

Rett Syndrome: A Case Report.

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Abstract:

Rett Syndrome (RS) is a neurodevelopmental disorder in which girls are predominantly affected, transmitted as an X linked dominant inheritance and caused by mutation in MECP2 gene. The basic presentation in RS is regression of previously acquired developmental milestones, lack of social interaction skills and acquired microcephaly after a certain age, which starts in early months of infancy. It is frequently misdiagnosed as autism, cerebral palsy or nonspecific developmental delay and is relatively frequent cause of delayed development in girls. Diagnosis is mainly clinical after excluding the neurodegenerative and other causes of delayed milestones. The chromosomal analysis, confirmatory tool for diagnosis is available in limited centers. The treatment is mainly speech therapy and counseling though few pharmacological agents have been tried with little response. A ten years age girl presented with the history of seizures, regression of speech and delayed motor milestones in our out patient clinic which was subsequently diagnosed as Rett Syndrome.

Key Words: Rett syndrome, Developmental Regression, X Linked Dominant.

The Case:

A 10 years old girl presented in OPD of Shree Birendra Hospital for recurrent generalized tonic clonic seizures, impaired speech and delayed motor milestones. She could say Baba Mama at the age of 12 months, deterioration occurred in speech in that she could not say anything from the age of 18 month to 36 month of age. Subsequently she improved a bit spontaneously so as to be able to say Didi, Daju Papa Mama Bhai Babu (bi-syllabic words in native language) but only by imitating from the others. Further deterioration in speech appeared at 6 years of age, this time she could not utter any specific words except crying or laughing momentarily. At presentation her language was barely limited to three or four words, language skill at presentation being equivalent to approximately 8-10 month of age. At the same time her motor milestones were also impaired since infancy. She could sit with support at the age of 8 months, stand at 19-20 months and walk at 21 months.

She was a product of non-consanguinity, full term hospital delivery without any significant antenatal or peri-natal events. There was no history suggestive of similar problem in 1st degree relation however; a girl in the 2nd degree relation was known to have similar problems. There was no history suggestive of intra-cranial infection in the past, nor any nutrition related problems.

On examination she was fair looking, active, cheerful but easily annoyed, frequently irritable, constantly picking mouth with fingers. Her height, weight, and occipito-frontal circumference fell below the 3rd percentile of NCHS. She was having very poor social interactive skills for her age and possessed no self-caring ability. She Also had constant wringing movements of hands, patting, clapping, self mutilation behaviours (finger biting, head banging), easily annoyed and could utter 2-3 meaningless words. Systemic examination did not reveal any significant abnormalities. Her

routine blood examination, renal and hepatic function tests, MRI brain, and ECG were normal. She was on anticonvulsants and speech therapy with little response.

Fig. 1 : Picture Showing a Child with Rett Syndrome having self-mutilation behaviour (finger biting).



Discussion:

Rett syndrome (RS), first described by Austrian Doctor, Andrae Rett in 1966 as an X- linked dominant disorder of developmental regression commencing after a few months of infancy and occurring predominantly in girls and the frequency being approximately 1/15,000-1/22,000^{1,2,3}. The gene for RS (methyl-CpG binding protein-2 [MECP2]) was identified late in 1999. Infants and children with RS usually develop normally until approximately age 6 to 18 months. They may then cease to acquire new skills and gradually or suddenly lose previously acquired abilities (developmental regression), such as conscious control of the hands (purposeful hand movements) and the ability to vocalize most sounds or words. Repetitive, uncontrolled hand movements including hand clapping, mouthing, or “washing and wringing” gradually replace acquired hand and finger use. The hallmarks of Rett Syndrome are a period of normal development in the early infancy

followed by regression in language and motor development when the acquired micro-cephaly becomes evident ⁴.

Clinical course and prognosis: In females with classic RS, the disease course tends to follow a relatively predictable pattern, although the age at onset and symptom severity may be somewhat variable. Prior to symptom onset, growth and development before and shortly after birth are apparently normal. For example, newborns have a head circumference that is within normal limits. During the first months of life, infants tend to develop physical, mental, and behavioural skills—or reach “developmental milestones”—at the expected rate. There is loss of expressive language, mental retardation, regression of gross motor milestones, bruxism, characteristic hand movements (wringing, patting, clapping, tapping, and mouthing), generalized tonic clonic seizure in 50%, progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use, ataxia, irritability, insomnia, tremulousness, breath holding spells. Scoliosis and muscle wasting becomes apparent in girls of more than 10 years of age. Death occurs in adolescence or during third decade of infection or cardiac arrhythmia ^{5,6,7,8}.

Stages

Four stages of RS have been defined to help characterize the disorder and improve its recognition and diagnosis. These stages are as follows⁹.

Stage I, called *early onset*, generally begins between 6 and 18 months of age. Quite frequently, this stage is overlooked because symptoms of the disorder may be somewhat vague, and parents and doctors may not notice the subtle slowing of development at first. The infant may begin to show less eye contact and have reduced interest in toys. There may be delays in gross motor skills such as sitting or crawling. Hand wringing and decreasing head growth may occur, but not enough to draw attention. This stage usually lasts for a few months but can persist for more than a year. Stage II, or the *rapid destructive* stage, usually begins between ages 1 and 4 and may last for weeks or months. This stage may have either a rapid or a gradual onset, as purposeful hand skills and spoken language are lost. The characteristic hand movements begin to emerge during this stage and often include wringing, washing, clapping, or tapping, as well as repeatedly moving the hands to the mouth. Hands are sometimes clasped behind the back or held at the sides, with random touching, grasping, and releasing. The movements persist while the child is awake but disappear during sleep. Breathing irregularities such as episodes of apnea and hyperventilation may occur, although breathing is usually normal during sleep. Some girls also display autistic-like symptoms such as loss of social interaction and communication. General irritability and sleep irregularities may be seen. Gait patterns are unsteady and initiating motor movements can be difficult. Slowing of head growth is usually noticed during this stage. Stage III, also called the *plateau* or *pseudo-stationary* stage, usually begins between ages 2 and 10 and can last for years. Apraxia, motor problems, and seizures are prominent during this stage. However, there may be improvement in behavior, with less irritability, crying, and autistic-like features. An individual in stage III may show more interest in her surroundings, and her alertness, attention span,

and communication skills may improve. Many girls remain in this stage for most of their lives. The last stage, stage IV — called the *late motor deterioration* stage can last for years or decades and is characterized by reduced mobility. Muscle weakness, rigidity, spasticity, dystonia and scoliosis are other prominent features. Girls who were previously able to walk may stop walking. Generally, there is no decline in cognition, communication, or hand skills in stage IV. Repetitive hand movements may decrease, and eye gaze usually improves.

Additional abnormalities: Increased risk of sudden death may be due to abnormalities in the transmission of electrical impulses that coordinate contractions of the heart (cardiac conduction system). Long QT syndrome may lead to irregular heart rhythms (arrhythmias), potentially resulting in a sudden loss of consciousness (or syncope) due to insufficient blood supply to the brain and sudden death^{10,11}. In addition, in some RS patients, life-threatening complications may occur as a result of weakened lung function (e.g., due to pneumonia, scoliosis, etc.), malnutrition, or other associated abnormalities. RS patients have decreased bone density and an associated increased risk of bone fractures. There may also be reduced bone density in the hands, shortening of certain bones of the hands and feet (e.g., fourth metacarpals and metatarsals), and shortening of the inner bones of the forearms (ulna)^{12,13,14}.

Diagnosis:

RS remains a clinical diagnosis made on the basis of fulfilling the consensus diagnostic criteria. More than 95% of females fulfilling these criteria will have a mutation in MECP2. Most mutations are sporadic, occurring only once in a family.. Because researchers now understand that the MECP2 mutation also causes other disorders, it is possible to have the MECP2 gene mutation and not have RS. The mutation is on MECP2 gene on long arm of X chromosome. This mutation results in shortage of MECP2 protein, which is required to recruit other genes during early brain development. The diagnostic criteria for RS developed by Rett Syndrome Diagnostic Criteria Work Group (1988)¹⁵.

Symptoms and findings required for a diagnosis of classic RS:

- Normal or apparently normal development until approximately age 6 to 18 months.
- Head circumference that is within normal limits at birth with subsequent slowing of head growth (acquired microcephaly).
- Loss of purposeful hand movements, severe impairment of receptive and expressive language, and apparently severe mental retardation (that may be difficult to accurately assess due to motor and verbal impairments).
- Development of uncontrolled, persistent (stereotypic) hand movements, including repeated hand clapping, mouthing, tapping, washing, and/or wringing.
- Impaired ability to coordinate movements required for walking (in those who are able to walk), resulting in a stiff, unsteady, widely based gait and possible “toe-walking.”

- Fine tremors of the torso and, possibly, the limbs, particularly during periods of agitation.
- Supportive criteria for a diagnosis of RS (not required for diagnosis but may be present or develop with age).
- Breathing irregularities (e.g., periodic apnea and hyperventilation).
- Abnormal brain wave patterns as seen by EEG, possibly including abnormal sleep patterns and seizure activity.
- Increasing motor impairment.
- Restricted movements of certain muscles due to progressively increased muscle rigidity (spasticity).
- Permanent flexion or extension of affected joints in fixed postures (joint contractures).
- Scoliosis.
- Chewing and swallowing difficulties.
- Constipation.
- Growth retardation.

So, the case reported meets majority of clinical criteria viz. regression of milestones acquired in early infancy, language impairment, poor social interaction ability, characteristic hand movements, outbursts of crying and laughing, self mutilation behavior, acquired microcephaly and seizures with no evidence of other causes of delayed development. We could not confirm the disorder with chromosomal analysis due to unavailability of genetic studies in our setting.

Management is essentially symptomatic and supportive; the results of pharmacological treatment are not promising. Speech physiotherapy and long term occupational therapy are being practiced with limited results. L dopa has been tried for rigidity during regression in motor development. Naltraxone may improve irregular breathing, seizure and screaming. L-carnitine and naltrexone tried in some patients has shown to improve language skill^{16,17}.

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