, Hat J, DeSyo D, Lupret V, Beroš V.* Recommendations for stroke management - 2006 update. Acta Clin Croat 2006;45:219-285

[2] *Demarin V, Lovrenčić-Huzjan A, Šerić V, Vargek-Solter V, Trkanjec Z, Vuković V, Lupret V, Kalousek M, DeSyo D, Kadojić D, Lušić I, Dikanović M, Vitas M.* Recommendations for stroke management. Acta Clin Croat 2001; 40:127-154.

[3] *Demarin V, Lovrenčić-Huzjan A, Šerić V, Vargek-Solter V, Trkanjec Z, Vuković V, Lupret V, Kalousek M, DeSyo D, Kadojić D, Lušić I, Dikanović M, Vitas M.* Recommendations for stroke management. Neurol Croat 2002;51:41-87,127-174.

[4] *Demarin V, Lovrenčić-Huzjan A, Šerić V, Vargek-Solter V, Trkanjec Z, Vuković V, Lupret V, Kalousek M, DeSyo D, Kadojić D, Lušić I, Dikanović M, Vitas M.* Preporuke za zbrinjavanje bolesnika s moždanim udarom. Prvi dio: Organizacija skrbi za bolesnike s moždanim udarom, liječenje moždanog udara i neurorehabilitacija. Liječ vjes 2002; 7-8:200-112.

[5] *Lovrenčić-Huzjan A, Vuković V, Demarin V.* Neurosonology in stroke. Acta Clin Croat 2006;45:385-401.

[6] *Babikian VL, Feldmann E, Wechsler LR,* et al. Transcranial Doppler ultrasonography: year 2000 update. J Neuroimag 2000;10:101–115.

[7] *Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP,* et al. Assessment: Transcranial Doppler ultrasonography. Report of the Therapeutics and Technology Assessment

Subcommitteee of the American Academy of Neurology. Neurology 2004;62:1468-1481.

[8] *Lovrenčić-Huzjan A, Demarin V, Bosnar M, Vuković V, Podobnik- Šarkanji S.* Color Doppler flow imaging (CDFI) of the vertebral arteries – the normal appearance, normal values and the proposal for the standards. Coll Antropol 1999;1:175-181.

[9] *Lovrenčić-Huzjan A, Demarin V, Rundek T, Vuković V.* The role of vertebral artery hypoplasia in migraine aura. Cepahalalgia 1998;18:684-686.

[10] *Demarin V, Škarić-Jurić T, Lovrenčić-Huzjan A, Bosnar-Puretić M, VukovićV.* Vertebral artery hypoplasia- sex- specific frequencies in 36 parent-offspring pairs. Coll Antropol 2001;25:501-509.

[11] *Bartels E, Fuchs HH, Flügel KA.* Duplex ultrasonography of vertebral arteries: examination technique, normal values and clinical applications. Angiology 1992;43:169-180.

[12] *Chaturvedi S, Lukovits TG, Chen W, Gorelick PB.* Ischemia in the territory of a hypoplastic vertebrobasilar system. Neurology 1999;52:980-983.

[13] *Lovrenčić-Huzjan A, Vuković V, Bosnar-Puretić M, Demarin V.* Sonographic features of vertebral artery occlusion (The role of color and power Doppler imaging). Acta clin Croat 1999;38:279-284.

[14] *Kimura K, Yasaka M, Moriyasu H, Tsuchiya T, Yamaguchi T.* Ultrasonographic evaluation of vertebral artery to detect vertebrobasilar axis occlusion. Stroke 1994;25:1006-1009.

[15] *Ries S, Steinke W, Devuyst G, Artemis N, Valikovics A, Hennerici M.* Power Doppler imaging and color Doppler flow imaging for the evaluation of normal and pathological vertebral arteries. J Neuroimaging 1998;2:71-74.

[16] *Saito K, Kimura K, Nagatsuka K, Nagano K, Minematsu K, Ueno S, Naritomi H.* Vertebral artery occlusion in duplex color-coded ultrasonography. Stroke 2004;35:068-1072.

[17] *Wityk RJ, Chang HM, Rosengart A, Han WC, De Witt LD, Pessin MS, Caplan LR.* Proximal extracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. Arch Neurol 1998;55:470-8.

[18] *Caplan LR, Wityk RJ, Glass TA, Tapia J, Pazdera L, Chang HM,* et al. New England Medical Center Posterior Circulation Registry. Ann Neurol 2004;56:389-98.

[19] *Lovrenčić-Huzjan A.* The role of ultrasound in diagnosing nonatherosclerotic vasculopathies of the nervous system. Acta clin Croat 1998;37(suppl 1):68-72.

[20] *Sun Y, Yip P-K, Jeng J-S, Hwang B-S, Lin W-H.* Ultrasonographic study and long-term follow-up of Takayasu's arteritis. Stroke 1996;27:2178-82.

[21] *Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ.* Color duplex ultrasonography in the diagnosis of temporal arteritis. N Engl J Med 1997;337:1336-1342.

[22] *Pfadenhauer K, Weber H.* Giant cell arteritis of the occipital arteries – a prospective color-coded duplex sonography study in 78 patients. J Neurol 2003;250:844-849.

[23] *Reinhard M, Schmidt D, Schumacher M, Hetzel A.* Involvement of the vertebral arteries in giant cell arteritis mimicking vertebral dissection. J Neurol 2003; 250: 1006-1009.

[24] *Lee Y-S, Jung K-H, Roh J-K.* Diagnosis of Moyamoya disease with transcranial Doppler sonography: correlation study with magnetic resonance angiography. J Neuroimaging 2004;14:319-323.

[25] *Arning C, Grzyska U.* Color Doppler imaging of cervicocephalic fibromuscular dysplasia. Cardiovasc Ultrasound 2004;2:7-10.

[26] *Lovrenčić-Huzjan A, Bosnar-Puretić M, Vuković V, Demarin V.* Sonographic features of craniocervical artery dissection. Acta clin Croat 2002;41:307-312.

[27] *Arning C.* Ultrasonographic criteria for diagnosing a dissection of the internal carotid artery. Ultraschall Med 2005;26:24-28.

[28] *Sturzenegger M, Mattle HP, Rivoir A, Rihs F, Schmid C.* Ultrasound findings in spontaneous extracranial vertebral artery dissection. Stroke 1993;24:1910–1921.

[29] *Bartels E.* Dissection of the extracranial vertebral artery: clinical findings and early noninvasive diagnosis in 24 patients. J Neuroimaging 2006;16:24-33.

[30] *Lovrenčić-Huzjan A, Jurašić M-J, Lovrenčić-Prpić G, Vuković V, Demarin V.* Aortic arch dissection presenting with hemodynamic spectrum of aortic regurgitation on transcranial Doppler. Ultraschall Med 2005;27:280-283.

[31] *Lovrenčić-Huzjan A, Klanfar Z, Bosnar-Puretić M, Demarin V.* Embolic stroke due to internal carotid dissection: non-invasive monitoring of recanalisation by color Doppler flow imaging and transcranial Doppler. Acta clin Croat 2002;42:201-205.

[32] *Srinivasan J, Newell DW, Sturzenegger M, Mayberg MR, Winn HR.* Transcranial Doppler in the evaluation of internal carotid artery dissection. Stroke, 1996;27:1226-1230.

[33] *Steinke W, Rautenberg W, Schwartz A, Hennerici M.* Noninvasive monitoring of internal carotid artery dissection. Stroke 1994;25:998-1005.

[34] *Molina CA, Alvarez-Sabín J, Schonewille W, Montaner J, Rovira A, Abilleira S, Codina A.* Cerebral microembolism in acute spontaneous internal carotid artery dissection. Neurology 2000;55:1738-1741.

[35] *Bartels E, Flûgel K.* Evaluation of extracranial vertebral artery dissection with duplex color-flow imaging. Stroke 1996;27:290-295.

[36] *Arnold M, Bousser MG, Fahrni G, Fischer U, Georgiadis D, Gandjour J, Benninger D, Sturzenegger M, mattle HP, Baumgartner RW.* Vertebral artery dissection: presenting findings and predictors of outcome. Stroke 2006;37:2499-503.

[37] *Aaslid R, Markwalder TM, Nornes H.* Noninvasive Transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57:769-774.

[38] *Alexandrov AV, Demarin V.* Insonation techniques and diagnostic criteria for transcranial Doppler sonography. Acta clin Croat 1999;38:97-108.

[39] *Alexandrov AV, Demchuk AM, Wein TH, Grotta JC.* Yield of transcranial Doppler in acute cerebral ischemia. Stroke 1999;30:1604-1609.

[40] *Baumgartner RW, Mattle HP, Schroth G.* Assessment of greater than/equal to 50% and less than 50% intracranial stenoses by transcranial color-coded duplex sonography. Stroke 1999;30:87-92.

[41] *Camerlingo M, Casto L, Censoi B,* et al. Prognostic use of ultrasonography in acute non-hemorrhagic carotid stroke. Ital J Neurol Sci 1996;17:215-218.

[42] *Toni D, Fiorelli M, Zanette EM, Sacchetti ML, Salerno A, Argentino C, Solaro M, Fieschi C.* Early spontaneous improvement and deterioration of ischemic stroke patients: a serial study with transcranial Doppler ultrasonography. Stroke. 1998;29:1144 -1148.

[43] *Molina CA, Alexandrov AV, Dechuk AM, Saqqur M, uchino K, Alvarez-Sabin J.* Improving the predictive acuracy of recanalization on stroke outcome in patients treated with tissue plasminogen activator. Stroke 2004;35:151-157.

[44] *Allendoerfer J, Goertler M, von Reutern GM.* For the Neurosnology for Acute Ischaemic Stroke (NAIS) Study Group. Prognostic relevance of ultra-early Doppler sonography in acute ischaemic stroke: a prospective multicenter study. Neurology Lancet 2006;5:835-840.

[45] *Wong KS, Li H, Chan Yl,* et al. Use of transcranial Doppler ultrasound to predict outcome in patients with intracranial large-artery occlusive disease. Stroke 2000; 31:2641-2647.

[46] *Chernyshev OY, Garami Z, Calleja S, Song J, Campbell MS, Noser EA, Shaltoni H, Chen C-I, Iguchi Y, Grota JC, Alexandrov AV.* Yield and accuracy of urgent combined carotid/transcranial ultrasound testing in acute cerebral ishemia. Stroke 2005;36:32-37.

[47] *Seidel G, Kaps M, Gerriets T.* Potential and limitation of transcranial color-coded sonography in stroke patients. Stroke 1995;26:2061-2066.

[48] *Becker G, Winkler J, Hofmann E, Bogdahn U.* Differentiation between ischemic and hemorrhagic stroke by transcranial color-coded real-time sonography. J Neuroimaging 1993;3:41-7.

[49] *Gerriets T, Stolz E, Modrau B, Fiss I, Seidel G, Kaps M.* Sonographic monitoring of midline shift in hemispheric infarctions. Neurology 1999;52:45-49.

[50. *Maurer M, Shambal A, Berg D, Woydt M, Hofmann E, Georgiadis D, Lindner A, Becker G.* Differentiation between intracerebral hemorrhage and ischemic stroke by transcranial color-coded duplex-sonography. Stroke 1998;29:2563-2567.

[51] *Aaslid R, Huber P, Nornes H.* Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. J Neurosurg 1984;60:37-41.

[52] *Baumgartner RW, Mattle HP, Kothbauer K, Schroth G.* Transcranial color-coded duplex sonography in cerebral aneurysms. Stroke 1994;25:2429–2434.

[53] *Wardlaw JM, Cannon JC.* Color transcranial "power" Doppler ultrasound of intracranial aneurysms. J Neurosurg 1996;84:459-461.

[54] *Griewing B, Motsch L, Piek J, Schminke U, Brassel F, Kessler C.* Transcranial power mode Doppler duplex sonography of intracranial aneurysms. J Neuroimaging 1998; 8:155-158.

[55] *Rundek T, Demarin V, Lovrenčić M, Vargek-Solter V, Carrillo-Pintos J.* Transcranial Doppler diagnostic criteria in the evaluations of arteriovenous malformations. Neurol Croat 1991;40:259-67.

[56] *Baumgartner RW, Mattle HP, Schroth G.* Transcranial colour-coded duplex sonography of cerebral arteriovenous malformations. Neuroradiology 1996;38:734-737.

Sažetak

Uloga neurosonologije u vertigu

Vertigo je čest simptom koji može predstavljati i ozbiljan neurološki poremećaj. Ako vertigo naglo nastane, može biti simptom akutnog moždanog udara.

Neurosonologija se može upotrijebiti u cerebrovascularnih poremećaja kako bi se procijenilo stanje krvnih žila, ili u dijagnostici različitih bolesti kraniocervikalnih arterija. Mogu se prikazati aterosklerotske promjene, upalne bolesti, disekcije, vaskulopatije i vaskularne malformacije. Primjenom transkranijskog doplera može se procijeniti intrakranijska hemodinamika, može se prikazati nastanak kolateralnih puteva u ekstra- i intrakranijakim i okluzivnim bolestima, može se ispitati cerebralna vazomotorna reaktivnost, a primjena novih softwera omogućuje detekciju mikroembolijskih signala.

Neurosonologija se može primijeniti u različitim neurološkim poremećajima koji imaju vertigo kao simptom.

Ključne riječi: Vertigo, obojeni dopler, transkranijski dopler, karotidna arterija, vertebralna arterija

UDK 616.28-008.5-08
Review
Received: 17 January 2007
Accepted: 25 April 2007

PHARMACOTHERAPY OF VERTIGO

Zlatko Trkanjec, Anka Aleksić-Shibabi[1], Vida Demarin

University Department of Neurology, Sestre Milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Vinogradska 29, Zagreb, Croatia
[1]Department of Neurology, Šibenik General Hospital, Šibenik, Croatia

Summary

Pharmacotherapy of vertigo can be symptomatic or specific. There is no ideal drug for the management of vertigo. Acute vertigo is usually managed with vestibular suppressants and antiemetic medications. Anticholinergics, antihistamines, dopaminergic antagonists, and monaminergics are most often used in the treatment of vertigo and associated symptoms. Some other drugs are also used in its treatment. However, vertigo is a subjective feeling which makes it difficult to measure the drug effect. Therefore, many papers dealing with vertigo treatment suffer from methodological pitfalls, making it difficult to establish a generally acceptable consensus about the treatment of vertigo.

Key words: vertigo, therapy, pharmacotherapy

INTRODUCTION

Vertigo is primarily due to an imbalance between the two vestibular labyrinths whose activity is modulated by the central vestibular system.

Treatment of acute vertigo has two components: to control the acute episode, and to speed up the recovery and prevent future episodes.

There is no ideal drug for the treatment of vertigo. Most of the existing drugs have essentially been found during clinical use rather than developed specifically for the treatment of vertigo. The treatment of vertigo can be symptomatic or specific. The symptomatic treatment involves controlling the acute symptoms and autonomic complaints,

Correspondence to: Zlatko Trkanjec, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: ztrkanj@zg.t-com.hr

while the specific treatment should target the underlying cause of vertigo. However, some types of vertigo have a recognized pathophysiology, while pathophysiology of other types is still unknown.

In the vestibular nuclei cholinergic and H1 histaminergic receptors are the main receptor types. Sensory information from the vestibular, visual and proprioceptive systems is processed, integrated and stored. A mismatch of the sensory input produces vertigo. It seems that the cholinergic system is responsible for neural storage, the histaminergic system for stimulating the vomiting center, the GABA-ergic system inhibits signals from the cerebellar Purkinje cells, while the noradrenergic system projecting from the brainstem to the vestibular nuclei inhibits vestibular activity. Stimuli from the gastrointestinal tract are transmitted to the vomiting center through the serotonergic pathway. The chemoreceptor trigger zone in the area postrema acts on the vomiting center and can be blocked by D2 dopamine agonists, while the vestibular nuclei act on the vomiting center through the H1 histaminergic system [1- 4].

Pharmacotherapy of vertigo

Many articles on vertigo treatment have been published. Searching the Pub Med on February 28, 2007 with the key words pharmacotherapy and vertigo revealed 1719 articles. However, there are few well designed, placebo-controlled, double-blind, randomized clinical trials.

Vertigo is a subjective feeling which makes it difficult to measure the drug effect. Most often more or less subjective scales are used to measure the drug effect. On the other hand, mechanisms of central compensation make most types of vertigo diminish with time. In patients with Ménière's disease Ruckenstein et al. found a remission in 60-80% of patients regardless of therapy [5]. Silverstein et al. found a remission in 59% of patients after two years and in 70% of patients after 8 years in non treated groups of patients with Ménière's disease [6]. In benign paroxysmal positional vertigo (BPPV) a remission was found in 98% patients after 3-14 days [7], and in 84% patients after one and in 93% patients after two procedures [8].

Medications are most useful for treating acute vertigo that lasts a few hours to several days. Vertigo lasting more than a few days is suggestive of a permanent vestibular injury, and medications should be stopped to allow the brain to adapt to a new vestibular input. A wide variety of medications are used to treat vertigo and the frequently concurrent nausea and vomiting.

Acute vertigo is usually managed with vestibular suppressants and antiemetic medications. Vestibular suppressants should be used for a few days at most because they delay the brain's natural compensatory mechanism for peripheral vertigo.

Four general classes of drugs are mostly used in the treatment of vertigo and its associated symptoms - anticholinergics, antihistamines, dopaminergic antagonists, and monaminergics. However, some other drugs can also be used for vertigo therapy.

Anticholinergics

It seems that the most effective drug for the prophylaxis and treatment of motion sickness is anticholinergic scopolamine. In a non-randomized study 37 patients with Méniére's disease for four weeks received anticholinergic glycopyrrolate 2x2 mg compared with placebo [9]. Glycopyrrolate significantly decreased the severity of vertigo and improved the quality of life [10].

The side effects include dry mouth, drowsiness, midriasis and accommodation disorders causing blurred vision, addiction and dependency. Anticholinergics are contraindicated in patients with a glaucoma. Newer data show that the anticholinergics selective for M2 subtypes of muscarinic receptors in the vestibular system could have fewer side effects [11].

Antihistamines

Antihistamines include *meclizine*, dimenhydrinate, and promethazine. They usually last for 4-6 hours, except for meclizine which is supposed to remain in the system for 24 hours. They generally have fewer side effects than the anticholinergics, with a sedation and drowsiness being the most prominent. However, some of these agents have some anticholinergic activity, therefore, their antivertigo action could be due to the anticholinergic activity. Such antihistamines have similar side effects as the anticholinergics [12]. The newer, nonsedating antihistamines do not enter the central nervous system and have no value in the treatment of vertigo and motion sickness.

Betahistine is an H1 receptor agonist and H3 receptor antagonist. H1 agonism causes a vasodilatation, while H3 autoreceptor antagonism increases the histamine secretion facilitating the histaminergic neurotransmission, and H3 heteroreceptor antagonism increases the secretion of other neurotransmiters improving the coordination of neuronal electrical activity in the vestibular nuclei [13].

In a double-blind, placebo controlled, crossover study 114 patients with paroxysmal vertigo were randomized to betahistine 46 mg daily versus placebo during 10 weeks. In 82 patients that finished the study betahistine decreased the frequency and intensity of vertigo [14]. In another study 81 patients with Méniére's disease were randomized to either betahistine 2x8mg daily or placebo during 3 months. Betahistine also decreased the frequency and intensity of vertigo [15]. Another study showed that in 30 vertigo patients receiving betahistine 48 mg daily during 6 weeks the frequency of vertigo diminished 61.66% after 7 days, 95.29% after three weeks, and completely vanished after

five weeks. In the same study the duration of vertigo was reduced by 53.18% after one week, and by 93.88% after three weeks [16]. However, those studies have some pitfalls. Therefore, the Cochrane Database analysis of a betahistine therapy in Méniére's disease, after analyzing the data from 6 studies including 162 patients that fulfilled the analysis inclusion criteria, concluded that there is insufficient evidence to prove that betahistine has any effect on Méniére's disease [17].

Dopaminergic antagonists

Dopaminergic antagonists such as *prochlorperazine* and chlorpromazine act at the chemoreceptor trigger zone, reducing the neural impulses to the vomiting center. These drugs do not prevent vertigo and motion sickness, but may be useful in treating the accompanying nausea and vomiting. Metoclopramide and thiethylperazine are mainly used as antiemetics, and in vertigo treatment they are mostly used to control the vomiting. Metoclopramide is a dopaminergic antagonist as well as a serotoninergic antagonist which speeds gastric emptying and has a central antiemetic effect, while thiethylperazine acts mainly centrally on the chemoreceptor trigger zone in the medulla oblongata. The side effects of these drugs include sedation, dry mouth and extrapyramidal symptoms [18]. Newer antiemetics are serotonin 5-HT3 receptor antagonists, like ondansetron, tropisetron and granisetron, they inhibit the afferent vagal impulses and the vomiting center in the medulla oblongata and are well established in patients with nausea and vomiting associated with cancer chemotherapy, radiotherapy or anesthesia and surgery. They are expensive drugs and are only seldom used in vertigo treatment [19].

Another dopaminergic antagonist, sulpiride, has antipsychotic, antidepresive, and antiemetic effects and could be used in vertigo treatment. Zanetti et al. found that 87 patients with peripheral vertigo treated with sulpiride for 10 days had a faster recovery than 56 patients treated with either metoclopramide, thiethylperazine, or diazepam [20].

Monoaminergic drugs

Monoaminergic drugs in vertigo treatment most often include amphetamines and ephedrine. They appear to potentiate the effects of scopolamine and may be used in combination with one of the antihistamines for intense symptoms or in those who do not respond adequately to a single-drug therapy [21,22].

Benzodiazepines

Benzodiazepines act as a vestibular suppressant through the GABAergic system. Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the vestibular system. Benzodiazepines enhance the action of GABA in the central nervous system

(CNS) and are effective in relieving vertigo. Benzodiazepines can also minimize the associated anxiety and panic disorders that occur with vertigo. Most often prescribed benzodiazepins are diazepam, lorazepam, clonazepam and alprazolam [23,24].

Calcium channel blockers

Calcium channel blockers cinarizine and flunarizine are possible vestibular suppressants. However, they also have anticholinergic, antihistaminic and dopaminergic effects [25]. Cirek et al. compared the effect of betahistine 3x12 mg daily and cinarizine 20 mg plus dimenhydrinate 40 mg 3x daily during four weeks. The combination of cinarizine and dimehydrinate reduced vertigo intensity two times more than betahistine and reduced the intensity of accompanying symptoms. In this study no significant side-effects were recorded [26). Another calcium channel blocker, nimodipine, was shown to be effective in Ménière's disease [27].

Other drugs

Extracts of ginkgo biloba reduce blood viscosity, improve microcirculation and are antioxidants. They increase the speed of the central compensation of vertigo in experimental animals [28], and a study showed that extracts of ginkgo biloba have similar efficiency as betahistine in the treatment of vertigo [29].

Piracetam is a nootropic agent that is a cyclic derivate of GABA. Nootropics are supposed to facilitate learning and protect the brain from physical and chemical damage [30]. Piracetam alleviates vertigo after a head injury or vertigo of central origin, as, for example, in vertebrobasilar insufficiency and in peripheral vestibular disorders, especially in middle-aged and elderly subjects. Piracetam decreases the frequency, but probably not the severity of exacerbations in patients with a chronic or recurrent vertigo [31].

Trimetazidine is an antianginalgic drug acting by elective inhibition of the enzyme of fatty acid â-oxidation, the long-chain 3-ketoacyl CoA thiolase (3-KAT), optimizing the myocardial metabolism in ischemia [32]. However, it has been shown that this drug could be effective in vertigo treatment. In 20 patients with Ménière's disease trimetazidine 3x20mg daily compared with betahistine 3x8mg daily during 3 months decreased vertigo frequency and intensity, while there was no difference in the hearing, tinnitus, sensation of ear fullness and quality of life [33]. Another study on 45 patients with Ménière's disease showed that trimetazidine 3x20mg daily compared with betahistine 3x12mg daily during 2 months had beneficial effects on vertigo intensity, while there was no difference in the hearing and tinnitus [34].

Some antiepileptics are also efficient in vertigo therapy, like phonation which is effective in motion sickness [35], as well as gabapentine, carbamazepine and oxcarbazepine [24]. Gabapentine suppresses nystagmus possibly through GABAergic action [36].

References

[1] *Usami SI, Takumi Y, Matsubara A, Fujita S, Ottersen OP.* Neurotransmission in the vestibular endorgans – glutamatergic transmission in the afferent synapses of hair cells. Biol Sci Space 2001;15:367-70.

[2] *Landwehr S, Dicke U.* Distribution of GABA, glycine, and glutamate in neurons of the medulla oblongata and their projections to the midbrain tectum in plethodontid salamanders. J Comp Neurol 2005;490:145-62.

[3] *Gliddon CM, Darlington CL, Smith PF.* GABAergic systems in the vestibular nucleus and their contribution to vestibular compensation. Prog Neurobiol 2005;75:53-81.

[4] *Nishiike S, Takeda N, Kubo T, Nakamura S.* Noradrenergic pathways involved in the development of vertigo and dizziness-a review. Acta Otolaryngol Supp. 2001;545:61-4.

[5] *Ruckenstein MJ, Rutka JA, Hawke M.* The treatment of Méniére's disease: Torok revisited. Laryngoscope 1991;101:211-8.

[6] *Silverstein H, Lewis WB, Jackson LE, Rosenberg SI, Thompson JH, Hoffmann KK.* Changing trends in the surgical treatment of Méniére's disease: results of a 10-year survey. Ear Nose Throat J 2003;82:185-7.

[7] *Brandt T, Daroff RB.* Physical therapy for benign paroxysmal positional vertigo. Arch Otolaryngol 1980;106:484-5.

[8] *Levrat E, van Melle G, Monnier P, Maire R.* Efficacy of the Semont maneuver in benign paroxysmal positional vertigo. Arch Otolaryngol Head Neck Surg 2003;129:629-33.

[9] *Spinks AB, Wasiak J, Villanueva EV, Bernath V.* Scopolamine for preventing and treating motion sickness. Cochrane Database Syst Rev 2004;3:CD002851.

[10] *Storper IS, Spitzer JB, Scanlan M.* Use of glycopyrrolate in the treatment of Méniére's disease. Laryngoscope 1998;108:1442-5.

[11] *Bosch D, Schmid S.* Activation of muscarinic cholinergic receptors inhibits giant neurones in the caudal pontine reticular nucleus. Eur J Neurosci 2006;24:1967-75.

[12] *Takeda N, Morita M, Hasegawa S, Kubo T, Matsunaga T.* Neurochemical mechanisms of motion sickness. Am J Otolaryngol 1989;10:351-9.

[13] *Lacour M, Sterkers O.* Histamine and betahistine in the treatment of vertigo: elucidation of mechanisms of action. CNS Drugs 2001;15:853-70.

[14] *Canty P, Valentine J.* Betahistine in peripheral vertigo: a double-blind, placebo-controlled, cross-over study of Serc versus placebo. J Laryngol Otol 1981;95:687-92.

[15] *Mira E, Guidetti G, Ghilardi L, Fattori B, Malannino N, Maiolino L, Mora R, Ottoboni S, Pagnini P, Leprini M, Pallestrini E, Passali D, Nuti D, Russolo M, Tirelli G, Simoncelli C, Brizi S, Vicini C, Frasconi P.* Betahistine dihydrochloride in the treatment of peripheral vestibular vertigo. Eur Arch Otorhinolaryngol 2003;260(2):73-7.

[16] *Bradoo RA.* Managment of acute vertigo with betahistine. Ind J Otorynolaringol Head Neck Surg 2000; 52: 178-80.

[17] *James AL, Burton MJ.* Betahistine for Ménière's disease or syndrome. Cochrane Database Syst Rev. 2001;(1):CD001873.

[18] *Pyykko I, Magnusson M, Schalen L, Enbom H.* Pharmacological treatment of vertigo. Acta Otolaryngol Suppl 1988;455:77-81.

[19] *Wilde MI, Markham A. Ondansetron.* A review of its pharmacology and preliminary clinical findings in novel applications. Drugs 1996;52:773-94.

[20] *Zanetti D, Civiero N, Balzanelli C, Tonini M, Antonelli AR.* Improvement of vestibular compensation by Levo-sulpiride in acute unilateral labyrinthine dysfunction. Acta Otorhinolaryngol Ital 2004;24:49-57.

[21] *Johnson GD.* Medical management of migraine-related dizziness and vertigo. Laryngoscope 1998;108:1-28.

[22] *Shah KU, Shah A.* Labyrinthine vertigo treatment with ephedrine nasal douche. J Assoc Physicians India 1981;29:819-23.

[23] *Takeno K, Shimogori H, Takemoto T, Tanaka K, Mikuriya T, Orita H, Yamashita H.* The systemic application of diazepam facilitates the reacquisition of a well-balanced vestibular function in a unilateral vestibular re-input model with intracochlear tetrodotoxin infusion using an osmotic pump. Brain Res 2006;1096:113-9.

[24] *Hain TC, Uddin M.* Pharmacological treatment of vertigo. CNS Drugs 2003;17:85-100.

[25] *Verspeelt J, De Locht P, Amery WK.* Postmarketing study of the use of flunarizine in vestibular vertigo and in migraine. Eur J Clin Pharmacol 1996;51:15-22.

[26] *Cirek Z, Schwarz M, Baumann W, Novotny M.* Efficacy and tolerability of a fixed combination of cinnarizine and dimenhydrinate versus betahistine in the treatment of otogenic vertigo: A double-blind, randomised clinical study. Clin Drug Invest 2005;25:377-89.

[27] *Theopold HM.* Nimodipine (Bay e 9736) a new therapy concept in diseases of the inner ear? Laryngol Rhinol Otol (Stuttg) 1985;64:609-13.

[28] *Schlatter M, Kerr DR, Smith PF, Darlington CL.* Evidence that the ginkgo biloba extract, EGb 761, neither accelerates nor enhances the rapid compensation of the static symptoms of unilateral vestibular deafferentation in guinea pig. J Vestib Res 1999;9:111-8.

[29] *Cesarani A, Meloni F, Alpini D, Barozzi S, Verderio L, Boscani PF.* Ginkgo biloba (EGb 761) in the treatment of equilibrium disorders. Adv Ther 1998;15:291-304.

[30] *Nicholson CD.* Pharmacology of nootropics and metabolically active compounds in relation to their use in dementia. Psychopharmacology (Berl) 1990;101:147-59.

[31] *Oosterveld WJ.* The effectiveness of piracetam in vertigo. Pharmacopsychiatry 1999;32 (Suppl 1):54-60. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res. 2000;86:580-588.

[32] *Kluyskens P, Lambert P, D'Hooge D.* Trimetazidine versus betahistine in vestibular vertigo. A double blind study. Ann Otolaryngol Chir Cervicofac. 1990;107 (Suppl 1):11-9.

[33] *Martini A, De Domenico F.* Trimetazidine versus betahistine in Ménière's disease. A double blind method. Ann Otolaryngol Chir Cervicofac 1990;107 (Suppl 1):20-7.

[34] *Knox GW, Woodard D, Chelen W, Ferguson R, Johnson L.* Phenytoin for motion sickness: clinical evaluation. Laryngoscope 1994;104:935-9.

[35] *Stahl JS, Rottach KG, Averbuch-Heller L, von Maydell RD, Collins SD, Leigh RJ.* A pilot study of gabapentin as treatment for acquired nystagmus. Neuroophthalmology 1996;16:107-13.

Sažetak

Farmakoterapija vertiga

Farmakoterapija vertiga može biti simptomatska ili specifična. Ne postoji idealni lijek za liječenje vertiga. Akutni vertigo se obično liječi vestibularnim supresorima i antiemeticima. U liječenju vertiga i pridruženih simptoma najčešće se primjenjuju antikolinergici, antihistaminici, dopaminergički antagonisti i monaminergici. I neki drugi lijekovi se također primjenjuju u liječenju vertiga. Međutim, vertigo je subjektivni osjećaj, što otežava mjerenje učinka lijekova. Stoga mnogi radovi o liječenju vertiga imaju metodološke poteškoće, što otežava donošenje opće prihvaćenog konsenzusa o liječenju vertiga.

Ključne riječi: vertigo, terapija, farmakoterapija

UDK 616.89:616-036.1
Review
Received: 17 January 2007
Accepted: 25 April 2007

PSYCHOLOGICAL-PSYCHIATRIC FACTORS IN CHRONIC DIZZINESS

Danijel Buljan, Iva Ivančić

University Department of Psychiatry, Sestre Milosrdnice University Hospital, Zagreb, Croatia

Summary

Investigations demonstrated a correlation between oto-neurological illnesses manifested subjectively by instability and dizziness and anxiety and other psychiatric disorders.

The concept of chronic vertigo offered a systematic approach to patients with a lasting dizziness not caused by an evident patophysiological vestibular damage. According to newer neurobiological investigations, there are three subtypes of chronic dizziness: otogenic, psychogenic and interactive.

Nowadays there is a greater diagnostic accuracy and insight into the basic pathophysiological processes of the vestibular migraene, post-concussional syndrom and dysautonomias that can cause chronic dizziness.

Selective serotonin reuptake inhibitors, rehabilitation therapy for restoring the balance, and cognitive- behavioural therapy can be effective in treatment, but this effectiveness is limited.

Key words: anxiety, phobia, chronic dizziness, postconcussional syndrome, dysautonomia, migraine

INTRODUCTION

Psychosomatic medicine points out the uniqueness of the body and soul, as well as their interaction. Today there is a growing consensus that psychological factors are important in the development of all diseases as well as in chronic dizziness. They play a role in the predisposition to the illness, its emergence, progression, course, severity

Correspondence: Danijel Buljan, M.D. Ph.D., Professor of Psychiatry, Department of Psychiatry, University Hospital "Sestre Milosrdnice", Vinogradska cesta 29, Zagreb, Croatia
E-mail: dbuljan@kbsm.hr

and, finally, in the reaction to the somatic illness. Psychosomatic medicine involves a great part of behavioural medicine. The American National Academy in 1978 defined the behavioural medicine as an interdisciplinary branch dealing with the development and integration of behavioural and biomedical scientific cognitions and techniques important for the health and disease, and the application of this knowledge and techniques in the prevention, diagnosis, treatment and rehabilitation [1].

Through decades the chronic dizziness without identifiable vestibular deficits was called *psychogenic dizziness*. It was, however, a vague idea which could not include the complex correlation between the psychiatric and oto-neurological factors of chronic dizziness. In 1980 Brandt contributed to a better clarification of the psychogenic chronic dizziness concept. He introduced the concept of *phobic postural vertigo (PPV)*, a syndrome of subjective unsteadiness and illusory perturbations of posture, frequently accompanied by anxiety and autonomic arousal. Patients with PPV tend to have obsessive-compulsive personalities and may develop a PPV after vestibular insults, other medical illnesses, or periods of stress. Brand emphasized the importance of the positive identification of the core features of PPV rather that considering it to be a diagnosis of exclusion [2]. Recent studies confirmed that PPV could be reliably differentiated from other neuro-otological illnesses [3]. Treatment studies gave different results. The physical symptoms of PPV generally improved, but rarely resolved and often recurred. The majority of patients with PPV developed anxiety or depressive disorders that required psychiatric interventions [3]. Thus, PPV offers a more specific neuro-otological concept than psychogenic dizziness, but does not account for the range of psychiatric symptoms in patients with chronic dizziness and has not produced fully effective treatments [1].

Further, it was found that patients with vestibular disorders had high rates of panic disorders, and that patients with a panic disorder had high rates of dizziness and non-specific abnormalities on balance function tests (e.g. changes non diagnostic of a specific vestibular illness). It is considered that anxious disorders can cause psychosomatic dizziness and that vestibular dysfunction can cause somatopsychic anxiety [4].

Recent retrospective and prospective studies examined the longitudinal relationship between physical oto-neurological illnesses and anxiety disorders in chronic dizziness [5]. Also, studies of pharmacological, psychotherapeutic and rehabilitative procedures emerged [6-9]. These investigations paralleled research into the causes and treatments of other somatoform disorders such as noncardiac chest pain [10].

Taking this information into account the concept of *chronic subjective dizziness (CSD)* was introduced, which reformulates PPV and updates the psychosomatic dyad to provide clearer insights into the events that trigger and sustain chronic dizziness, a better understanding of therapeutic shortcomings, and the potential for preventive interventions [6,8].

Separate investigations examined three conditions that are easily confused with CSD, specifically vestibular migraine, traumatic brain injury and dysautonomia. All three may cause chronic or recurrent dizziness in the absence of identifiable vestibular deficits and are frequently accompanied by anxiety or depressive symptoms that mask the physical illnesses. Key clinical features distinguish them from CSD and other chronic neuro-otological conditions, allowing for appropriate diagnoses.

Definition and classification

The term psychosomatic is eliminated from the revised 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The psychological factors influencing the somatic state are described (one or more psychological or behavioural factors that significantly affect the course and development of the general physical condition or significantly increase the risk of an adverse outcome).

According to the DSM-IV-TR diagnostic criteria psychological factors can unfavourably affect the general medical condition by one of the following ways:

1. Influencing the course of the general health condition, which can be estimated by a narrow time linkage between the psychological factors and the deterioration or delay of recovery of the general health condition.
2. Impeding the treatment of the general health condition.
3. Containing additional health risks for the patient.
4. Psychological reactions to stress precipitate or impair the general health condition.

The term psychological factors (I consider it better to use the term psychologic-psychiatric factors, because not only the psychological symptoms, stress reactions, personal characteristics and behavioural disorders are included, but psychiatric diseases as well) is based on the nature and way they affect the general health condition causing chronic dizziness or some other psychosomatic illness.

Mental disorders, i.e. great depressive disorders, slow the recovery of chronic dizziness caused by vestibular neuronitis, psoriasis, myocardial infarction, and cerebral insult.

Psychological symptoms, i.e. anxious and depressive symptoms, cause the delay of the recovery of chronic dizziness, asthma, and urticaria.

Psychological reaction to stress causes the deterioration of the stress related chronic dizziness, arterial *hypertension, tension headache, neurodermitis, urticaria, and arythmia ecc.*

Personal characteristics, i.e. continuous anxiety, insecurity, lack of self-confidence, depressiveness, phobia of problem solving, have been linked with chronic dizziness.

Unadapted behavioural patterns (overeating, reduction of physical activity, unsettled sexual life).

Other or nonspecific behavioural patterns, i.e. interpersonal, cultural and spiritual factors.

The criteria of the International Classification of Illnesses and Health Problems, tenth revision (MKB-10) are more general, and are related to the psychological and behavioural factors linked with disorders or illnesses not classified in the chapter of psychiatry but in other chapters of somatic medicine. The psychiatric diagnostic category F54 is to be used when the influence of the psychological and behavioural factors on somatic disorders or illnesses is considered significant for the appearance and course of the somatic disorder [12]. It is the question of long lasting, mild psychological factors as worry, emotional conflict, anxiety, depressiveness, isolation, which cannot be classified by themselves, either in the group of mental or behavioural disorders in MKB10. Chronic dizziness related to the psychological and somatic factors which are in a changeable interrelation together responsible for the appearance, deterioration, gravity and duration of the disorder can be classified in the psychiatric diagnostic category F54 when the influence of the psychological and behavioural factors is considered significant [12].

From the above mentioned psychologic-psychiatric factors influencing the occurrence of the illness excluded are the following mental disorders with somatic symptoms:

1. classic mental disorders with somatic symptoms in the clinical picture, i.e. conversive disorders in which the somatic symptoms are caused by a psychological conflict;
2. Somatic disorders in which there is no organic basis for the somatic symptoms;
3. Hypochondria, when the patient expresses an exaggerated worry for his/her health;
4. Mental disorders with somatic symptoms, i.e. dystimic disorders associated with the somatic symptoms like muscle weakness, fatigue, exhaustion;
5. Drug abuse and dependency with somatic symptoms (i.e. cough in smokers, fat infiltration in the liver because of the alcohol abuse).

A review of somatoform disorders is indispensable for the evaluation of the concept of chronic subjective dizziness. The fourth edition of DSM-IV-TR and the tenth edition of MKB-10 don not have well defined categories for the medically inexplicable somatic symptoms emerging from one organic system, like chest pain without heart damage, chronic dizziness without neurological or vestibular damage and others. They are called undifferentiated somatoforms. These disorders are defined as somatic symptoms lasting for 6 months continuously during most of the time without the evidence of organic damage. The dominant disorder is a persistent, vigorous, anxious and distressing dizzi-

ness that cannot be completely explained by physiological and somatic disorders and is considered to be caused by the stress as a response to an emotional conflict or psychosocial problems. Persistent somatoform dizziness (chronic subjective dizziness) is caused by psychological factors, which have a major role in its appearance, deterioration, maintenance and intensity. It is preoccupation with dizziness without the influence of a somatic illness. The somatic disorder, if it exists, has no significant influence on dizziness [12].

Clinical picture and diagnosis

Table 1 shows the usual characteristics of undifferentiated somatoform disorders using the non-cardiac chest pain as an example. Chronic dizziness has similar characteristics. The two steps approach to somatoform syndromes is considered better than DSM-10 approach [10]. The first step is to identify and precisely describe the somatic symptoms. The second step is to identify the psychiatric comorbidity.

The concept of CSD follows this approach, solves the border diagnostic problems, clears up the definition of somatoform dizziness and enables the treatment of anxious

Table 1. Common characteristics of monosymptomatic somatoform syndromes

Characteristics	Examples (Chest pain)
• Somatic symptoms involve one organ	• chest pain, heart palpitations, fluttering
• Patient seeks help from a specialist of somatic medicine, not a psychiatrist	• internist, cardiologist, primary care doctor
• There are no somatic disorders or they have not been diagnosed	• short attacks of supraventricular tachycardia on holter
• There is a low correlation between symptoms and the somatic state	• there is no correlation between chest pain, EKG and biochemical findings
• Patients have a phobic-anxious or neurotic, not hysteric personality	• specific phobia, panic disorder, generalized anxiety
• High correlation with a variety of anxious disorders	• catastrophic fear of grave illnesses, anticipatory anxiety, phobic avoidance
• Illness is determined by psychological not somatic factors	• chest pain is not correlated with heart disease
• Diagnoses in medical literature are descriptive syndromic	• β-blockers can control somatic symptoms linked with anxiety
• Organ directed treatment has limited effect	• In some cases placebo can also be effective
• Treatment with SSRIs is more effective	• 30% of patients with chest pain not orrelated to organic heart disorder continuously use unnecessary heart medications
• Disorder shows tendency of recurrence and chronicity	

and depressive disorders of these patients [3]. Chronic subjective dizziness can appear together with the cardiovascular, gastrointestinal, neurological, vestibular and other somatic symptoms, which can lead to diagnostic and therapeutic difficulties. The advance in the diagnosis and treatment in one field always has a positive influence on the progress in other fields.

Table 2 contains the diagnostic criteria for CSD [6]. Dominant sensations are persistent unsteadiness, rocking, swaying or fullness in the head, but patients may experience fleeting spins or tilts. They feel unstable while walking, but they do not have ataxia and rarely fall.

Table 2. Criteria and definition of chronic subjective dizziness

Somatic symptoms
Subjective dizziness and unsteadiness: Persistent ($\geq$ 3 months) sensation of dizziness without dizziness, mild headache, grave headache, sense of imbalance lasting for the great part of the day. *Motion hypersensitivity:* chronic oversensitivity ($\geq$ 3 months) to one's own movement which is not direction specific, and to the movement of objects in the environment. *Visual vertigo:* aggravation of symptoms following a complex visual stimulation such as in groceries, or when performing precision visual task (e.g. using a computer).
Neuro-otological evaluation
History and exam: Absence of active physical neuro-otological illnesses, definite medical conditions, or medications that may cause dizziness. History may include episodes of true vertigo or ataxia until the withdrawal of the state causing the vertigo. *Neuroimaging:* Normal radiographic imaging of the brain. *Balance function tests:* Normal or nondiagnostic findings. Included in these criterions are patients who clinically recovered from past neuro-otological illnesses and demonstrate fully compensated vestibular deficits on balance function tests and those with isolated test abnormalities that cannot explain the presenting symptoms.

They are very sensitive to vestibular, visual and proprioceptive motion stimuli and can develop a visual and spatial dependency with a tendency to favour the visual and proprioceptive over vestibular factors in motion and keeping balance. Patients are also intolerant to complex visual environments and demanding visual tasks. However, they do not report diplopia or oscilloscopia. These visual disturbances are defined as visual vertigo, which is proved not to be caused by ocular illnesses [13]. A neuro-otological examination of patients with a possible CSD can discover the signs of an overcome vestibular insult without any evident active oto-neurological disfunction or existing organic cause of dizziness.

Anxiety is responsible for most of the morbidity in somatoform dizziness, but it is not included in the core definition of CSD for diagnostic and therapeutic purposes. The best clinical approach to a patient with chronic dizziness is the evaluation of the neuro-otological state, and only when that is done, the patient can be examined for anxiety and the diagnosis of CSD can be made. Clinicians concentrating on anxiety first may fail to diagnose the existence of an active neuro-otological illness and could prematurely conclude that the only cause of dizziness is a psychiatric disorder [3,4]. Recent advances in the psychology, genetics and neurophysiology of anxious disorders can help in differentiating the somatoform dizziness and various anxious disorders.

Stress and chronic dizziness

It is considered that a particular psychosomatic illness, besides to the stress or intensity, is related to a specific personality and to intrapsychic conflict. Specific psychic stress can be defined as specific for a given personality, or as an unconscious conflict that disrupts the homeostatic equilibrium thus contributing to the development of a psychosomatic illness. Thus, there is a special type of a coronary personality with aggressive impulses, competitive and prone to coronary illnesses, and the opposite personality type, which is calm and relaxed, and not prone to cardiac illnesses [14].

For the majority of experts the non-specific theory of stress is more acceptable than the specific one. Chronic stress, usually associated with changeable anxiety, has physiological correlates that, combined with genetic organic oversensitivity or weakness, make predisposition to psychosomatic illnesses. The sensitive organ can be in any part of the body. The susceptibility or weakness is probably genetic in origin, but the susceptibility can also be acquired (like pulmonary insufficiency in smokers). Various organs and systems can be susceptible, so patients can be: "gastric reactors", "cardiovascular reactors", "skin reactors", "vestibular reactors", etc. [15-17].

Many investigations confirmed the connection between the dizziness, temperament and anxious disorders. Temperaments are innate, highly heritable and stable behavioural patterns. Research on the temperament as a predisposing factor for psychiatric illnesses began in 1950s, but expanded rapidly in the recent years with the ability to link behavioral and physiological processes to genetic polymorphism. Two temperaments - phobic/anxious and neurotic, are characteristic for anxiety disorders. Epidemiological studies showed that the phobic/anxious temperament predisposes to panic and phobic disorders, while neuroticism predisposes to general anxiety disorders and major depression [18].

Neurotic persons are chronically worried, often of a bad mood, and react to stress by psychosomatic symptoms rather than an acute autonomic arousal. This construct of neuroticism is narrower than older formulations, which included an obsessive personality that is a part of PVV [18].

There is a mild association between neuroticism and the short allele of the serotonin transporter gene promoter region (5HTTLPR) [19]. Functional neuroimaging studies found that human homozygotes for the short allele had reduced amygdala and cingulate gyrus gray matter volumes as compared with those for the long allele [20], reduced hyppocampal activity [21] and overactive, but uncoupled frontolimbic feed-back loops that extinguish negative affects. Short allele homozygotes also had a reduction in the serotonin 1A receptors throughout the brain [22,23].

Persons with phobic/anxious temperaments are timid, withdrawn, and prone to exaggeration. They avoid new situations and slowly adapt to them [18]. They have a high cerebrospinal fluid level of corticoctrophin releasing hormone and serum cortisol (24) and disproportionate amygdalar responses [25]. Persons with a single nucleotide polymorphism affecting the gene for catechol-O-methyltransferase had twice more often the prevalence of the panic disorder and phobic behaviour than unaffected persons, but no differences in the levels of neuroticism or rates of generalized anxiety [26].

Characteristics of chronic subjective dizziness

A longitudinal investigation of 122 patients with CSD and anxiety demonstrated three possible patterns of correlation between oto-neurological illnesses and anxious disorders [5].

Otogenic CSD is caused by transitory neuro-otogenic illnesses, such as vestibular neuronitis, and sustains psychological-psychiatric symptoms and illnesses, such as pathologic phobic avoidance, anticipated anxiety and panic attacks, in patients without a pre-morbid anxiety. Pathologic avoidance is defined as avoidance of situations and activities provoking dizziness because of the anticipated anxiety and fear from the consequences. Panic attacks occur in situations incited by dizziness, as well as in those independent of dizziness. Their physical symptoms are considered to be caused by the same pathophysiological mechanisms as anxiety; they are a counterpart of their anxiety. It is considered, nevertheless, that they are less sensitive to psychological manifestations of anxiety. Patients with CSD, with or without anxiety, also demonstrate visual vertigo [27] and somatoform PPV [3].

CSD symptoms can be found in some DSM-IV diagnoses [11], such as panic attack, agoraphobia without panic, specific phobia, anxious disorders, undifferentiated and in other parts classified somatophorm disorders. Pathophysiological processes at the basis of CSD manifest themselves in anxiety, personal characteristics and the response to treatment. The sensation of dizziness in persons with a predisposed character is incited by innate anxious answers (e.g. fight/flight), the increase of awareness of the stimulus causing CSD and anxiety. In the prospective study of the systems threat/stress in organic

CSD 17 from 20 patients had a high-level anxiety during an acute vestibular crisis [7]. They developed oversensitivity to motion and obsession with dizziness in spite the fact that they had physically recovered.

Patients with psychogenic CSD have panic attacks and there are no neuro-otological illnesses in their medical history [5]. It is considered that a panic attack occurs when innate anxious answers are caused by a harmless physical stimulus i.e. transitory unsteadiness, which produces conditioned and exaggerated worrying and expectation of a hypothetic catastrophic outcome with anticipatory anxiety, phobic avoidance and recurrent panic attacks. Therefore, the treatment of the hypothetic and conditioned exaggerated worrying can also be applied to otogenic and psychogenic CSD. In both cases of stimulus conditioning motions are of cardinal importance. The use of visual and proprioceptive, at a higher rate than vestibular, stimuli can cause visual dependency. For the diagnosis and treatment of otogenic and psychogenic subtypes of CSD necessary are only the simple and well-defined pathophysiological mechanisms, and not the two way process in terms of somatophysic and psychosomatic dizziness [4].

In the interactive CSD transitory neuro-otological illnesses, occurring in the preexisting symptoms of anxiety, produce CSD and stimulate anxiety by the prevalence of general anxiety disorders and not panic and phobic disorders [5]. The mechanism stress/conditioning is operable in general anxiety. Interactive CSD is consistent with anxious disorders and is in a closer relationship to the neurotic than to phobic/anxious character. Three observations support this concept: in psychogenic CSD the original panic disorder is significantly linked to the phobic/panic predisposition [6], in otogenic CSD the correlation to the phobic-anxious temperament is not so pronounced, and in various interactive CSDs there is a neurotic and generalized anxious disorder at the same time.

Treatment

Selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of CSD [6]. Significantly more patients with otogenic and psychogenic CSD reach full remission after being treated with SSRI, as compared to those with interactive CSD. There are no controlled treatment trials for CSD, but the use of SSRI, vestibular and balance rehabilitation therapy (VBRT) and cognitive behavioural therapy (CBT) is recommended.

SSRIs were effective in more than 63% of patients with CSD and psychiatric symptoms. Patients with the panic disorder and at least one long allele 5HTTLPR responded better than the short allele homozygotes [8]. A vestibular and balance rehabilitation therapy can be psychologically useful since they lessen the hypersensitivity to motion stimuli, improve confidence in balance and diminish avoidance behaviour [9]. A cognitive behavioural therapy is accepted for anxious and depressive disorders and is therefore ideal for CSD [27].

Chronic dizziness and other medical conditions

Chronic dizziness can be triggered by various causes besides CSD. Symptoms similar to CSD can be caused by vestibular migraena, traumatic brain injuries and dysautonomia. These patients can also have symptoms of anxiety and depression. According to DSM-IV-TR diagnostic criteria psychological factors adversely influencing general health condition can significantly contribute to the development of CSV: psychiatric illnesses like depression, psychological symptoms like anxiety and depressiveness, psychological reactions to stress, personal characteristics (continuous worrying, insecurity, lack of self-confidence, anxiety, depressiveness, phobia of problem solving), non-healthy behavioural patterns (overeating, decrease in physical activity, unsettled sexual life) and other non-specific psychological factors (interpersonal, cultural or spiritual factors) [11,12].

Postconcussional cerebral syndrome. Postconsussional syndrome can be defined by symptoms such as headache, short-term memory loss, sleep disturbances, as well as persistent dizziness and depressiveness [11]. Many patients complaining of dizziness following a traumatic brain insult or whiplash have subjective dizziness and unsteadiness, hypersensitivity to motion cues and visual vertigo, which are similar to CSD [28]. True vertigo and ataxia occur rarely in those suffering a direct vestibular trauma or developing a posttraumatic benign paroxysmal vertigo. Patients with symptoms of CSD have no significant neuro-otological deficiencies. CSD following a traumatic brain injury is, however, associated with poorer psychosocial functioning and a smaller possibility of returning to work [29]. Patients who develop benign positional vertigo or vestibular migraena after a cerebral trauma return to work much faster than those with CSD-like symptoms [28].

In patients with a milder traumatic brain injury or a whiplash dizziness and unsteadiness could not be confirmed objectively. Besides, many patients have financial claims and the possibility of malingering cannot be excluded [30].

Vestibular migraena. This term does not exist in the International Headache Society (IHS) nomenclature for migraine. Nevertheless it is very probable that migraena is the most common cause of recurrent vertigo attacks and subjective dizziness [31]. Migraena is present in 60-80% of patients with a recurrent subjective dizziness without auditory symptoms, but there is no consistent temporal relationship between dizziness and headache. Migraena and anxiety disorders often appear in comorbidity. More than 35-50% of those suffering from migraena suffer also from anxiety, so that it was proposed to name this disorder descriptively as a migraine-anxiety related dizziness [32].

Dysautonomia. A neurovegetative dysfunction leading to a neurocardiogenic syncope and orthostatic intolerance can cause persistent dizziness. Symptoms are very similar

to those of CSD, but their symptoms usually appear or increase during position changing (rising), standing for a long period of time, or after physical exhaustion [33]. Six out of 345 CSD patients treated in the Balance Rehabilitation Center had a dysautonomia [34]. These persons are usually the first to visit cardiologists, otolaryngologists and neurologists.

Conversive disorder, factitious disorder and malingering are rare in patients with somatoform dizziness [27]. Conversive patients have unusual gait and posture abnormalities, while those with a factitious disorder and malingering simulate their symptoms, which are therefore often unconvincing and inconstant.

Conclusion

A close correlation was found between the disorders presenting with "dizziness without dizziness", subjective sensation of unsteadiness and other psychiatric symptoms of oto-neurological disorders and anxiety. The term CSD was introduced and the need of a systematic approach to patients with persistent dizziness without any evident vestibular damage was emphasized. According to newer neurobiological investigations there are three subtypes of CSD: otogenic, psychogenic and interactive.

Better diagnostic possibilities and better insight into the basic pathophysiological processes enabled the definition of the key features of some disorders causing chronic dizziness.

Treatment studies need further evaluation. SSRIs have, however, been undoubtedly effective in the majority of patients, as well as balance rehabilitation and cognitive behavioural therapy.

CSD caused by a vestibular migraena, traumatic brain injury and dysautonomia can cause diagnostic difficulties and can be misdiagnosed as a psychogenic disorder.

References

[1] *Stoudemire A, McDaniel JS.* History, classification, and current trends in psychosomatic medicine. In: Sadock BJ, Sadock VA. eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 7th ed. Vol. 2. Baltimore: Lippincott Williams & Wilkins: 2000:1765.

[2] *Brandt T.* Phobic postural vertigo. Neurology 1996;46:1515-1519.

[3] *Huppert D, Strupp, Rettinger N,* et al. Phobic postural vertigo – a long-term follow-up (5 to 15 years) of106 patients. J Neurol 2005;252:564-569.

[4] *Jacob RG, Furman JM.* Psychiatric consequences of vestibular dysfunction. Curr Opin Neurol 2001;14:41-46.

[5] *Staab JP, Ruckenstein MJ.* Which comes first? Psychogenic dizziness versus otogenic anxiety. Laringoscope 2003;113:1714-1718.

[6] *Staab JP, Ruckenstein MJ.* Chronic dizziness and anxiety: Effect of course of ilness on treatment outcome. Arch Otolaryngol Head Neck Surg 2005;131:675-679.

[7] *Godemann F, Koffroth C, Neu P, Heuser I.* Why does vertigo become chronic after neuropathia vwatibularis? Psychosom Med 2004;66.783-787.

[8] *Staab JP, Ruckenstein MU, Amsterdam JD.* A prospective trial of sertraline for chronic subjective dizziness. Laringoscope 2004;114:1637-1641.

[9] *Pavlou M, Lingesvaran A, Davies RA.* Stimulator based rehabilitation in refractory dizziness. J. Neurol 2004;251:983-995.

[10] *Mayou R, Kirmayer LJ, Simon G.* Somatoform disorders: time for a new aproach in DSM-IV. Am J Psychiatry 2005;162:847-855.

[11] American Psychiatric Association. Diagnostic and Statistical Manuall of Mental Disorders, 4th ed. (DSM-IV). American Psychiatric Association: Washington DC 1994.

[12] World Health Organisation. Classification of Mental and Behavioral Disorders 10th ed. World Helth Organisation and Longman Group Limited: Geneve 1994.

[13] *Bronstein AM.* Vision and vertigo: some visual aspects of vestibular disorders. J Neurol 2004;251:381-387.

[14] *Feifel H, Strack S, Nagy VT.* Degre of life-threat and differential use of coping modes. J Psychol Res. 1987;31:91.

[15] *Nakano K.* Application of self-control procedures to modofying type A behavior. Psychol Rec. 1996;46:595.

[16] *Kaplan HI, Sadock BI.* Pocket handbook of clinical psychiatry, 3rd ed. Lippincott Williams and Wilkins, Phyladelphia 2001.

[17] *Buljan D, Buljan M, Šitum M.* Psychodermatology: A Brief Review for Clinicians. Psychiatria Danubina, 2005; Vol. 17, No. 1-2, 76-83, Zagreb

[18] *Fox NA,Henderson HA, Marshal PJ.* Bihavioral inhibition: linking biology and behavior within a developmental framework. Annu REv Psychol 2005;56:235-262.

[19] *Schinka JA, Busch RM, Robichaux Keene N.* A meta-analysis of the association between the serotonin transporter gene polymorfism (5-HTTLPR) and trait anxiaty. Molecular Psychiatry 2004;9:197-202. (Analiza više studija upućuje na hipotetičku povezanost između gena i temperamenta.)

[20] *Pazawas L, Mayer-Lindenberg A, Drabant EM.* 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 2005;8:828-834. (Primjer suvremenih imiđing studija koje pokušavaju povezati funkciju mozga i genetiku u anksioznim poremećajima)

[21] *Gallinat J, Strohle A, Lang UE.* Association of human hippocampal neurocemistry, serotonin transporter genetic variation, and anxiety. Neuroimage 2005;26:123-131.

[22] *Graff-Guerrero A, De la Fuente-Sandoval C, Camarena B.* Frontal and limbic metabolic differences in subjects selected according to genetic variation of the SLC6A4 gene polymorphism. Neuroimage 2005;25:1197-1204.

[23] *David SP, Murty NV, Rabiner EA.* A functional genetic variation of the serotonin (5-HT) transporter affects 5-HT1A receptor binding in humans. J Neurosci 2005;25:2586-2590.

[24] *Erickson K, Gabry KE, Schulkin J.* Social withdrawal behaviors in nonhuman primates and changes in neuroendocrine and monoamine concentrations during a separation paradigm. Dev Psychobiol 2005;47:196-197.

[25] *Schwartz CE, Wright CI, Shin LM.* Inhibited and uninhibited infants „grown up": adult amygdalar response to novelty. Science 2003;300:1952-1953.

[26] *Olsen CA, Anney RJ, Lotfi-Miri M.* Association between the COMT Val158Met polymorphism and propensity to anxiety in an Australian population-based longitudinal study of adolescent health. Psychiatr Genet 2005;15:109-115.

[27] *Staab JP, Ruckenstein MJ.* A psychiatric approach to chronic dizziness. Psychiatric Annals 2005;35:330-338.

[28] *Hoffer ME, Gottshall KR, Moore R.* Characterizing and treating dizziness after mild head trauma. Otol Neurotol 2004;25:135-138.

[29] *Chamelia L, Feinstein A.* Outcome after mild to moderate traumatic brain injury: the role of dizziness. Arch Phys Med Rehabil 2004;85:1662-1666.

[30] *Kaufman KR, Brey RH, Chou LS.* Comperison of subjective and objective measurements of balance disorders following traumatic brain injury. Med Eng Phys 2005;22.

[31] *Brantberg K, Trees N, Baloh RW.* Migraine-associated vertigo. Acta Otolaryngol 2005; 125:276-279.

[32] *Fuman JM, Balaban CD, Jacob RG, Marcus DA.* Migraine-anxiaty related dizziness (MARD): a new disorder? J Neurol Neurosurg Psychiaty 2005;76:1-8.

[33] *Staab JP, Ruckenstein MJ, Solomon D, Shepard NT.* Exertional dizziness and autonomic dysregulation. Laryngoscope 2002; 112:1346-1350.

[34] The Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatement) of syncocpe-update 2004. Europace 2004;6:467-537.

Sažetak

Psihološko-psihijatrijski čimbenici kronične vrtoglavice

Istraživanja su pokazala da postoji povezanost između nekoliko neuro-otoloških kliničkih stanja koja se javljaju subjektivnim osjećajem nestabilnosti i vrtoglavice uz anksioznost i druge psihijatrijske simptome.

Pojam kronične subjektivne vrtoglavice ponudio je sustavni pristup bolesnicima sa ustrajnom vrtoglavicom koja nije uzrokovana očitim patofiziološkim vestibularnim oštećenjem. Sukladno sa novim neurobiološkim istraživanjima postoje tri podtipa kronične subjektivne vrtoglavice (otogeni, psihogeni, interaktivni) koje čine fizički i psihološki simptomi. Danas postoji veća dijagnostička točnost i uvid u temeljne patofiziološke procese vestibularne migrene, postkontuzijskog sindroma mozga i distonije autonomnog živčanog sustava, koji mogu prouzročiti simptome nalik kroničnoj subjektivnoj vrtoglavici.

Selektivni inhibitori ponovne pohrane serotonina-SIPPSa, rehabilitacijska terapija ravnoteže i kognitivno-bihevioralna terapija pokazuju ograničenu, ali korisnu učinkovitost u liječenju kronične subjektivne vrtoglavice.

Ključne riječi: kronična subjektivna vrtoglavica, neuro-otološka stanja, anksioznost, fobičnost

UDK 616.084.44:616.28-008.5+616.857
Original scientific paper
Received: 17 January 2007
Accepted: 25 April 2007

PREVALENCE OF VERTIGO AND DIZZINESS IN MIGRAINE PATIENTS AND NON-HEADACHE SUBJECTS

Vlasta Vuković*, Davor Plavec**, Ivana Galinović*, Arijana Lovrenčić-Huzjan*, Vida Demarin*

* University Department of Neurology, Sestre Milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
**Childrens Hospital Srebrnjak, Research Department, Zagreb, Croatia

Summary

The aim of this study was to assess the prevalence of vertigo and dizziness in patients with migraine as compared to the control group without a headache. A total of 327 patients with migraine and the control group of 324 subjects were evaluated for vertiginous signs and dizziness, time of onset of the symptoms, frequency of the symptoms and temporal association of the symptoms with the migraine attack. More than half of the migraine patients had in their lifetime experienced a sense of vertigo or dizziness: 169 patients (51.7%), and 102 subjects (31.5%) in the control group. Vertigo symptoms were associated with a migraine attack always in 38 (22.5%), sometimes in 38 (22.5%) and were not associated in 93 (55.0%) patients. Patients having migraine with aura significantly more often have migraine attacks associated with symptoms of vertigo or dizziness. Our study, together with other similar studies, suggests that migraine should be considered in the differential diagnosis of vertigo.

Key words: Vertigo, headache, migraine, migraine with aura, migraine without aura

INTRODUCTION

Headache is one of the most frequent complaints in the general practice, and migraine is the second most frequent primary headache [1]. Many patients with migraine

Correspondence to: Vlasta Vuković, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: vlasta9vuk@zg.t-com.hr

complain because of dizziness, sense of disequilibrium and head motion intolerance or a more specific vertigo. Recently, migrainous vertigo was recognized as a frequent cause of recurrent vertigo in patients presenting to specialized dizziness and headache clinics [2,3]. Migraine headaches and vestibular vertigo concur in the general population about three times more often than expected by chance [4]. An epidemiologic study carried out in the general population of adults showed that the lifetime prevalence of migrainous vertigo is 0.98% and 1 year prevalence 0.89% [4]. Since migrainous vertigo is a relatively frequent disorder it also has a considerable impact both on personal and social level [4].

The aim of this study was to assess the prevalence of vertigo and dizziness in the patients with migraine as compared with the control group.

Methods

A total of 327 consecutive patients with migraine with or without aura presenting to the Headache clinic were clinically assessed between March 2005 and December 2006.

The control group consisted of 324 subjects who were not diagnosed with migraine or frequent headaches; they were chosen randomly outside the hospital between March and December 2006. A medical doctor (I.G.) working as a research fellow at the Neurology Department was trained to perform a face-to-face interview to select subjects for the control group.

Both groups were evaluated for vertiginous signs and dizziness, the time of the onset of symptoms, frequency of the symptoms and temporal association of the symptoms with the migraine attack. Migraine with or without aura was diagnosed according to the revised IHS criteria [5] during a clinical interview by a neurologist, (headache specialist V. V.); and a clinical neurological examination was included. When investigating for the presence of dizziness, the study group and the control group were specifically asked to describe their symptoms; dizziness symptoms implying non-vestibular dizziness such as orthostatic hypotension were not included. Vertigo was not counted as an aura symptom for the diagnosis of migraine with aura. None of these patients fulfilled the IHS criteria for basilar migraine. The prevalence of vertigo and dizziness was assessed as lifetime prevalence. The group of patients with migraine who had experienced vertiginous symptoms in their lifetime are referred to as the MVL group (Migraine Vertigo Lifetime), and subjects in the control group who experienced vertiginous symptoms in their lifetime as the CVL group (Control Vertigo Lifetime). The migraine patients who met the diagnostic criteria for migrainous vertigo are referred to as the MV group (definite migrainous vertigo). Although the diagnostic category of probable migrainous vertigo was proposed for the patients who did not entirely fulfill the criteria for migrainous vertigo [2], in this study only the patients that met the proposed diagnostic criteria for definite migrainous vertigo are referred to as the MV group.

The diagnosis of definite migrainous vertigo was based on the following criteria [2]:

1. Episodic vestibular symptoms of at least moderate severity (rotational vertigo, other illusory self or object motion, positional vertigo, head motion intolerance - sensation of imbalance or illusory self or object motion that is provoked by head motion).
2. Migraine according to the IHS criteria.
3. At least one of the following migrainous symptoms during at least two vertiginous attacks: migrainous headache, photophobia, phonophobia, visual or other auras
4. Other causes ruled out by appropriate investigations.

Further diagnostic works such as extracranial color Doppler, transcranial Doppler, brainstem auditory-evoked potentials, MRI, vestibular tests (calorimetrics) and laboratory tests were performed individually when considered appropriate.

Statistical analysis was performed using the the χ^2 test and Fisher's exact test to compare proportions. Mean and SD were used to describe continuous variables, and Student's t-test to compare them between different groups and subgroups. STATISTICA release 6.0 (StatSoft Inc., Tulsa, OK, USA) was used for all analyses. $P<0.05$ was considered significant.

Results

The patients in the migraine group and the control group did not differ significantly in age or gender. There was a preponderance of female patients in the sample of the migraine group, 289 (88.4%) women, 38 (11.6%) men, as was in the control group, 263 (81.2%) women and 61 (18.8%) men; $P=0.065$.

Mean age of the patients with migraine was 39.9±12.2 (39.9±12.3 for women, 40.5±11.5 for men); mean age of the control group was 39.8±12.1 (39.5±11.5 for women and 43.0±11.5 for men); $P=0.86$.

The mean number of migraine headaches per month was 3.4±3.3; 3.3±3.3 in women and 3.7±3.0 in men; $P=0.48$.

Slightly over a half of the migraine patients had in their lifetime experienced a sense of vertigo or dizziness (MVL) - 169 (51.7%), as compared with 102 (31.5%) in the control group (CVL); $P<0.0001$.

In the MVL group the onset of vertiginous symptoms was earlier than in the CVL group: vertigo or dizziness began 14.6±19.2 years prior to our testing in the MVL group, and 9.9±17.0 years ago in the CVL group; $P=0.0011$. Furthermore, the patients were asked to define the time of onset of vertiginous symptoms and they stated as follows (MVL vs. CVL): a) from childhood in 8 (2.45%) vs. 6 (1.85%) patients; b) symptoms began later in life in 67 (20.49%) vs. 54 (16.67%) patients; c) symptoms began just recently in 94 (28.75) vs. 42 (12.96%) patients; d) 158 (48.32%) vs. 222 (68.5%) patients never had such symptoms, $P<0.0001$.

There was no significant difference in the proportion of the patients in the MVL group and CVL group who had symptoms of dizziness or vertigo; in the MVL group 113 (34.56%) patients stated that they had dizziness (head motion intolerance – sensation of imbalance or illusory self or object motion that is provoked by head motion) vs. 66 (20.37%) patients in the CVL group, while 56 (17.13%) MVL patients stated that they had a sense of vertigo (rotational vertigo, other illusory self or object motion, positional vertigo) vs. 36 (11.1%) patients in the CVL group, $P=0.716$.

There was no statistical difference between the MVL and CVL groups regarding the appearance of symptoms: vertigo or dizziness appeared only in relation with the movement of the head in the migraine group in 61 (18.65%) patients vs. 39 (12.04%) in the control group,, and during movement of the head and in a steady state in the MVL group in 100 (30.58%) patients vs. 58 (17.9%) in the CVL group; $P=0.395$.

There was no statistical difference between the MVL and CVL groups regarding the frequency of attacks: every or every other day in 14 (4.28%) vs. 10 (3.09%) patients, couple of times per month in 85 (25.99%) vs. 41 (12.66%) patients and one to three attacks of vertigo during the lifetime in 64 (19.57%) vs. 50 (15.43%) patients; $P=0.185$. Results regarding the differences between the MVL and CVL groups are shown in Table 1.

Table 1. Differences between the MVL and CVL groups of patients

		MVL (%)	CVL (%)	*P*-values
Number of individuals		169 (51.7)	102 (31.5)	*<0.0001*
Individuals with vertigo		56 (17.13)	36 (11.1)	*<0.716*
Individuals with dizziness		113 (34.56)	66 (20.37)	
Appearance of symptoms in relation to head movement		61 (18.65)	39 (12.04)	*<0.395*
Appearance of symptoms during head movement and in a motionless state		100 (30.58)	58 (17.9)	
Frequency of attacks	Every or every other day	14 (4.28)	10 (3.09)	*<0.185*
	A couple of times a month	85 (25.99)	41 (12.66)	
	1-3 attacks in the lifetime	64 (19.57)	50 (15.43)	

MVL: migraine patients who have experienced a sense of vertigo or dizziness in their lifetime
CVL: individuals in the control group who have experienced a sense of vertigo or dizziness in their lifetime

Vertigo symptoms were associated with a migraine attack: always in 38 (22.5%), sometimes in 38 (22.5%) and were not associated in 93 (55.0%) patients. According to the proposed criteria 76 (23.2%) migraine patients from our study met the criteria for definite migrainous vertigo.

Migraine without aura (MO) was diagnosed in 199 (60.9%) patients, while 128 (39.1%) had migraine with aura (MA); patients having MA were regarded as such if they had at least one aura sign. Signs of visual aura were present in 111 (86.7%) MA patients: scintillating scotomata in 73 (57.0%), partial loss of vision in 17 (13.3%), and "vague" vision in 21 (16.4%) patients. Paresthesiae in the arm or face unilaterally were present in 5 (3.9%) patients and speech problems in 11 (8.6%).

The patients with MA had significantly more often migraine attacks in association with symptoms of vertigo or dizziness: a) MA always in 19 (14.84%) vs. MO in 19 (9.55%) patients or b) sometimes MA in 28 (21.88%) vs. MO in 10 (5.03%) patients; $P<0.0001$. The results regarding migraine patients with or without aura are shown in Table 2.

Table 2. Differences between migraine patients with or without aura.

	Migraine with aura (%)	Migraine without aura (%)	*P*-value
Number of individuals	128 (39.1)	199 (60.9)	
Always migraine with vertigo/dizziness	19 (14.84)	19 (9.55)	*<0.0001*
Sometimes migraine with vertigo/dizziness	28 (21.88)	10 (5.03)	

Discussion

Studies investigating migraine and vertigo have shown data that support the observation that there is an association between migraine and vertigo, which is not a pure coincidence. However, the epidemiologic evidence for this association from control studies is not as sufficient as one might expect since migraine has long been associated with vertigo [6,7].

The prevalence of migraine worldwide ranges from 6 to 18% in women and 3-6% in men [8-11). Population studies show that the prevalence of dizziness in the general population is over 20% [12] and the lifetime prevalence of vertigo is 7% [13]. A neurology survey revealed that 3.2% of the general population had both vestibular vertigo and migraine; in that study 1% of the population was diagnosed with migrainous vertigo [4). 1% of the population could be expected to have a concurrence of vertigo and migraine by chance, if the lifetime prevalence of 7% for vertigo and 16% for migraine were taken into account [11,13]; so authors [4] suggested that the remaining 1% out of the original 3.2% might have probable migrainous vertigo or other vestibular disorders, including BPPV or Meniere's disease, since both were associated with migraine [14-16). In one study a high proportion of patients (81%) diagnosed with the «vestibular Meniere's

disease» had migraine, however, a certain number of these patients might in fact had had migrainous vertigo [17].

Vertigo was found to be three times more common in the migraine patients than in the control group: vertigo occurred in 24-27% of the migraine patients, as compared with 8-10% in the control group [6,18]. However, these studies did not use the IHS criteria for migraine. Our study included only the patients with migraine diagnosed according to the revised IHS criteria. The results of our study showed that a significant proportion of the migraine patients experienced a sense of vertigo or dizziness in their lifetime: 51.7%, as compared with 31.5% in the control group ($P=0.001$).

A high prevalence of migraine of 30 to 61% was found in the patients with vertigo [19-21]. The lifetime prevalence of definite migrainous vertigo was 7% in the dizziness clinic group and 9% in the migraine clinic group; probable migrainous vertigo was found in a further 4% of the patients in the dizziness clinic [2]. In a retrospective study, 6% of the patients presenting to the dizziness clinic had «vestibular migraine» [22].

In our study vertiginous symptoms began earlier in life in the MVL patients than in the control group with vertigo (14.6 ± 19.2 years ago vs. 9.9 ± 17.0; $P=0.0011$); this may reflect the common pathophysiological pathways in migraine and vertigo.

In our study the proportion of women in the MVL and CVL groups did not differ significantly; from a different point of view, the proportion of women did not differ among migraineurs with or without dizziness, suggesting that the female preponderance among the patients with migrainous vertigo reflects the female preponderance among migraineurs in general [4].

There was no significant difference between the proportion of the patients in the MVL group and the CVL group who had symptoms of dizziness or vertigo; dizziness was reported more frequently (34.56%) than vertigo (17.13%) in the MVL group, as was in the CVL group (20.27% reported dizziness and 11.1% reported vertigo). Since either vertigo or dizziness provoked by head motion are required for the diagnosis of migrainous vertigo, having either of these symptoms does not make any difference. These data reflect only the preponderance of dizziness in the general population as observed in studies [12,13].

There was no statistical difference between the MVL group and the CVL group regarding the appearance of symptoms: 30.58% of the MVL patients had symptoms in a motionless state or during head movement, as compared with 17.9% in the control group, and symptoms were present only during head movement in 18.65% of the patients in the MVL group, as compared with 12.04% in the control group; $P=0.395$. These data show that more migraine patients have dizziness or vertigo even in a motionless state along with head movement as compared with the control group, which might indicate that in the migraine patients additional pathophysiological pathways may

play a role in provoking (and maintaining) such symptoms. The vertical vestibulo-ocular reflex plays an important role in the visual stabilization during daily activities such as normal ambulation; in the patients with a migraine aura and dizziness an abnormal vertical vestibulo-ocular reflex at higher head movement frequencies has been found [3].

The majority of the MVL and CVL patients have vertiginous symptoms a couple of times per month, although there was no statistical difference between the two groups regarding the frequency of attacks: every or every other day in 14 (4.28%) vs. 10 (3.09%) patients, a couple of times per month in 85 (25.99%) vs. 41 (12.66%) patients and one to three attacks of vertigo in the lifetime in 64 (19.57%) vs. 50 (15.43%) patients respectively; $P=0.185$.

Vertiginous symptoms may last from seconds, minutes, hours, to even more than a day, and in some patients occur on a daily basis [2, 24]. One study revealed that the majority of patients have short lasting dizziness attacks (less than 5 minutes) and a minority over a day lasting dizziness (3%), which is probably why only one third of the participants consulted a doctor because of their vertigo [4); this may reflect the causes of underdiagnosis of migrainous vertigo in the migraine population.

Among the patients with migrainous vertigo, vertigo was regularly associated with migrainous headache in 24% to 45% of patients; in 48% of patients vertigo occurred with or without a headache and in two patients a headache and vertigo never occurred together [2,4]. Similar findings were shown in other studies [6,26], as well as in our study: vertigo symptoms were associated with a migraine attack always in 38 (22.5%), sometimes in 38 (22.5%) and were not associated in 93 (55.0%) patients. This means that the lifetime prevalence of migrainous vertigo is 23.2% in the population of our migraineurs according to the proposed criteria.

A relatively high proportion (33%) of patients with migrainous vertigo report visual auras, which is not significantly higher than in the group of the dizziness free migraineurs (26%) [4]. These results regarding a visual aura in the patients with migrainous vertigo are very similar to ours. Significantly more often the MA patients have migraine in association with symptoms of vertigo or dizziness: always 19 MA (14.84%) vs.19 MO (9.55%) patients, or sometimes 28 MA (21.88%) vs. 10 MO (5.03%) patients; $P<0.0001$.

Migrainous vertigo is not sufficiently recognized among clinicians. The diagnosis of migrainous vertigo is not easy, since there may be an overlap of symptoms of different disorders. Migrainous vertigo may present as episodic positional vertigo, Factors that help to distinguish migrainous positional vertigo from BPPV include short-duration symptomatic episodes and frequent recurrences, manifestation early in life, migrainous symptoms during episodes with positional vertigo and atypical positional nystagmus

[26]. Another study revealed spontaneous rotational vertigo in 67% and positional vertigo in 24% of patients with migrainous vertigo [4].

A study among the patients presenting to a neurology dizziness clinic showed that 31% had a benign paroxysmal positional vertigo (BPPV), 20% psychogenic vertigo, 7% definite and 4% probable migrainous vertigo, 7% vestibulopathy of unknown origin, 7% neurological gait disorder, 5% Meniere's disease, 5% orthostatic hypotension, 4% central vestibular syndromes, 3% vestibular neuritis [2]. In this study the patients with non-traumatic BPPV of the posterior semicircular canal had a significantly higher prevalence of migraine than the control patients.

In the IHS classification the criteria for migrainous vertigo are still lacking. In children benign paroxysmal vertigo of childhood is recognized and accepted as a separate entity within the IHS classification; it affects 2.6% of school children according to a population based study [27]. Basilar migraine is recognized as a category of migraine with aura, requiring at least two symptoms originating in the posterior circulation territory which should last between 5 and 60 minutes to fulfill the aura criteria; whereas patients with migrainous vertigo have only vestibular symptoms, which puts them in a distinct category. So far, most patients with vertiginous symptoms in epidemiological studies have shown symptoms that were not strictly in the temporal relation required for an aura, but occurred in various time lengths.

The diagnosis of migrainous vertigo should probably be a distinct entity, since the majority of patients with definite migrainous vertigo do not meet all the IHS criteria for migraine with aura or basilar migraine. Usually the temporal distribution and length of symptoms do not fulfill the IHS criteria for migraine with aura. Studies have shown that the diagnosis of migrainous vertigo should be given only in cases where all other possible causes of vertigo have been excluded [2].

A reason for the underdiagnosis of migrainous vertigo may be in part due to the fact that some patients, when their migraine is accompanied by vertigo, have an attenuated headache as compared with their usual migraine attacks [22]. The diagnosis of migrainous vertigo in such cases should rely on the presence of accompanying migraine symptoms, such as photophobia or phonophobia, which are related to the vertiginous attacks of migraine. Detailed history should be taken in patients with migraine and vertiginous symptoms in order to establish a connection, if one exists. Making a correct diagnosis in such cases might save the doctor and the patient time, as well as health insurance money, because the unnecessary diagnostic tests can be avoided. In most cases a comprehensive diary could help to establish weather migraine and vertigo are related or are separate entities in an individual. Migraine diaries have been proved to help establish a correct diagnosis [28,29], however, similar diaries for the diagnosis of vertiginous disorders are not a standard recommendation in clinical work. Migraine should be easy to diagnose

since strict diagnostic IHS criteria are proposed [5], and, if diagnostic uncertainties exist, the diagnosis should be easier to establish after reviewing a diary. However, diagnosing a vertiginous disorder is not always as easy, and, unlike for migraine where no specific diagnostic work-up is warranted, especially in typical cases, in most patients with vertigo certain diagnostic tests should be done in order to exclude more serious causes. In the remaining patients who meet the proposed criteria for definite migrainous vertigo, a diagnosis can be set. Even if in some patients not all criteria can be fulfilled, a diagnosis of «probable migrainous vertigo» can be set in order to help guide the therapeutic course [2]. Therefore, physicians dealing with patients with migraine and vertigo should keep in mind not only the IHS criteria [5] and the guidelines for the treatment of migraine headaches [30], but should also be aware of a relatively high percentage of patients that might in fact have „migrainous vertigo", rather than two separate disorders, i.e. migraine and vertigo.

There are studies in favor of the fact that migraine and vertiginous symptoms are in association which have shown that preventive antimigraine therapy is often useful in such patients [24,25,31].

The mechanisms of migraine pathophysiology are still not understood; perhaps patients with migrainous vertigo share common pathophysiological pathways which may help to elucidate the nature of migraine attacks, at least in the subgroup of patients with migrainous vertigo. Hypoplasia of a vertebral artery is frequently found in migraine patients, especially in migraine with aura, which might at least in part play a role in migraine pathophysiology [32]. It is well accepted that migraine is a heterogeneous disorder. Specific forms of migraine, such as familial hemiplegic migraine, are linked with mutations on the gene for the á1 subunit component of a voltage-gated calcium channel [33]. In some patients with a cerebellar dysfunction a neuronal calcium channelopathy can be detected [34] and because the cerebellum and the vestibular system are connected, these patients often have symptoms originating from the vestibular system. A genetic study performed on 14 genetically unrelated patients with migrainous vertigo did not gain evidence that genes causing familial hemiplegic migraine and episodic ataxia type 2 represent major susceptibility loci for MV [35]. Extensive genetic work-up is needed, especially in patients with migrainous vertigo, in order to try to establish the existence of a genetic background if such exists. First of all, other causes of vertigo should be excluded, and even then in a relatively small proportion of patients (12.5 to 16.7%) with migraine and vertigo an abnormal vestibular function can be found [21,24]. The search for a genetic pattern will not be easy since patients with vertiginous symptoms are probably as heterogeneous as are migraine patients. Still, research is worth a try in a subgroup of such patients.

In some studies a significant association between migrainous vertigo and coronary heart diseases, and marginally with diabetes, was found [4], while in others a higher

cardiovascular profile was found among adult migraineurs, especially with migraine with aura [36], however the causal relationship remained unknown.

The results of this study show that migrainous vertigo affects a significant proportion of patients with migraine, and are in favor of the association between dizziness/vertigo and migraine. Although there is no «gold standard» for the diagnosis of migrainous vertigo and further research is needed, we hope that the results of this study will help to establish the criteria for migrainous vertigo that will be helpful to clinicians in their everyday work with patients with migraine and vertigo.

In conclusion, a significant number of migraine patients have dizziness or vertiginous symptoms; however, vertigo can only be attributed to migraine after other causes have been excluded. Our study, together with other similar studies, suggests that migraine should be considered in the differential diagnosis of isolated vertigo of unknown cause.

References

[1] *Demarin V.* Glavobolja-najčešća dijagnoza u medicini. U:Znanstveni pristup dijagnostici i terapiji glavobolja. Ur. Demarin V. Hrvatska akademija znanosti i umjetnosti, razred za medicinske znanosti. Zagreb 2005:9-15.

[2] *Neuhauser H, Leopold M, von Brevern M, Arnold G, Lempert T.* The interrelations of migraine, vertigo and migrainous vertigo. Neurology 2001;56:436-441.

[3] *Brandt T.* A chameleon among the episodic vertigo syndromes: «migrainous vertigo» or «vestibular migraine». Cephalalgia 2004;24:81-82.

[4] *Neuhauser HK, Radtke A, von Brevern M, Feldman M, Lezius F, Ziese T, Lempert T.* Migrainous vertigo: prevalence and impact on quality of life. Neurology 2006;26:1028-1033.

[5] The International Classification of Headache Disorders, 2nd edition. Cephalalgia 2004;24 (suppl 1):1-160.

[6] *Kayan A, Hood JD.* Neuro-otological manifestations of Migraine. Brain 1984;107:1123-1142.

[7] *Moretti G, Manzoni GC, Caffarra P, Parma M.* «Benign recurrent vertigo» and its connection with migraine. Headache 1980, 20:344-346.

[8] *Rasmussen BK, Stewart WF.* Epidemiology of migraine. In: Olesen J, Tfelt-HansenP, Welch KMA eds. The Headachs. 2nd ed. Philadelphia:Lippincott Williams & Wilkins; 2000:227-233.

[9] *Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M.* Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache 2001;41:646-657.

[10] *Morillo LE, Alarcon F, Aranaga N,* et al. Prevalence of migraine in Latin America. Headache 2005;45:106-117.

[11] *Rasmussen BK, Jensen R, Schroll M, Olesen J.* Epidemiology of headache in a general population-a prevalence study. J Clin Epidemiol 1991;44:1147-1157.

[12] *Kroenke K, Price RK.* Symptoms in the community. Prevalence, classification and psychiatric comorbidity. Arch Intern Med 1993;153:2474-2480.

[13] *Neuhauser HK, von Brevern M, Radtke A,* et al. Epidemiology of vestibular vertigo: a neurotological survey of the general population. Neurology 2005;65:898-904.

[14] *Ishiyama A, Jacobson KM, Baloh RW.* Migriane and benign postitonal vertigo. Ann Otol Rhinol Laryngol 2000;109:377-380.

[15] *Radtke A, Lempert T, Gresty MA, Brookes GB, Bronstein AM, Neuhauser H.* Migriane and Meniere's disease: is there a link? Neurology 2002;59:1700-1704.

[16] *Lempert T, Leopold M, von Brevern M, Neuhauser H.* Migraine and benign positional vertigo. Ann Otol Rhinol Laryngol 2000;109:1176.

[17] *Rassekh CH, Harker LA.* The prevalence of migraine in Meniere's disease. Laryngoscope 1992;102:135-138.

[18] *Kuritzky A, Ziegler DK, Hassanein R.* Vertigo, motion sickness nad migraine. Headache 1981;21:227-231.

[19] *Aragones JM, Fortes-Rego J, Fuste J, Cardozo A.* Migraine:an alternative in the diagnosis of unclassified vertigo. Headache 1993;33:125-128.

[20] *Savundra PA, Carroll JD, Davies RA, Luxon LM.* Migraine associated vertigo. Cephalalgia 1997;17:505-510.

[21] *Lee H, Sohn SI, Jung DK, Cho YW, llm JG, Yi SD, Yi HA.* Migriane and isolated recurrent vertigo of unknown cause. Neurol Res 2002;24:663-665.

[22] *Dietrich M, Brandt T.* Episodic vertigo related to migraine (90 cases):vestibular migraine? J Neurol 1999;246:883-892.

[23] *Helm MR.* Vestibulo-ocular reflex abnormalities in patients with migraine. Headache 2005;45:332-336.

[24] *Waterston J.* Chronic migrainous vertigo. J Clin Neurosci 2004;11:384-388.

[25] *Cass SP, Ankerstjerne JKP, Yetiser S, Furman J, Balaban C, Aydogan B.* Migraine-related vestibulopathy. Ann Otol Rhinol Laryngol 1997;106:182-189.

[26] *von Brevern M, Radtke A, Clarke AH, Lempert T.* Migrainous vertigo presenting as episodic positional vertigo. Neurology 2004;62:469-472.

[27] *Abu-Arafeh I, Russell G.* Parxysmal vertigo as a migraine equivalent in children: a population-based study. Cephalalgia 1995;15:22-25.

[28] *Phillip D, Lyngberg AC, Jensen R.* Assessment of headache diagnosis. A comparative population study of a clinical interview with a diagnostic headache diary. Cephalalgia 2007;27:1-8.

[29] *Lipton RB, Cady RK, Stewart WF, Wilks K, Hall C.* Diagnostic lessons from the Spectrum study. Neurology 2002;58 (suppl 6):27-31.

[30] *Demarin V, Vuković V, Lovrenčić-Huzjan A, Lušić I, Jančuljak D,Wilheim K, Zurak N.* Evidence based guidelines for treatment of primary headaches. Report of The Croatian Neurovascular Society. Acta Clin Croat 2005;44:139-183.

[31] *Baloh RW.* Neurotology of migraine. Headache 1997;37:615-621.

[32] *Lovrenčić- Huzjan A, Demarin V, Rundek T, Vuković V.* Role of vertebral artery hypoplasia in migraine. Cephalalgia 1998;18:684-686

[33] *Ophoff RA, Terwindt GM, Vergouwe MN,* et al. Familial hemiplegic migraine and episodic ataxia type 2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 1996;87:543-552.

[34] *Montagna P.* Molecular genetics of migraine headaches: a review. Cephalalgia 2000;20:3-14.

[35] *von Brevern M, Shankar A, Wiste A, Siegel A, Radtke A, Sander T, Escayg A.* Migrainous vertigo: mutation analysis of the candidate genes CACNA1A, ATP1A2, SCN1A and CACNB4. Headache 2006;46:1136-1141.

[36] *Scher AI, Terwindt GM, Picavet HSJ, Verschuren WMM, ferrari MD, Launer LJ.* Cardiovascular risk factors and igraine. Neurology 2005;64:614-620.

Sažetak

Prevalencija vertiga u bolesnika s migrenom i u osoba bez glavobolje

Cilj ovog istraživanja bio je procijeniti prevalenciju vertiga u bolesnika s migrenom i u kontrolnoj skupini osoba bez glavobolja. Ukupno je 327 bolesnika s migrenom i 324 osobe u kontrolnoj skupini ispitano da li imaju simptome vrtoglavice, o vremenu nastanka simptoma, učestalosti simptoma i vremenskoj povezanosti simptoma s napadom migrene. Više od polovine bolesnika s migrenom je imalo osjećaj vrtoglavice: 169 bolesnika (51.7%), a u kontrolnoj skupini 102 osobe (31.5%). Simptomi vrtoglavice bili su povezani s napadom migrene uvijek u 38 bolesnika (22.5%), ponekad u 38 bolesnika (22.5%), a nisu bili povezani u 93 bolesnika (55.0%). Bolesnici koji imaju migrenu s aurom značajno češće imaju napade migrene povezane sa simptomima vrtoglavice. Ovo istraživanje, kao i ostala slična istraživanja, pokazuje da treba uzeti u obzir migrenu u diferencijalnoj dijagnozi vertiga.

Ključne riječi: Vertigo, glavobolja, migrena, migrena s aurom, migrena bez aure

UDK 616.831-005.1:616.3
Original scientific paper
Received: 17 January 2007
Accepted: 25 April 2007

THE INFLUENCE OF VERTEBRAL ARTERY OCCLUSION ON VISUAL EVOKED RESPONSES IN POSTERIOR CEREBRAL ARTERY

Marijana Bosnar Puretić, Arijana Lovrenčić Huzjan, Marina Roje Bedeković, Vida Demarin

University Neurology Department, Sestre Milosrdnice University Hospital, Zagreb
Reference Center for Neurovascular Disorders of the Croatian Ministry of Health

Summary

Stroke is the second leading cause of death and the leading cause of disability in Croatia. One-quarter of all ischemic strokes occur in the posterior circulation. One third of ischemic strokes are caused by large artery diseases. Transcranial Doppler sonography (TCD) is a non-invasive method with an excellent temporal resolution for real time investigations of cerebral hemodynamics and, among other methods, functional TCD tests are very useful tools for establishing the cerebral vasomotor capacity. TCD studies revealed that a proximal stenosis in the carotid circulation severely influences distal cerebral hemodynamics and autoregulative mechanisms.

The aim of this study was to establish the influence of a vertebral artery (VA) occlusion on visual evoked responses in the posterior cerebral artery (PCA) measured by means of TCD.

We measured mean blood flow velocities (MBFVs) in the PCA before and during a visual stimulation in patients with a VA occlusion by means of TCD.

Without visual stimuli there was no significant difference between the control group and the patients with a VA occlusion. During white light stimulation a statistically significant increase of MBFVs in the PCA in both groups occurred. In the control group the increase was 22.85±20.9% for the right PCA and 20.67±15.31% for the left PCA. In the group of patients with a VA occlusion the increase in the right PCA was 12.3±16.46% and in the left PCA 11.89±13.08%. In the patients with a VA occlusion repeated testing led

Correspondence to: Marijana Bosnar Puretić, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: mbos-puretic@inet.hr

to diminished responses, which could be an indicator of the exhaustion of the cerebrovascular vasomotor reserve.

Based on the results of our study we can conclude that there is a negative effect on the functioning of the distal small vessels in the case of a VA occlusion. Visually evoked functional TCD testing is a non-invasive and precise method for the estimation of vasoreactivity in the posterior circulation.

INTRODUCTION

Stroke is the second leading cause of death and the leading cause of disability in Croatia. One-quarter of all ischemic strokes occur in the posterior circulation [1]. One third of ischemic strokes are caused by large artery diseases; in the posterior circulation a vertebral artery (VA) occlusion has a significant role. Vertebral artery stenoses and occlusions account for approximately 20% of the posterior circulation strokes [2]. The most common cause of a VA occlusion is the development of an atherosclerotic plaque, but in a significant number of cases a distal embolism is present. In the extracranial part, a VA could be occluded due to the dissection of the artery, mostly after a traumatic event [3,4].

When an occlusion of the proximal VA occurs, ischemic events develop only in 9% of cases [5], the reason lies in good compensatory pathways. The most important one is an intact contralateral vertebral artery. In the case of a hypoplastic VA or additional vascular pathology the risk of an ischemic event in the vertebrobasilar territory and the development of posterior syndromes is higher [6,7].

Cerebral perfusion is maintained constant in different conditions due to protective mechanisms, cerebral autoregulation and cerebral vasoreactivity. Also, the cerebral circulation responds promptly to increased metabolic demands due to neuronal activity, known as neurovascular coupling. These three mechanisms are functioning on the level of small cerebral vessels, arterioles and capillaries. It is possible to make conclusions about the functioning of one mechanism based on the test results of one of the others because all three are representing the capability of cerebral vessels to constrict or dilate after some stimuli [8-11].

The introduction of the transcranial Doppler (TCD) in neurological diagnostic procedures and scientific studies enabled the estimation of the cerebral circulation in real time. Mean blood flow velocities (MBFVs) measured by TCD represent the size of the cerebral blood flow. Due to the very high temporal resolution of this method it is possible to watch and quantify the changes of the cerebral blood flow after different stimuli [12,13].

In the case a significant stenosis or occlusion of the cerebral artery, the distal blood flow remains normal if the collateral pathways and cerebral autoregulation function

properly. Some acute cerebral diseases, as well as chronic diseases like arterial hypertension, diabetes mellitus, atherosclerosis and others, impair the capacity of small cerebral vessels to constrict and dilate, with an inadequate compensation of the blood flow distal to the stenosis as a consequence. Previous studies investigated in detail the influence of a proximal internal carotid artery stenosis on the cerebral autoregulation in the area of the middle cerebral artery (MCA) [14]. They also revealed an association between the internal carotid artery stenosis, impaired autoregulation in the MCA and increased risk of an ipsilateral stroke. When the same tests were repeated after the carotid endarterectomy, the results showed a significant improvement [15,16]. Investigations of cerebral vasoreactivity, autoregulation and neurovascular coupling in the area of the posterior circulation are not as numerous as in the area of the MCA. In the posterior circulation a very reliable way of testing the neurovascular coupling is measuring the responses in the posterior cerebral artery (PCA) to light stimulation, as it is known that the light is the most powerful stimulus of metabolism in the visual cortex. This kind of testing was performed for the first time by R. Aaslid who found that MBFVs in the PCA significantly rose during watching at the white light [17].

The aim of this study was to investigate the velocity changes in the PCA during visual stimulation in patients with a VA occlusion by means of TCD. The main hypothesis in our study was that visually evoked flow responses in the PCA were reduced in patients with a VA occlusion.

Patients and methods

This study was performed in the Cerebrovascular Laboratory of the University Neurology Department, Sestre Milosrdnice University Hospital in Zagreb. It was a prospective study which included in- and outpatients with a VA occlusion. The same diagnostic tests were performed in the age and sex matched control group. Excluded from the study were patients with an intracranial stenosis of cerebral vessels, unconscious and demented patients and patients with hypertension and diabetes mellitus.

The VA occlusion in all patients was diagnosed by means of Color Doppler Flow Imaging using the Acuson 128 XP/10 device, Mountain View, California. For morphologic investigation a 7.5MHz linear probe, and for hemodynamic investigation a 5MHz probe were used. The VA occlusion was diagnosed according to the previously published criteria [18].

Transcranial Doppler sonography of the Willis circle and the vertebrobasilar region was performed using the MultiDop X4 DWL device, Electronische Systeme GmbH, Sipplingen, with a 2MHz probe. During the testing of the visual evoked flow responses in the PCA, a simultaneous recording of both PCAs by two Doppler channels was performed, using the software application for the evoked flow.

During the testing the patients were placed in a supine position in a quiet, dark room. The testing started after a 10 minute accommodation period with the patient's eyes closed. Both PCAs were insonated simultaneously through the temporal window in the P1 segment [13]. For light stimulation we used a light bulb of 100W placed 50cm far from the patient's eyes. First we measured MBFVs with the patient's eyes open, but without the light stimulation; thus obtained velocities were considered as MBFVs in basic, neutral conditions. Then the patient rested with the eyes closed for two minutes. After this period, MBFVs in both PCAs were measured for one minute with the patient's eyes closed. Then the patient was asked to open the eyes and to look at the light for one minute during which MBFVs in both PCAs were measured. These recordings were repeated three times in each patient, in the control group as well. For the visual evoked response calculation we took the mean value of MBFVs recorded during the one minute testing period. The size of the response was defined as the percentage of the PCA MBFVs change after light stimulation, as compared with the PCA MBFVs with subjects' eyes closed.

Statistical analysis was performed using standard statistical software. All results were presented as mean values with standard deviations. The differences between measurements were established using the T test and Kolgomor-Smirn test. For statistical significance the p value <0.05 was used.

Results

We investigated 30 patients with a VA occlusion, 24 males and 6 females. The mean age of the patients was 60.73 ± 11.63 years. The control group was age and sex matched and consisted of 26 subjects examined in our Cerebrovascular Laboratory on the basis of

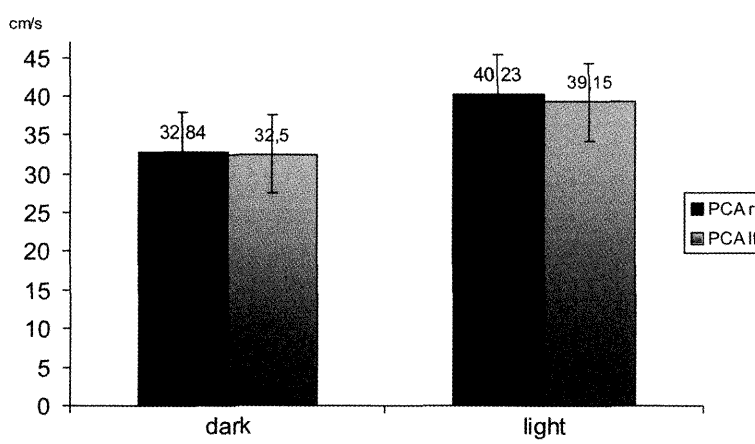


Figure 1. Visually evoked flow responses in the PCA in the control group.

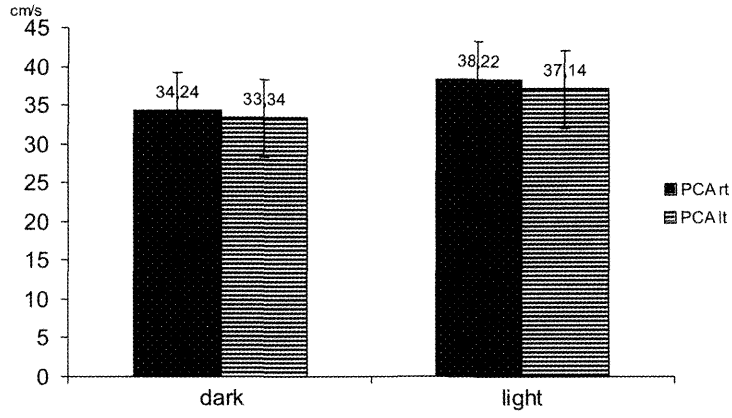


Figure 2. Visually evoked flow responses in the PCA in the patients with a vertebral artery occlusion.

cerebrovascular risk factors, but without any evidence of cerebrovascular diseases. In the male group most of the patients with a VA occlusion were in the age group between 55 and 74 years. In 57% of the patients the right VA was occluded, in 23% the left VA and in 20% both VAs were occluded. Majority of VA occlusions (58%) occurred in the extracranial part of the VA.

During recording of MBFVs in basic conditions, MBFV in the PCA did not differ significantly between patients and controls. In the control group MBFVs in the right VA were 36.3±12.4 cm/s and in the left VA 35.61±13.3 cm/s. In the patient group MBFVs in the right VA were 37.03±12.9 cm/s and in the left VA 35.60±11.52 cm/s. In the control group MBFVs in the PCA rose from 32.84cm/s in the right VA and 32.5cm/s in the left VA during the one minute recording in darkness to 40.23 cm/s in the right VA and 39.15cm/s in the left VA during the one minute recording with the light stimulus on. In the

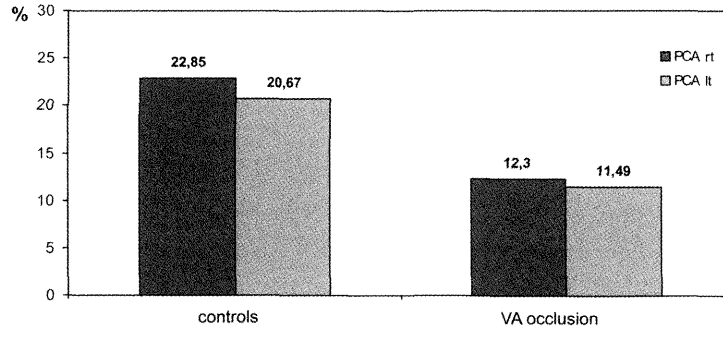


Figure 3. Percentage of visually evoked responses in both groups

patient group MBFVs in the PCA rose from 34.24cm/s in the right VA and 33.34cm/s in the left VA during the one minute recording in darkness to 38.22 cm/s in the right VA and 37.14 cm/s in the left VA during the one minute recording with the light stimulus on. In the control group the increase of MBFVs in the PCA during light stimulation was 22.85±20.9% for the right and 20.67±15.31% for the left PCA. In patients with a VA occlusion the right PCA showed increase of MBFVs by 12.3±16.46% and the left PCA showed increase by 11.89±13.08% (Figure 3). The visual evoked responses for the both groups and the comparison of responses in the form of percentages are shown in Figure 1 and 2. During the three consecutive testing periods, the values of MBFVs in the PCA in the patient group decreased for both types of conditions (darkness or white light) (Figure 4).

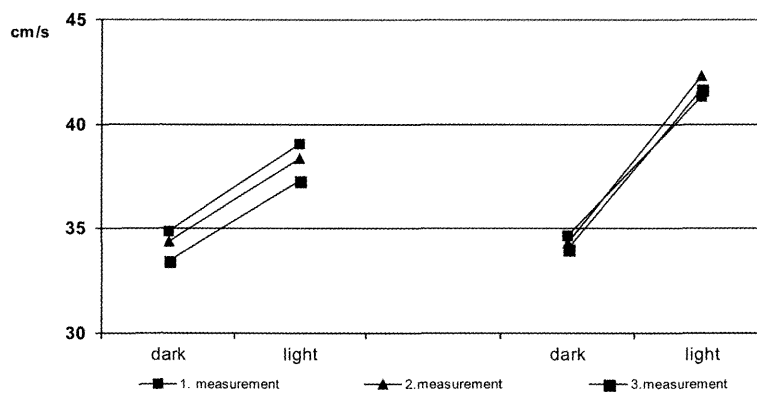


Figure 4. Reduction of evoked flow responses during repeated testing in patients with a VA occlusion in contrast with constant responses in the control group.

Discussion

Cerebrovascular ischemic incidents are in 30% of cases caused by large artery diseases. They are more frequent in the male population in the age group between 55-75 years. Our results showed a distribution of patients according to age and gender similar to the results of previous studies [19,20].

According to previous studies, 20% of ischemic events in the vertebrobasilar territory are caused by heart embolism and 20% by intraarterial embolism, usually from the VA [21]. The atherothrombotic process has a major role in vertebrobasilar ischemia. Usually it is located in the proximal, V1 part of the VA which is concordant with our results; 58% of VAs were occluded in the extracranial part. Similar to previous studies, our results showed that more often the right VA occlusion occurs [18]. Possible explanation is a vertebral artery hypoplasia that affects more often the right VA. This is a frequent inborn

condition, with a narrow lumen of the VA, 2mm in diameter or less. In a hypoplastic VA the hemodynamics is changed and the VA is more prone to an atherothrombotic process and occlusion [22-24].

MBFVs in the PCA with eyes open, without additional light stimuli, did not differ significantly between the control group and the patients with a VA occlusion. This is probably the result of a good compensatory mechanism of pathological changes in basic, physiological conditions.

During looking at a white light, in all investigated subjects occurred the increase of MBFVs in the PCA. This kind of study was for the first time performed in healthy volunteers by R. Aaslid in 1987. During watching at a white light MBFVs in the PCA rose for 16.4% and the regional blood flow volume rose for 20.2%. These changes developed in a very short time; 50% of the increase occurred in only 2.3 seconds [17]. Trkanjec and Demarin performed a similar study, but using different modes of light stimulation. Results showed that a flash light induced a greater response than continuous white light stimuli. Also, the responses depended of the wave-length of the light stimuli [23].

In our study results showed significantly lower responses in the PCA to light stimuli in the patients with a VA occlusion. Similar results were presented in the study of Urban, who performed similar testing in patients with an occipital infarction [26]. Before the light stimulation, MBFVs in the PCA in 13 patients and in the control group did not differ significantly. But, during the light stimulation in the control subjects MBFVs in the PCA rose for 30.6±9.7% and in the patient group this response was significantly lower, 3.4±4.1%. The magnitude of the response in patients depended on the size of the occipital lobe infarction. Haubrich et al. performed a dynamic cerebral autoregulation testing distally to the severe bilateral vertebral artery disease where they detected autoregulatory deficits of different degrees [27].

This kind of functional testing of the cerebral vasculature by means of TCD is more often involving the carotid circulation pathology. Responses to functional stimuli in patients with a carotid disease are good indicators of the autoregulative, vasoreactive capacity of small cerebral vessels distal to the stenosis or occlusion. Silvestrini et al. showed in their study the change of MBFVs in the middle cerebral artery (MCA) during a two-minute task of moving the fingers in patients with a significant carotid artery stenosis. In the control group MBFVs in the MCA rose for 5.52±2.4cm/s. In the patient group on the side of the carotid stenosis MBFVs increased by 1.76±1.6cm/s and on the contralateral, healthy side the increase was 3.82±2.1cm/s. After carotid endarterectomy (CEA), the response to motoric stimuli improved and differences between sides became insignificant [16]. In similar groups of patients with a carotid disease before and after CEA Demarin et al. performed vasoreactivity testing using acetazolamide (Diamox, 1000mg), one of the currently used tests for cerebrovascular reactivity assessment. This

carboanhydrase inhibitor increases the CO_2 level in blood and the hypercapnia is used as the most potent vasodilatatory stimulus for testing the cerebrovascular reactivity [28]. Patients with a carotid stenosis showed weaker responses after acotazolamide administration. On the side of the stenosis, the impairment of vasoreactivity correlated with the degree of stenosis. After the surgery, a significant recovery of vasoreactivity occurred[15]. Testing of the vasomotor reserve in patients with a carotid disease was also used as a possible predictor of ischemic events in the distal area [29,30].

In investigated subjects the measurement of MBFVs in the PCA was performed in three consecutive sequences. In the group of patients with a VA occlusion in every subsequent measurement, during resting as well as during the watching at the white light, MBFVs in the PCA became lower. The differences between the first and the third measurement were statistically significant. The possible explanation is the habituation during the repeated stimulation, but the possible cause lies in the exhaustion of the vasomotor reserve distal to the vertebral artery occlusion. In the control group we did not find any significant decrease of MBFVs in the PCA in the second and third sequence of testing.

Due to the anatomical position of VAs and the limited diagnostic and therapeutic possibilities, very few studies have dealt with vertebral artery pathology. Also, very few studies have dealt with the impaired autoregulation, vasoreactivity and neurovascular coupling in the posterior circulation up to now.

The advantages of functional testing by means of transcranial Doppler are non-invasiveness and regional selectivity. This is especially valid for the PCA and visual cortex, due to the exclusive irrigation of the visual cortex by PCAs, and very precise relations between the light stimulation, increase of neural metabolism and blood flow volume in the visual cortical area. Neurovascular coupling is functioning on the level of small cerebral vessels, which means that conditions that impair the cerebral autoregulation and cerebral vasoreactivity also affect the neuronal coupling. The diminished response after functional stimulation can be addressed to the functional or structural impairment of the neuronal area, impaired neurovascular coupling or compromised hemodynamics due to a proximal stenosis or occlusion [11].

The diminished answer in the PCA during light stimulation in the patients with a VA occlusion in our study probably reflects the hemodynamic impairment of the posterior circulation, which is not able to react properly to increased metabolic demands of the visual cortex. Also, it is possible that such results are also the consequence of a structural injury of the visual cortex, since in some patients a brain CT scan revealed ischemic changes in the PCA area.

Functional testing of the visual cortex by means of TCD is a non-invasive and reliable method for estimating the vasomotor reserve. In this study it revealed the impairment of the vasomotor reserve distal to the VA occlusion. The results of this study could

help in further investigations aimed at establishing the risks of ischemic events in the posterior circulation.

References

[1] *Bernasconi A, Bogusslavsky J, Basseti C, Regli F.* Multiple acute infarcts in the posterior circulation. J Neurol Neursurg Psychiatry 1996;60:289-296.

[2] *Khan S, Cloud G, Kerry S, Markus HS.* Imaging of vertebral artery stenosis: A systematic review. J Neurol Neurosurg Psychiatry 2007 Feb 7; [Epub ahead of print]

[3] *Caplan LR, Amarenco P, Rosengart A, Lafranchise EF, Teal PA, Belkin M, DeWitt LD, Pessin MS.* Embolism from vertebral artery origin occlusive disease. Neurology 1992;42:1505-12.

[4] *Iwase H, Kobayashi M, Kurata A, Inoue S.* Clinically unidentified dissection of vertebral artery as a cause of cerebellar infarction. Stroke 2001;32:1422-4.

[5] *Wityk RJ, Chang HM, Rosengart A, Han WC, DeWitt LD, Pessin MS, Caplan LR.* Proximal extracranial vertebral artery disease in New England medical center posterior circulation registry. Arch Neurol 1998; 55:470-8.

[6] *Chaturvedi S, Lukovits TG, Chen W, Gorelick PB.* Ischemia in the territory of a hypoplastic verterobasilar system. Neurology 1999; 52:980-3.

[7] *Perren F, Poglia D, Landis T, Sztajzel R.* Vertebral artery hypoplasia: a predisposing factor for posterior circulation stroke? Neurology 2007 Jan 2;68(1):65-7.

[8] *Thaller N.* Fiziologija i patofiziologija moždanog krvotoka. In: Demarin V, Štikovac M, Thaller N. Doppler sonografija krvnih žila. Zagreb: Školska knjiga; 1990. p. 24-36.

[9] *Aaslid R.* Cerebral Hemodynamics. In: Newell DW, Aaslid R. Transcranial Doppler. New York: Raven Press Ltd; 1992. p.49-57.

[10] *Rundek T.* Moždana autoregulacija. In: Demarin i sur. Moždani krvotok-klinički pristup. Zagreb: Naprijed; 1994. p.15-25.

[11] *Daffertshoffer M,* Functional Doppler testing. In: Hennerici MG, Meairs S. Cerebrovascular ultrasound: theory, practice and future developments. Cambridge: University Press; 2001. p.341-360.

[12] *Demarin V,* Transkranijski dopler. In: Demarin V, Štikovac M, Thaller N. Doppler sonografija krvnih žila. Zagreb: Školska knjiga; 1990. p.87-130.

[13] *Alexandrov AV, Demarin V.* Insonation techniques and diagnostic criteria for transcranial Doppler sonography. Acta clin Croat1999;38:97-108.

[14] *Bornstein NM, Gur AY.* Cerebralvasomotor reactivity and carotid occlusive disease. Acta Clin Croat 2006;45:357-364.

[15] *Rundek T, Demarin V, Despot I, DeSyo D, Podobnik-Šarkanji S.* Value of cerebral vasoreactivity testing in patients with carotid artery disease before and after carotid endarterectomy. Acta clin Croat 1993; 32:141-150.

[16] *Silvestrini M, Troisi E, Cupini LM, Matteis M, Pistolese GR, Bernardi G.* Transcranial Doppler assessment of the functional effects of symptomatic carotid artery stenosis. Neurology 1994;44:1910-4.

[17] *Aaslid R.* Visually evoked dynamic blood flow response of human cerebral cortex. Stroke 1987;18:771-5.

[18] *Lovrenčić-Huzjan A, Vuković V, Bosnar Puretić M, Demarin V.* Sonographic features of vertebral artery occlusion (the role of color and power Doppler flow imaging). Acta clin Croat 1999;38:279-285.

[19] *Lovrenčić-Huzjan A, Bosnar M, Huzjan R, Demarin V.* Frequency of different risk factors for ischemic stroke. Acta clin Croat 1999;38:159-163.

[20] *Warlow CP.* Epidemiology of stroke. Lancet 1997; 352:1-4.

[21] *Crawely F, Clifton A, Brown MM.* Treatable lesions demonstrated on vertebral angiography for posterior circulation ischemic events. The British Journal of Radiology 1998; 71:1266-70.

[22] *Lovrenčić-Huzjan A, Demarin V, Bosnar M, Vuković V.* Color Doppler Flow Imaging (CDFI) of the vertebral arteries-the normal appearance, normal values and the proposal for the standards. Coll. Antropol 1999; 231:175-181.

[23] *Demarin V, Škarić Jurić T, Lovrenčić Huzjan A, Bosnar Puretić M, Vuković V.* Vertebral artery hypoplasia, sex-specific fequencies in 36 parent-offspring pairs. Coll Antropol 2001;25:501-509.

[24] *Morović S, Škarić-Jurić T, Demarin V.* Veretbral artery hypoplasia: characteristics in a Croatia population sample. Acta Clin Croat 2006;45:325-329.

[25] *Trkanjec Z, Demarin V.* Transcranial Doppler sonography during visual stimulation. Acta clin Croat 1999;38:285-9.

[26] *Urban PP, Allaradt A, Tettenborn B, Hopf H, Pfenningsdorf S, Lieb W.* Photoreactive flow changes in the posterior cerebral artery in control cubjects and patients with occipital lobe infarctions. Stroke 1995;26:1817-9.

[27] *Haubrich C, Kohnke A, Diehl RR, Möller-Hartmann W, Klötzsch C.* Impact of vertebral artery disease on dynamic cerebral autoregulation. Acta Neurologica Scandinavica 2005;112 (5):309–316.

[28] *Bornstein NM, Gur AY.* Cerebral vasomotor reactivity and carotid occlusive disease. Acta Clin Croat 2006;45:357-364.

[29] *Markus H, Cullinane M.* Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain 2001; 124:457-467.

[30] *Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi I, Caltagirone C.* Impaired cerebral vasoreactivity and risk of sroke in patients with asymptomatic carotid artery stenosis. JAMA 2000;26:2122-7.

Sažetak

Utjecaj okluzije vertebralne arterije na odgovore u stražnjoj moždanoj arteriji tijekom vidnih podražaja

Moždani udar je po učestalosti drugi uzrok smrti i vodeći uzrok onesposobljenosti u Hrvatskoj. Četvrtina svih ishemijskih moždanih udara nastaje u području stražnje cirkulacije. Trećina svih ishemijskih moždanih udara uzrokovana je bolešću velikih krvnih žila. Transkranijska dopler sonografija (TCD) je neinvazivna dijagnostička metoda s izvrsnom vremenskom rezolucijom koja omogućava ispitivanje moždanog krvotoka u živom vremenu. Funkcionalni TCD testovi, između ostalih metoda, imaju značajnu ulogu u procjeni moždanog vazomotornog kapaciteta. Rezultati prethodnih TCD istraživanja ukazali su da proksimalna stenoza u karotidnoj cirkulaciji izrazito utječe na distalnu hemodinamiku i mehanizme autoregulacije.

Cilj ovog istraživanja bio je pomoću TCD-a utvrditi utjecaj okluzije vertebralne arterije na odgovore u stražnjoj moždanoj arteriji tijekom vidnih podražaja.

Odgovore tijekom vidnih podražaja u stražnjoj moždanoj arteriji u bolesnika s okluzijom vertebralne aterije bilježili smo TCD-om mjereći srednje brzine strujanja krvi (SBSK) u stražnjoj moždanoj arteriji prije i tijekom vidnih podražaja.

Mjereći SBSK u stražnjoj moždanoj arteriji bez vidnih podražaja, vrijednosti u kontrolnoj skupini nisu se značajno razlikovale od vrijednosti SBSK u skupini bolesnika s okluzijom vertebralne arterije. Tijekom vidnih podražaja bijelim svjetlom u obje skupine ispitanika zabilježeno je statistički značajno povećanje SBSK u stražnjoj moždanoj arteriji. U kontrolnoj skupini to povećanje SBSK iznosilo je 22,85±20,9% u desnoj, a 20,67±15,31% u lijevoj stražnjoj moždanoj arteriji. U skupini bolesnika s okluzijom vertebralne arterije povećanje u desnoj stražnjoj moždanoj arteriji iznosilo je 12,3±16,46%, a u lijevoj 11,89±13,08%. U bolesnika s okluzijom vertebralne arterije opetovani vidni podražaji doveli su do smanjenja odgovora u stražnjoj moždanoj arteriji što je mogući pokazatelj iscrpljivanja moždane vazomotorne rezerve.

Na temelju našeg istraživanja možemo zaključiti da postoji negativni utjecaj okluzije vertebralne arterije na distalnu hemodinamiku. Funkcionalni TCD testovi vidnim podražajima predstavljaju neinvazivu i preciznu metodu za procjenu vazoreakivnosti u stražnjoj moždanoj cirkulaciji.

Ključne riječi: vertebralne arterije, vidni evocirani odgovori, ultrazvuk, stražnja moždana arterija

UDK 616.073.432.13:616.13:616.711
Original scientific paper
Received: 17 January 2007
Accepted: 25 April 2007

THREE DIMENSIONAL UTRASOUND OF THE VERTEBROBASILAR SYSTEM

Iris Zavoreo, Miljenka Jelena Jurašić, Vida Demarin

University Department of Neurology, Sestre Milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia

Summary

Background: Transcranial color-coded sonography (TCCS) and power Doppler imaging (PDI) are used for the evaluation of the vertebrobasilar (VB) system. Due to the unfavorable angle of the vertebral arteries' (VA) junction and angle of insonation, all three vessels can rarely be visualized at the same time. Three-dimensional ultrasound (3D US) enables volumetric reconstruction of the VB junction.

Methods: 2D TCCS and PD as well as 3D US were applied in 25 patients in order to visualize the intracranial part of the VB system.

Results: In TCCS mode it was not possible to obtain all three vessels at the same time, in PD mode it was possible in 6/25 patients, and in 3D PD method in 19/25 patients. In 6 patients the VB angle could not be visualized (2 VAs were occluded – confirmed by angiography, in 4 cases there was a suboptimal suboccipital window), and volumetric reconstruction was applied.

Conclusion: 3D US enabled better visualization of the VB junction due to the possibility of volumetric reconstructions.

Key words: Ultrasound, three dimensional ultrasound, vertebral arteries.

INTRODUCTION

Vertebrobasilar ischemia is certainly less common than internal carotid artery diseases, but it must be diagnosed appropriately because it is a treatable vasculopathy. The

Correspondence to: Iris Zavoreo, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: iris_zavoreo@yahoo.com

most common disease affecting vertebral arteries is atherosclerosis. Less common pathological processes include trauma, fibromuscular displasia, Takayasu disease, osteophyte compression, dissections, aneurysms, and other arteritides. Such pathological states can result in a transient "end-organ" (brainstem, cerebellum, and/or occipital lobes) hypoperfusion. A number of medical conditions may mimic vertebrobasilar ischemia – the inappropriate use of antihypertensive medications, cardiac arrhythmias, anemia, brain tumors, benign vertiginous states, basilar artery migraine, vertebral artery hypoplasia and postsubarachnoid hemorrhage vasospasm. Regardless of the specific pathology, patients usually demonstrate reproducible symptoms following postural or positional changes. In general, hypoperfusion attributable to hemodynamic causes rarely results in infarction. Patients typically present with repetitive, short-lived symptoms such as visual disturbance, drop attacks, unsteadiness or incoordination, weakness, confusion, headache, hearing loss, numbness, speech disturbance, abnormal noise in the ears, and numbness around the mouth. However, they can sustain traumatic injuries resulting from the loss of balance.

Introduction of the color Doppler flow imaging (CDFI), power Doppler imaging (PDI), transcranial Doppler (TCD) and transcranial color coded Doppler imaging (TCCD) into the everyday vascular workup of the VB system was a big improvement, but also, because of the unfavorable angle of insonation, in a big percentage of patients it was hard to evaluate the VB junction morphology and haemodynamics, so that 3D ultrasound evaluation and mathematical reconstruction of the VB junction gave new possibilities in the evaluation of such patients. Main advantage of such analysis is multiangular examination of the desired arterial segment including the intravascular approach, thus providing a greater spatial resolution.

Patients and methods

The technique was applied in 25 healthy volunteers in order to visualize the intracranial parts of both vertebral arteries (VA) and the basilar artery (BA), and to calculate the angle of the VB junction according to the direction of the blood vessels. Interactive 3D imaging software was integrated into the ultrasound platform (Aloka Prosound 5500). Data acquisition was performed using a 2,5 MHz sector transducer, freehanded in a fixed length of time (10 seconds), allowing PDI. The images were postprocessed (TomTec imaging system). Vertebral arteries were insonated at four different levels: the origin (ostium and proximal portion-V1), the intertransversal course (V2), the atlas loop (V3), by means of 2D US, while the intracranial portion (V4) was visualized by 2D US-Picture 1 and 3D US-Picture 2 by the suboccipital approach. An occlusion, stenosis or hypoplasia of the vertebral and carotid arteries, and pathological flow phenomena, such as

subclavian steal syndrome, were excluded according to the standardized criteria of the Cerebrovascular Laboratory of the Referral Center for Neurovascular Disorders of the Ministry of Health.

Results

There were 25 healthy volunteers (mean age 56 years, range 23-78 years), 15 women (mean age 62 years) and 10 men (mean age 59 years) – Table 1. In TCCS mode it was not possible to obtain all three vessels at the same time, while in PD mode we were able to obtain all three vessels at the same time in 6/25 patients. 3D PD method enabled visualization of all three vessels at the same time in 19/25 patients, while in 6 patients the angle between the VA and BA origin could not be adequately visualized (2 VAs were occluded – diagnose confirmed by angiography; in 4 cases there was a suboptimal suboccipital window), therefore, 3D mathematical reconstruction was applied – Table 2.

Table 1. General characteristics of the investigated population.

	number of individuals	mean age
men	10	59
women	15	62
pooled	25	56

Table 2. Number of patients in correlation to the number of vessels visualized at the same time by means of 2D TCCS, 2D PD, and 3D PD.

	2D TCCS	2D PD	3D PD
3 vessels	0	6	19+6*
1 or 2 vessels	25*	19*	0
Total	25	25	25

*2 VA were occluded – diagnose confirmed by angiography; in 4 cases suboptimal suboccipital window, 3D mathematical reconstruction was applied.

Discussion

The main advantage of the 3D analysis of the intracranial part of the circulation is a multiangular examination of the desired blood vessel including an intravascular approach with a greater spatial resolution than the standard ultrasound techniques. Other advantages are noninvasiveness, volumetric analysis, oblique planimetry with additional interpolation whenever a standard visualization does not suffice. 3D US has high

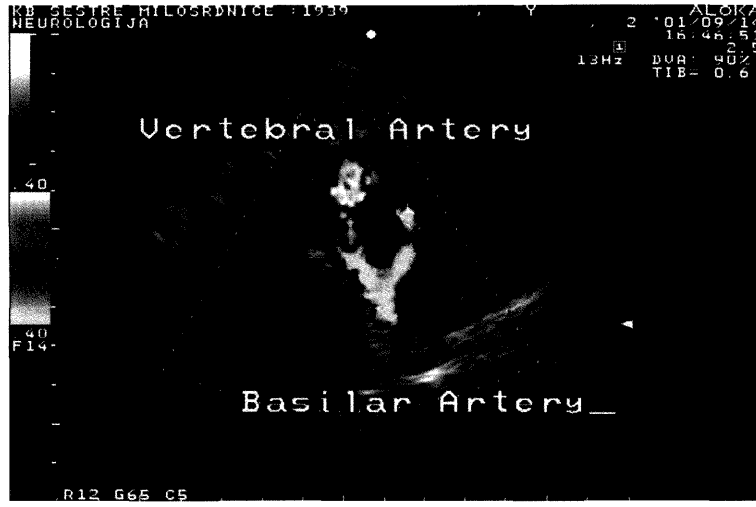


Figure 1. Color coded 2D ultrasound of the VB system.

levels of reproducibility, sensitivity and specificity in correlation with digital subtractional angiography (DSA) of the brain vessels (r=0,98). In comparison with magnetic resonance imaging (MRI), 3D also showed satisfactory results: transaxial resolution of 5

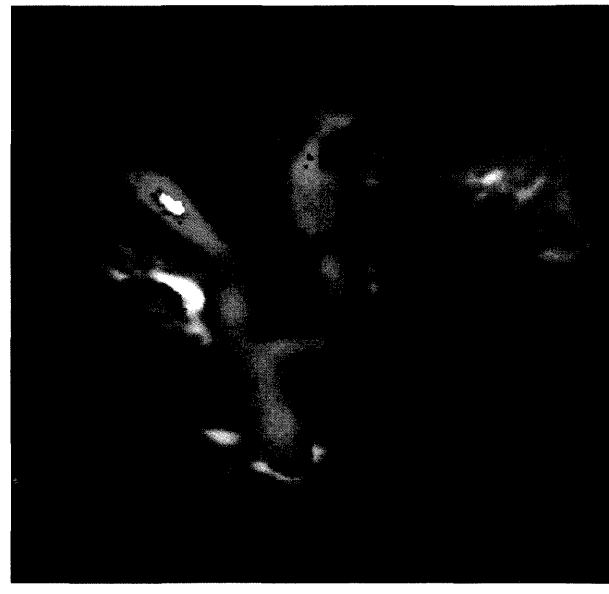


Figure 2. 3D ultrasound of the VB system.

mm, longitudinal resolution of 10 mm, and rotational resolution of 40°. Disadvantages of the 3D US are the lack of a proper differentiation between the periarterial and intraarterial tissue, which causes thresholding problems in tissue segmentation, higher costs as compared to conventional US examination, high operator skills and various artifacts (cardiac rhythm in cases without ECG synchronization, hand movement, swallowing or respiration).

This study showed that 3D US is better than 2D US in the visualization of the VB junction due to the multiangular examination and volumetric reconstruction possibility.

Further studies should be performed in order to evaluate the impact of 3D US of the VB junction hemodynamics in the differential diagnosis of the posterior fosse symptoms.

References

[1] *Byrd SM.* An overview of transcranial color flow imaging: a technique comparison. Ultrasound Quarterly. 1996;13(4):197-210.

[2] *Ritter MA, Ringelstein EB.* The Venturi effect and cerebrovascular ultrasound. Cerebrovasc Dis 2002; 14:98-104.

[3] *Drinković I, Lovrenčić M, Marotti M, Agbaba M.* Novije tehnike slikovne dijagnostike. In: Radiologija. Hebrang A, Lovrenčić M (eds) Medicinska naklada, Zagreb. 2001; 51-62.

[4] *Lovrenčić-Huzjan A, Demarin V, Bosnar M, Vuković V, Podobnik-Šarkanji S.* Color doppler flow imaging (CDFI) of the vertebral arteries – the normal appearance, normal values and the proposal for the standards. Collegium Antropologicum. 1999;1:175-181.

[5] *Meiars S.* Three and four dimensional cerebrovascular ultrasonography. In: Hennerici G, Meiars S. Cerebrovascular ultrasound. Cambridge University Press 2001; 1807-13.

[6] *Vuković V, Demarin V.* CDFI and PDI findings in extracranial artery disease. Acta clin Croat. 2000;39:263-268.

[7] *Demarin V.* Stroke- a challenge in the diagnosis and therapy. Acta Med Croatica 2001; 55:145-8.

[8] *Mehler MF.* The rostral basilar artery syndrome: Diagnosis, etiology, prognosis. Neurology. 1989;39:9-16.

[9] *Caplan L.* Posterior ischemia: Then, now and tomorrow-the Thomas Willis lecture 2000. Stroke. 2000;31:2011-2023.

[10] *Ries S, Steinke W, Devuyst G, Artemis N, Valikovics A, Hennerici M.* Power Doppler imaging and color Doppler flow imaging for the evaluation of normal and pathological vertebral arteries. J Neuroimag. 1998;8:71-74

[11] *Kimura K, Yasaka M, Moriyasu H, Tsuchiya T, Yamaguchi T.* Ultrasonographic evaluation of vertebral artery to detect vertebrobasilar axis occlusion. Stroke. 1994;25:1006-1009.

[12] *Kenton AR, Martin PJ, Evans DH.* Power Doppler an advance over color Doppler for transcranial images? Ultrasound in Med boil. 1996;22:313-317

[13] *Martin PJ, Evans DH, Naylor AR.* Transcranial color-coded sonography of the basal cerebral circulation. Stroke. 1994;25:390-396.

[14] *Koga M, Kimura K, Yasaka M, Otsubo R, Hasegawa R, Minematsu K, Yamaguchi T.* Three dimensional Power Doppler imaging of vertebrobasilar circulation in adults.AJNR. 1999; 20: 943-944.

[15] *Hayashi T, Ichiyama T, Nishikawa M, Kaneko J, Nakashima K, Furukawa S.* Three Dimensional reconstruction of the power Flow Doppler imaging of intracranial structures in neonate. J Nueoimaging. 1998;8:94-96.

[16] *Schneider PA, Rossman ME, Bernstein EF, Ringelstein EB, Torem S, Otis SM.* Noninvasive evaluation of vertebrobasilar insufficiency. J Ultrasound Med. 1991;10(7):373-379.

[17] *Bendick PJ, Brown W, Hernandez D, Glover Jl, Bove PG.* Three Dimensional vascular imaging using Doppler ultrasound. Am J Surg. 1998;176:183-187.

Sažetak

Trodimenzionalni ultrazvuk vertebrobazilarnog sustava

Uvod: Transkranijska bojom kodirana sonografija (TCCS) i osnaženi dopler (PD) se upotrebljavaju za procjenu vertebrobazilarnog (VB) sustava. Zbog nepovoljnog kuta spoja vertebralnih arterija (VA) i kuta insonacije, rijetko se mogu prikazati sve tri žile istovremeno. Trodimenzionalni ultrazvuk (3D UZ) omogućava volumetrijsku rekonstrukciju VB spoja.

Metode: Primijenili smo 2D TCCS, PD i 3D UZ u 25 bolesnika kako bismo prikazali intrakranijski dio VB sustava.

Rezultati: Primjenom TCCS nije bilo moguće prikazati sve tri krvne žile istovremeno, primjenom PD to je bilo moguće u 6 od 25 bolesnika, a primjenom 3D PD u 19 od 25 bolesnika. U 6 bolesnika VB kut se nije mogao prikazati (2 VA su bile okludirane što je potvrđeno angiografijom, u 4 slučaja bio je suboptimalni okcipitalni prozor), pa je primijenjena volumetrijska rekonstrukcija.

Zaključak: 3D UZ omogućuje bolji prikaz VB spoja zbog mogućnosti volumetrijske rekonstrukcije.

Ključne riječi: Ultrazvuk, trodimenzionalni ultrazvuk, vertebralne arterije

UDK 616.13
Original scientific paper
Received: 17 January 2007
Accepted: 25 April 2007

MORPHOLOGIC AND HEMODYNAMIC CHARACTERISTICS OF VERTEBRAL ARTERIES IN MEN AND WOMEN

Sandra Morović, Tatjana Škarić-Jurić[1], Vida Demarin

University Department of Neurology, Sestre Milosrdnice University Hospital, Zagreb, Croatia
[1]Institute of Anthropology, Zagreb, Croatia

Summary

Introduction: Men and women differ in diameters and MBFVs in VAs.

Aim: to compare morphology and hemodynamics of VAs between sexes.

Patients and methods: We examined 155 subjects using a linear 7.5 MHz probe (Aloka Prosound SSD-5500). Measurements were obtained at the V2 segment of VAs. Criteria: VA diameter of 2-4mm, systolic MBFVs of 0.35-0.70m/s, normal resistance pattern. Investigated parameters: diameters of VAs, MBFVs in VAs, sum of VA diameters, sum of MBFVs in VAs, diameter of the narrower and wider VA, and age.

Results: 68 men and 87 women; 88 with a dominant left VA (56% of men and 58% of woman), 11 (7%) showed no dominance. Group differences: men had both VAs wider, and a larger diameter of the "wider" VA. There were no differences in MBFVs between men and women.

Conclusion: Left VA is dominant in both sexes. There was no difference in MBFVs among sexes. Men have a wider VA than women.

Key words: Vertebral artery, Croatian population

INTRODUCTION

The anatomical position of vertebral arteries caused them to be neglected in research until ultrasound methods became widely available [1,2]. The ultrasound allows a non-

Correspondence to: Sandra Morović, University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia
Vinogradska 29, Zagreb, Croatia
E-mail: sandra_morovic@hotmail.com

invasive view into the human body, and by performing color Doppler flow imaging (CDFI) of the blood vessels of the head and neck[3] we can painlessly, at bedside, assess cerebral circulation [4,5].

Vertebral arteries are responsible for one third of the brain's blood supply. They form the rear part of the Willis' circle and are responsible for the blood supply of the cerebellum, pons, middle ear, as well as the upper parts of the spinal cord and its meninges.

Changes in the morphology and hemodynamics of vertebral arteries can be the cause of many disorders. For example, 15% of all strokes occur in the irrigational territory of vertebral arteries, and stroke is still the leading cause of death and disability in Croatia. Vertigo, on the other hand, is not always a sign of a serious illness, but is a symptom which has a great effect on the quality of patients' lives. Changes on vertebral arteries, both atherosclerotic and congenital, can also serve as unfavorable prognostic factors in chronic degenerative changes on the cervical spine and trauma [9], or atherosclerotic [10] changes on other vessels.

All this makes the investigation of vertebral arteries worthwhile.

Studies have shown that men and women differ in the diameters and mean blood flow velocities (MBFVs) in vertebral arteries (VAs) [6-8].

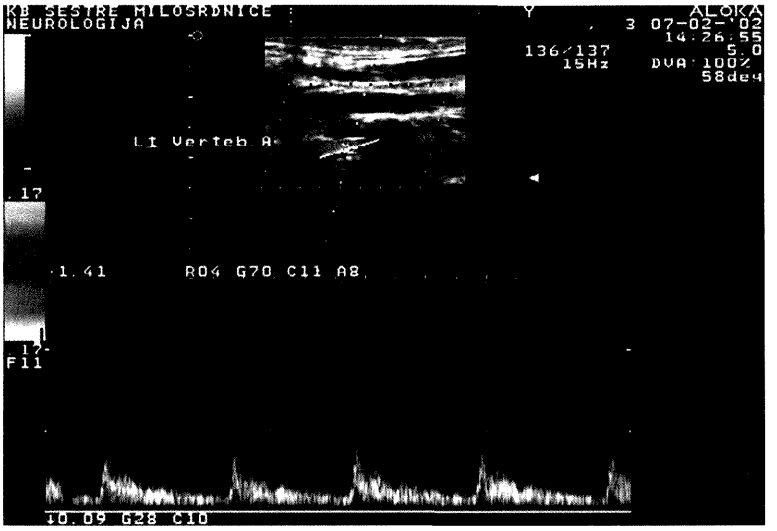
The aim of this study is to compare the morphology and hemodynamics of VAs between men and women in the Croatian population.

Patients and methods

We examined 155 subjects at The University Department of Neurology, University Hospital Sestre Milosrdnice, Zagreb, Croatia. There were 68 men and 87 women. The subjects participating in the study were chosen among the hospitalized and out-patient subjects on whom CDFI of vertebral arteries was performed during the investigation of vertebral arteries as a part of the screening method for possible cerebrovascular disorders. All examined subjects had no apparent pathology of vertebral arteries such as an occlusion, hypoplasia, and aplasia of vertebral arteries or severe hemodynamic changes. The subjects with abnormalities of vertebral arteries were excluded from the study (abnormalities such as a vertebral artery stenosis, occlusion of vertebral artery, extravertebral flow, etc.). All the subjects in the study had normal vertebral arteries.

All measurements were done using the extracranial color Doppler technique, with a 7,5 MHz probe, on an Aloka Prosound 5500. Vertebral arteries were measured at the V2 segment, between the vertebrae C6 and C5. The criteria used for normal vertebral arteries were: lumen diameter of 2,5-4,5 mm, mean blood flow velocities of 0,35-0,70 m/s, and absence of increased resistance pattern (diastolic velocities above 0,05 m/s). All measurements were done with the patient lying on his/her back, head in mid-position, lifted to 45 degrees, chin facing upwards. By moving the probe horizontally, keeping in contact with the skin, a vertebral artery appears [8,13,14]. (Figure)

The two groups were compared in several categories: sex, age, diameter of the right, left, and both vertebral arteries, narrower vertebral artery (being the one with a smaller



Normal vertebral artery as seen by CDFI.

diameter in both groups), hemodynamics in the right and left vertebral artery, and resistance patterns.

Data were analyzed descriptively, and the differences among groups were analyzed using the student t-test and χ-square.

Results

Color Doppler flow imaging reports of vertebral arteries preformed on 155 healthy subjects were analyzed. There were 68 men (44%) and 87 (56%) women. Among men and women the right vertebral artery was noticed to be narrower than the left vertebral artery in most cases (Table 1). The term "narrower" relates to a smaller vertebral artery lumen when both sides are compared. Fifty-seven percent of subjects had a narrower right vertebral artery as opposed to 36% of subjects with a narrower left vertebral artery. Vertebral arteries of equal width were found in 10% of subjects. A similar percentage of men and women were found to have narrower right vertebral arteries - 56% of men and 58% of women. Results were similar for the other side also, 36% of men and 37% of women had a narrower left vertebral artery. Eight percent of men and 5% of women had an equal width of vertebral arteries. (Table 1)

Table 1. Side of the "narrower" vertebral artery

	Right	Left	Right = left	Total
Men	37	24	7	68
	(56%)	(36%)	(8%)	
Women	51	32	4	87
	(58%)	(37%)	(5%)	
Men and women	88	56	11	155
	(57%)	(36%)	(6%)	

Table 2. Comparison of mean values of tested parameters among examined subjects.

Tested parameter	Men	Women
Age	*36,19*	*47,35****
AV-R	3,26	3,11
AV-L	3,43	3,26
AV-R hemo	0,46	0,46
AV-L hemo	0,47	0,48
AV-R+AV-L	*6,69*	*6,37***
AV-R+L hemo	0,93	0,94
Narrower	3,02	2,88
Wider VA	*3,67*	*3,49***

*p=0.005 ** p=0.01 *** p=0.001

Age = mean age of patients
AV-R = diameter of the right vertebral artery
AV-L = diameter of the left vertebral artery
AV-R hemo = hemodynamics of the right vertebral artery
AV-L hemo = hemodynamics of the left vertebral artery
AV-R+AV-L = diameter of both vertebral arteries
AV-R+L hemo = hemodynamics of both vertebral arteries
Narrower = diameter of the narrower vertebral artery
Wider VA = diameter of the "wider" vertebral artery

Men and women differed greatly in some examined parameters. Women were in average eleven years older than men. Men had the right and left vertebral artery wider than women even though the differences were not statistically significant. But, when we compared both diameters together, the difference between men and women was statistically significant. Men had both vertebral arteries wider than women. There were no great differences in mean blood flow velocities in the left and right vertebral artery between men and women. Also, when compared, the sum of mean blood flow velocities in both vertebral arteries showed no difference between men and women. The difference in the diameters of the "narrower" vertebral artery was not significant between

these two groups. But, men showed a statistically significant wider diameter of the "wider" vertebral artery. (Table 2)

Discussion

Because of their anatomic location and inconvenient access for surgical procedures vertebral arteries stayed neglected in research for a long time[16-19], even though they are the second largest blood supplier of the brain. They are responsible for 30% of the brain's blood supply and form the rear part of the Willis' circle. Circulatory changes in vertebral arteries can cause serious conditions such as stroke, or uncomfortable symptoms such as vertigo. A greater interest in vertebral arteries followed the introduction of noninvasive ultrasound methods to the study of blood vessels [20,21].

The results obtained by this investigation confirmed some earlier findings on this subject. Back in 1999 Seidel [22] showed that mean blood flow velocities are lower in right vertebral arteries and that lumen diameters of right vertebral arteries are smaller than those of the left side. Our results showed different findings in regard to mean blood flow velocities which didn't differ greatly between the right and left vertebral artery, but confirmed dominance of the left vertebral artery. Our investigation confirmed some results of earlier studies done by Karayenbuehel and Yasargila in 1957. They found that vertebral arteries had different diameters in 74% of the population, and 42% of the population had a dominant left vertebral artery. Our study showed different diameters of the right and left vertebral artery in 92% of men and 95% of women. Touboul et al. [14] found a dominant left vertebral artery in 48% of subjects, with 14% having a dominant right vertebral artery. In 1999 Lovrenčić-Huzjan et al. [8] found 64% of dominant left vertebral arteries in the Croatian population. This investigation on a larger number of subjects showed 57% of dominant left vertebral arteries. Also, women were in average eleven years older than men, which was found to be statistically significant. We have found no apparent reason for this difference until now. Possibly, this could partly be explained by a longer life expectancy of women in our population. Or there could be another undetermined reason since this study compared groups only by the characteristics of vertebral arteries. Other risk factors were not investigated or compared in this study.

Conclusion

This investigation showed dominance of the left VA in diameter (57%) in both men and women, as was presented by some authors in earlier investigations. But, as opposed to earlier findings, this investigation showed no difference in MBFVs of both men and women. This investigation also showed that men have a larger sum of both VA diameters

and a larger diameter of the wider VA which leads to a conclusion that men have wider VA than women.

References

[1] *Bartels E.* Duplex ultrasound of the vertebral arteries. 1. Practical implementation, possibilities and limitations of the method. Ultraschall Med 1991;12(2):54-62.

[2] *Bartels E.* Duplex ultrasonography of the vertebral arteries. 2. Clinical applications. Ultraschall Med 1991;12(2):63-69.

[3] *De Bray JM, Dauzat M, Teisseire-Girod F, Davinroy M, Emile J.* The Doppler effect applied to the study of vertebral arteries. Nouv Presse Med 1978;7(1):39-42.

[4] *Bluth EI, Merritt CR.* Doppler color imaging. Carotid and vertebral arteries. Clin Diagn Ultrasound 1992;27:61-96.

[5] *Landwehr P, Schulte O, Voshage G.* Ultrasound examination of carotid and vertebral arteries. Eur Radiol 2001;11(9):1521-34.

[6] *Bartels E, Fluegel KA.* Advantages of color Doppler imaging for the evaluation of vertebral arteries. J. Neuroimaging 1993; 3(4):229-33.

[7] *Bartels E, Fuchs HH, Flugel KA.* Duplex sonography of vertebral arteries: examination, the normal values, and clinical applications. Angiology 1992;43(3):169-80.

[8] *Lovrenčić-Huzjan A, Demarin V, Bosnar M, Vuković V, Podobnik-Šarkanji S.* Color Doppler Flow Imaging (CDFI) of the Vertebral Arteries - The Normal Appearance, Normal Values and the Proposal for the Standards. Coll Antropol 1999;23:175-81.

[9] *Mann T, Refsauge KM.* Causes of complications from cervical spine manipulation. Aust J Pjysiother 2001;47(4): 255-66.

[10] *Ackerstaff RG, Grosveld WJ, Eikelboom BC, Ludwig JW.* Ultrasonic duplex sonography of the prevertebral segment of the artery in patients with cerebral atherosclerosis. Eur J Vasc Surg 1988;2(6):387-93.

[11] *Lovrenčić-Huzjan A, Demarin V, Rundek T, Vuković V.* Role of vertebral artery hypoplasia in migraine. Cephalalgia 1998;18:684-6.

[12] *Oder B, Oder W, Lang W, Marschnigg E, Deecke L.* Hypoplasia, stenosis and other alterations of the vertebral artery impaired blood rheology manifest a hidden disease? Acta Neurol Scand 1998;97(6):398-403.

[13] *Kremkau FW.* Diagnostic Ultrasound: Principles and Instruments. 6th edn. W. B. Saunders Company, New York 2002.

[14] *Touboul PJ, Bousser MG, LaPlane D, Castaigne P.* Duplex scanning of normal vertebral arteries. Stroke 1986;17:921-3.

[15] *Demarin V, Škarić-Jurić T, Lovrenčić-Huzjan A, Bosnar-Puretić M, Vuković V.* Vertebral Artery Hypoplasia – Sex-Specific Frequencies in 36 Parent-Offspring Pairs. Coll Antropol 2001;25:501-9.

[16] *Bluth El, Merritt CR, Sullivan MA, Bernhardt S, Darnell B.* Usefulness of duplex ultrasound in evaluating vertebral arteries. J Ultrasound Med 1089;8(5):229-35.

[17] *Delcker A, Diener HC.* The value of color duplex for sonography of the vertebral artery. Vasa Suppl 1991;33:204-5.

[18] *Delcker A, Diener HC.* Color-coded duplex sonography in evaluation of vertebral arteries Bildgebun 1992;59(1):16-21.

[19] *Delcker A, Diener HC.* Various ultrasound methods for studying the vertebral arteries- a comparative evaluation. Ultraschall Med 1992;13(5):213-20.

[20] *Bendick PJ, Glover JL.* Hemodynamic evaluation of vertebral arteries by duplex ultrasound. Surg Clin North Am 1990;70(1):235-44.

[21] *Bendick PJ, Jackson VP.* Evaluation of the vertebral arteries with duplex sonography. J Vasc Surg 1986;3(3):523-30.

[22] *Seidel E, Eicke BM, Tettenborn B, Krummenauer F.* Reference Values for Vertebral Artery Flow Volume by Duplex Sonography in Young and Elderly Adults. Stroke 1999;30:2692-6.

Sažetak

Morfološke i hemodinamske karakteristike vertebralnih arterija kod muškaraca i žena

Uvod: Muškarci i žene se razlikuju u promjerima i srednjim brzinama strujanja krvi (SBSK) u vertebralnim arterijama (VA).

Cilj: usporediti morfologiju i hemodinamiku VA među spolovima.

Ispitanici i metode: Pregledali smo 155 osoba upotrebom linearne sonde 7,5 mHz (Aloka Prosound SSD-5500). Mjerenja su vršena u V2 segmentu VA. Kriteriji: VA dijametar 2-4mm, sistoličke SBSK 0,35-0,70m/s, normalan otpor. Mjereni parametri: promjeri VA, SBSK u VA, ukupni promjeri VA, ukupne SBSK u VAs, promjeri "uže" i šire VA, i dob.

Rezultati: 68 muškaraca i 87 žena; 88 dominantnih lijevih VA (56% muškaraca i 58% žena), 11 (7%) bez dominacije. Razlike među grupama: muškarci imaju šire obje VA i promjer "šire" VA. Nije bilo razlika u sbsk među spolovima.

Zaključak: Lijeva VA je dominantna u oba spola, nema razlika u SBSK među spolovima. Muškarci imaju šire VA od žena.

Ključne riječi: Vertebralna arterija, Hrvatska populacija

INSTRUCTIONS TO AUTHORS

RAD Hrvatske akademije znanosti i umjetnosti – Medical Sciences is a peer-reviewed biomedical scientific journal that publishes contributions relevant to biomedicine. Manuscripts are accepted on the understanding that they are contributed to this journal alone.

General instructions for the preparation of manuscripts are given in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications issued by the International Committee of Medical Journal Editors **(http://www.icmje.org)**.

Manuscripts should be sent to the Address of the Editorial Office.

RAD (ISSN 1330-5301) offers free access to full-text articles on the Portal of Scientific Journals of Croatia – HRČAK **(http://hrcak.srce.hr).** The full text of RAD can be found on EBSCO Publishing's databases.

Address of the Editorial Office
Razred za medicinske znanosti
Hebrangova 1, 10000 Zagreb, Croatia
Tel. ++ 385 1 4895 171
E-mail: vocak@hazu.hr

Rad Hrvatske akademije znanosti i umjetnosti, knj. 497

Nakladnik: HRVATSKA AKADEMIJA ZNANOSTI I UMJETNOSTI

Za nakladnika: akademik Slavko Cvetnić, glavni tajnik; *Tehnički urednik:* Ranko Muhek
Naklada: 500 primjeraka; *Tisak:* Intergrafika