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CLINICAL UPDATES AND MANAGING OF RETT SYNDROME

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Summary

Rett syndrome is a neurological disorder caused by a defective protein involved in the transcription of methylated DNA. It affects almost exclusively girls. The causative gene is the methyl CpG-binding protein2-gene (MECP2) located on the X-chromosome. The diagnosis is made clinically, based on internationally accepted criteria that were last revised in 2010. More than 95% of the MECP2 mutations occur de novo. Over 95% mutation detection rate occurs in individuals with typical Rett syndrome when standard techniques are used to analyze the coding region and through complementing MLPA analysis for large deletions and gross rearrangements in the gene. Early diagnosis and comprehensive life-long management of Rett syndrome can significantly improve the health and longevity of affected individuals. Management is optimized by the involvement of a multidisciplinary team consisting of many different medical and paramedical specialists and an individualized approach at every age. Parents are an integral part of this team, as they become the greatest experts concerning their affected child's history, behavior, and needs.

Key words: Rett syndrome, methyl CpG-binding protein2-gene (MECP2), multidisciplinary team

Introduction

The prevalence of the classic syndrome is estimated to be 1 in 10,000 females [1] but varies according to countries from 1/8000 – 1/15.000. Current understanding of the typical and atypical forms suggests that the overall prevalence is probably much higher. It is the third most common cause of intellectual disability in females next to chromosomal anomalies (e.g. Down syndrome) and the X-linked familial intellectual disability (e.g. Fragile X syndrome in 20% of the female carriers).

Rett syndrome was thought to be an X-linked dominant condition with lethality in hemizygous males for a long time. Rett syndrome in boys with a normal 46, XY karyotype is very rare. Typical RTT, like in girls, can only occur in a boy with an additional X chromosome (carrying the MECP2 mutation) in all cells (47, XXY or Klinefelter syndrome) or in only part of the body cells (somatic mosaic). On the other hand, there are the MECP2 mutations that cause the typical syndrome in girls and where the mother is a healthy skewing carrier. These mutations will lead to intrauterine death or early infantile epileptic encephalopathy with early death before or around the first year of life. In addition, there are the more sporadically occurring variants in MECP2 in males who are hardly seen in RTT girls and whose disease-causing properties are not immediately clear, certainly not when such a case has never been described before. Often these variants in MECP2 are compatible with a long survival. The clinic is then very different without meeting the necessary criteria for the diagnosis of typical or atypical RTT: non-specific intellectual disability; intellectual disability with motor deficits (speech and writing difficulties and / or neurological problems with coordination in motor skills); severe intellectual disability with spasticity with symptoms similar to RTT (scoliosis, hyperventilation, intense visual interaction); intellectual disability with psychiatric disorders (bipolar disorder or juvenile schizophrenia) and tremors; intellectual disability with psychosis, spasticity and macro-orchidism (PPM-X syndrome).The current advances in DNA diagnostics are now more common with MECP2 mutation in males. One estimates the frequency of MECP2 mutation between 1.3 and 1.7% of the male population with intellectual impairment. The clinic in boys is not unequivocal as described in the girls. It is therefore referred to as MECP2 related disorders in males because the clinical phenotype does not meet the diagnostic criteria for RTT (Table 1). In addition, MECP2 duplication syndrome, FOXG1 syndrome and CDKL5 syndrome are considered separate entities, although with many intersections.

Table 1. MECP2 related Sex-associated Syndromes and Symptoms

MECP2	Female	Male
Loss of function	Typical RTT	Infantile epileptic encephalopathy
	Atypical RTT	Typical RTT (47, XXY or somatic mosaic)
	ID with seizures	ID with motor deficits
	Mild ID	Bipolar disease, ID and tremors
	Learning difficulties	Juvenile onset schizophrenia, ID and tremors
	Autism	ID, psychosis, pyramidal signs, macroorchidism (PPMX syndrome)
	Normal carrier	
Overexpression	Preserved speech	Severe ID and RTT features
		Non specific XLMR

The MECP2 duplication syndrome occurs in both sexes with severe intellectual disability in the male and preserved speech in the female, recurrent infections and motor impairment in combination with features similar as in RTT (epilepsy, hyperventilation, autonomic disturbance, etc.) or as a non-specific form of intellectual impairment with or without autistic features. The clinical severity is mainly determined by the extent of the duplication and whether or not other important genes are involved in this duplication.

The pathology of Rett syndrome differs from other disorders with mental retardation in that the pattern of dendritic changes in the brain is unique [2,3]. Brain weight is reduced in girls with Rett syndrome but does not diminish with age. The defined cause of this arrest in brain development and how this results in altered neurophysiology is not yet well understood. There is evident failure of dendritic arborization in specific sites of the brain, correlating with the cortical localization of some of the significant motor and behavioral symptoms. In relation to the peculiar movement disorder in Rett syndrome, the substantia nigra,

basal ganglia, cerebellum, and spinal cord have been found to show specific alterations (Table 2). Various neurotransmitter systems have also been studied with varied and inconclusive results apart from the demonstration of monoaminergic dysfunction. [4].

The disturbances in autonomic function have been studied and related to immaturity of brainstem autonomic centers resulting in hypersensitivity to sympathetic stimuli with insufficient parasympathetic control. This is the so-called sympathicovagal imbalance which is unique in Rett syndrome. [5,6]. New insights into the brainstem phenomena have led to the neurophysiologic delineation of cardiorespiratory phenotypes, such as "forceful breathers," "feeble breathers," and "apneustic breathers." Each of these cardio-respiratory phenotypes has a specific therapeutic approach that will be discussed later.

Table 2. The six (6) cardinal features of RTT in relation to pathology

Affected Part	Reported Pathology	Clinical Observations
Cortical	Decreased dendritic arborization and smaller than normal brain	Severe mental retardation
Cortical	Epilepsy	Seizures
Extrapyramidal	Monoaminergic dysfunction	Dystonia, incoordination of motor activities, orthopedic deformities, and secondary muscle wasting with contractures
Brainstem	Monoaminergic dysfunction	Dyspraxia, agitation, and sleep disturbances
Brainstem	Immaturity with incompetence of inhibitory neuronal networks	Abnormal breathing rhythms and lack of integrative inhibitions, which are likely causes of sudden deaths
Brainstem	Dysautonomia	Cold and blue extremities and sympatho-vagal imbalance

Manifestation and management

Early intervention and comprehensive lifelong management can have a significant impact on the health and longevity of affected individuals. Good management requires the involvement of a multidisciplinary team consisting of many medical and paramedical specialists and the development of an individualized approach. Parents are critical members of the team, as they become the greatest experts concerning their own child's history, behavior, and needs. Many of the suggestions and recommendations described below are the result of over 35 years of personal experience together with review of international scientific expertise.

Growth and feeding

Physical growth retardation and feeding problems are common features of Rett syndrome. The mechanisms causing this growth failure are poorly understood and the role of MeCP2 in physical growth is yet to be investigated. Both nutritional and no nutritional factors are thought to contribute. Height, weight for height, and head circumference are important parameters to follow at each physician visit. Assessment of daily caloric intake by a dietician is important in poor feeders. The influence of involuntary movement activity, abnormal breathing patterns and epilepsy on the balance between nutritional intake and energy expenditure should be considered. Consider the increased likelihood of gastroesophageal regurgitation if food aversion is obvious, and evaluate this in a standard way. Caloric supplements can be added when caloric intake is insufficient and oromotor problems are minimal. A gastrostomy-button should be placed when the child is not able to eat comfortably and without risk of aspiration, to assure sufficient nutritional and caloric intake. Treatment of gastroesophageal regurgitation is standard.

Development and Behavior

Communication

All girls with Rett syndrome have intellectual disability. The absence of speech in most affected girls, the dyspraxia, and the short attention span with lack of interest in play make developmental testing a difficult task. Girls with Rett syndrome are able to make choices and take causally related action. Therefore, parents and caregivers should be aware that the time they require to show what is wanted or to produce their answer to a specific situation is prolonged.

The intense eye contact behavior is further accentuated in older affected females in a typical eye-pointing behavior, which expresses wishes and remains present even in the most severely affected female. Teachers can use this behavior to develop eye communication in habilitation programs, in training emerging literacy and in augmentative communication through eye gaze computer technology. Some girls with Rett syndrome have preservation of speech or use words and sentences in a meaningful way. Many of them continue to learn new words and names far into stage III and into adulthood. This intense eye contact and eye-pointing behavior is very distinct and separates Rett syndrome from other conditions with severe intellectual disability and/or autism.

Intense Hand Stereotypies

These stereotypies disturb communicative interaction through distraction and agitation. They cause difficulty in concentration on objects for a long time. By forcing the girls to stop the arm and hand movements by gently fixing the elbows or by bracing them during sessions of interaction, the child will appear more quiet and concentrated. In this way, some girls will be more cooperative in sessions with the occupational therapist.

Screaming Spells

Some teens and adults experience periodic sudden violent screaming spells. They are often associated with extreme pain though no specific organ pathology is present and thorough examination does not reveal any somatic abnormality. This is not an epileptic phenomenon but rather is defined as "brain-pain-crying," and can last for hours. Others are abnormally prone to agitation and scream when they do not feel safe for whatever reason. The situation returns to normal when moments of rest and peace are given.

Sleep Abnormalities

These are more or less pronounced, and are a constant feature of Rett syndrome. Night laughter, prolonged wakefulness or early morning waking causes great concern for parents, especially in young preschool girls. These problems may persist into adult life. Night laughter clearly does not disturb the child. The fact that affected children and adults are prone to short periods of daytime sleeping is seen as a need for recovery. The mechanism behind this disruptive night awakening and daytime sleeping is not yet well understood. It might be related to the other autonomic dysfunctions that are associated with midbrain

and brainstem immaturity. Melatonin appeared to improve total sleep time and sleep efficiency in the girls with the worst baseline sleep quality. [7,8]. Pipamperon can be used as a regulator of circadian rhythm with little hypnotic side effects (personal experience). It mainly acts as a serotonin-antagonist, with less adrenolytic and anti-dopaminergic action. It is particularly useful when the girl is abnormally prone to agitation. Pipamperon is not available in the United States as of this writing. The use of eye gaze computer is recommended early after clinical diagnosis in order to obtain more information about speech & language development.

Treatment

Augmentative communication methods should be used to capitalize on the intense visual communicative ability. Guidelines for communication in Rett syndrome are to be published in 2018 by an expert group of speech therapists. During therapy sessions, agitation and distraction should be avoided as much as possible, and gently immobilizing the hands may contribute to the quality of the interaction. To establish visual contact behavior, the examiner's face should be brought closely in front of the subject with avoidance of distraction and agitation as much as possible. Bracing the elbows may help with dominant and intense hand stereotypies. Braces in soft but resisting materials can be used. Allow the child daytime periods without them. Evaluate the effect of bracing on behavior. In case of agitation, bracing should be abandoned. In the presence of agitation, moments of private rest and peace should be granted, according to individual needs. Identification of the trigger and its avoidance is the first line treatment. The use of time-out in sensory deprivation can be tried if this fails. Drugs of choice are resperidone (Risperidal®) or pipamperon (Dipiperon®). Regulation of circadian rhythm can be useful. Melatonin and l-tryptophan are useful in initiating sleep; pipamperon, if available, can be used in low normal dosage when agitation is present. Music therapy is recommended in Rett syndrome as affected people seem to enjoy it and perform better. [9].

Neurologic symptoms

Seizures

Epilepsy is present in up to 80% of affected girls at some time in their lives. [10,11]. It usually starts after age 4 years and tends to diminish in severity in adulthood. Many become seizure. The most common seizure types are partial complex, tonic-clonic, tonic, and myoclonic seizures. Although about 50% of sei-

zures can be controlled by medication, intractable epilepsy occurs significantly more frequently in girls with obvious deceleration of head growth. The electroencephalogram is usually abnormal in Rett syndrome, but there is no diagnostic pattern. Electroencephalogram patterns frequently seen in Rett syndrome include generalized slowing, monorhythmic theta waves, and focal and generalized spikes and sharp waves. Neurophysiologists can use an EEG staging system according to the presence or absence of sleep characteristics like K-spindles and reversed vertex waves, slow wave activity and the intensity of generalized spikes and sharp waves. [12]. These EEG stages do not always coincide with the clinical stage.

The age of onset of seizures is later than usually found in severe mental handicap in general. It is surprising that most children with Rett syndrome, although severely impaired, only experience the onset of epilepsy in stages III and IV and not in the rapid regression stage II. Rarely, infantile seizures, variant infantile spasms or other intractable seizures are present before the appearance of classical Rett syndrome features. In spite of this early and severe onset of epilepsy, no negative effect on the long-term course and prognosis of Rett syndrome has been identified. Status epilepticus does not occur more often than in severely mentally retarded children in general. The probability of death associated with epilepsy is estimated at 9%.

Brainstem events may be confused with seizures or are difficult to interpret as such by parents and care takers. Signs of abnormal brainstem activity include blinking of the eyes, facial twitching, vacant spells with no associated epileptiform activity, and hypocapneic attacks with tetany and cyanosis. Classifying these clinical events requires simultaneous neurophysiological monitoring of brainstem and cortical functions and correlation with behavior. Facial twitching with or without sudden changes in attention and eye deviation should not be *a priori* interpreted as epileptic paroxysms in a young child. This reflects more the ongoing process of immature brainstem activity and is not influenced by antiepileptic drugs. Immature brainstem activity also accounts for the screaming spells, laughing spells, prolonged staring, and so on.

Autonomic Cardiorespiratory Manifestations

Irregular breathing in the waking state associated with nonepileptic vacant spells is the most distressing feature in Rett syndrome. It reflects the immaturity of the brainstem and may contribute to sudden death. Low resting cardiac vagal tone and weak vagal response to hyperventilation and breath-holding suggest inadequate parasympathetic control. Neurophysiological studies have

shown that these baseline brainstem functions are affected in Rett syndrome, whereas the baseline sympathetic tone remains at a neonatal level. Insight into these phenomena has introduced new terminology such as "brainstem storm" and "brainstem epilepsy" as phenomena of abnormal spontaneous brainstem activation (ASBA) associated with altered breathing patterns. [5].Evaluating the brainstem functions in Rett syndrome requires detailed neurophysiology. [6]. The primary pathophysiology is related to a defective control mechanism of carbon dioxide exhalation causing respiratory alkalosis or acidosis. Three cardiorespiratory phenotypes are described, each demanding a specific approach [6]. Forceful breathers usually have fixed low levels of pCO_2 (chronic respiratory alkalosis); feeble breathers usually have fixed high levels of pCO_2 (chronic respiratory acidosis) due to weak respiration; apneustic breathers accumulate carbon dioxide due to delayed and inadequate expirations. Agitation in individuals with Rett syndrome is associated with unrestrained sympathetic activity.

Treatment

There is no general rule for the anti-epileptic treatment in Rett syndrome. Each case should be assessed individually. The most commonly used anti-epileptic drugs are sodiumvalproate, lamotrigine, and carbamazepine. Monotherapy is successful in 50%. Polypharmacy should be avoided as much as possible. Individuals with Rett syndrome are sensitive to anti-epileptic drugs and have a tendency to be easily over-sedated, cognitively depressed, and confused. Feeble breathers and apneustic breathers are very sensitive to opiates and benzodiazepines. These drugs should be avoided in them. Gradual withdrawal of anti-epileptic medication should be considered when individuals become seizure-free.

Treatment of brainstem dysfunctions is extremely difficult and hazardous. There is little experience with medication. Vagal nerve stimulation, as in intractable epilepsy, is under debate. To interrupt an episode of forceful breathing, we recommend first short periods of re-breathing in a total face mask, allowing for surrounding air to flow in, connected with a tube between 40 and 60 cm long as dead space. Long-term weaning from the chronic respiratory alkalosis requires Carbogen treatment (5% CO_2 in oxygen mixture) to move the pCO_2 toward normal (39–44 mm Hg). The use of a mixture with 60% oxygen/40% carbon dioxide given by nasal prongs and under medical surveillance is recommended to lift the low pCO_2 to about 40 mm Hg. [13]. In feeble breathers, oral theophylline is the first choice of drug for respiratory stimulation but its clinical tolerance is very poor. Physical activity during person-to-person contact can stimulate breathing but is short-lived. Continuous positive airway pressure (CPAP) can

be used at night. The end point of treatment is to establish normal breathing rhythm at normal or near normal pCO_2. Feeble breathers have great sensitivity to opiates and benzodiazepines. Weaning from artificial ventilation in intensive care is difficult. In apneustic breathers, oral buspirone is the drug of choice because of its effect on apneusis. [14]. Treatment end point and risks are otherwise similar to feeble breathers.

In general, if one considers the sympathicovagal imbalance in RTT, more parasympathetic feedback can easily be offered through the following means: watching favorite video, vibroacoutic stimulation and/or music [9]., bathing and playing with water, personal physical body contact, horseback riding, walking in open air and physical activity in general, frequent small meals. Parents and care givers should keep in mind that a minimum of 2x60 minutes of movement a day can be easily reached through the moments of individual care, nursing and interactions that may be allowed to last longer.

Cardiovascular symptoms

Females with Rett syndrome have a higher incidence of prolonged QT interval, and heart rate variability is diminished. These abnormalities likely result from impairment of autonomic nervous system control, reducing the electrical stability of the heart and precipitating sudden dysrhythmia's. Imbalance between preserved sympathetic tone and insufficient parasympathetic control is known to cause cardiac arrhythmia. Individuals with prolonged QT interval associated with abnormal breathing pattern are particularly at risk for cardiac arrhythmia, especially the forceful breathers. Of the deaths reported to the International Rett syndrome Association in individuals less than 23 years of age, 22% have been sudden, unexpected death, in comparison with 2.3% in the general population up to the same age. [15].

Cold extremities caused by poor perfusion because of altered autonomic control are common. This is more related to the central abnormalities than to vascular conditions. In the long term, it leads to abiotrophic changes.

Musculoskeletal symptoms

Scoliosis

Scoliosis develops in early school age with various degrees of severity. Sometimes progression is very rapid, depending on asymmetry in muscle tone and the degree of dystonia and muscle wasting. In ambulatory girls, scoliosis appears unpredictable—it may never be present or may only develop to a small

extent. In nonambulatory girls with typical Rett syndrome stage IVB scoliosis develops in spite of preventive measures. Most commonly a double curve develops with a longer upper part (most frequently dextro convex) and a shorter lower part (sinistro convex). When there is no neurologic asymmetry, the spine deformity is usually much more benign.

Kyphosis occurs more in ambulatory girls. It may be related to the degree of extension in the ankle muscles. Tiptoe walking in girls with Rett syndrome, in contrast to other circumstances with neurologic deficit, is related to uncertainty and anxiety about falling. Girls gain support and stability by bending forward on stiff legs, giving them more balance against gravity. When sitting and drowsy, girls tend to drop their heads forward causing more bending of the cervical and high thoracic vertebral column. A high kyphosis is not uncommon in the many milder or variant forms of Rett syndrome and can progress by age.

Foot Deformities

The foot deformities most common in Rett syndrome are equinus and equinovalgus/varus positions. As long as the Achilles tendon can be flexed over 90° with the knee in extension, normal walking remains possible. Further shortening of the Achilles tendons is then compensated for by an "escape" in the valgus or varus position. Young girls do not suffer from this and continue to develop walking ability. If there is hyperextension of the ankles, the need for compensation rises to the knees, the hips and the spine, threatening loss of balance and making walking very difficult if not impossible. Affected girls develop a preference for one leg, putting it forward in every step and using the other leg as support and balance. Direction is chosen through the preferential leg. Sometimes the other leg is placed more to the side causing a girl to walk in circles; sometimes the girl tilts it high up and then forward simulating an involuntary movement.

With careful follow-up of muscle tone and posture, especially of the spine and feet, and with timely corrective measures, walking can be preserved for a long time. Abnormal muscle tone in the flexor/adductor muscles of the hip can lead to dislocation especially in non-walking girls. If orthopedic surgery is considered, an evaluation of feeding, epilepsy, skin problems, and behavior should be carried out before hospitalization. The approach to orthopedic deformities in Rett syndrome requires input from parents, therapists, pediatrician, orthopedic surgeon, and a rehabilitation specialist to find a treatment goal related to the individual's level of function in daily life activities. Good sitting and sleeping positions are important. Botox treatment of spasticity can be used in Rett syndrome

as in spasticity in general, but should be done in consultation with the rehabilitation specialists and orthopedic surgeons. [16] Results depend on good advance selection of affected individuals. The effect, however, is limited in time. Braces or orthoses are used for the spine, the foot and the ankle to prevent further deformation and/or to support walking. Severe tonic-clonic seizures should be well controlled by medication before spinal surgery. Early casting of the trunk as a conservative treatment will not prevent surgical intervention in progressive cases. Kyphosis rarely needs surgical correction.

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