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Rett Syndrome in Two Iranian Girls

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Abstract

Rett syndrome is a disorder of early brain development characterized by developmental regression and deceleration of brain growth after a period of relatively normal developmental course. It occurs predominantly in girls. Nearly all cases of Rett syndrome caused by mutation in the methyl CPG binding protein 2 or MECP2 gene. It is characterized by developmental regression of language and motor milestones and acquired microcephaly after 7-8 months. Hallmark of Rett syndrome is repetitive hand wringingmovement and loss of purposeful and spontaneous use of hands. These finding may not appear until 2-3 year of age. Here we report two case with this syndrome from two family that confirmed by molecular analysis.

Keywords: MECP2 gene, Rett syndrome, developmental regression, hand wringing

Introduction

Rett syndrome or cerebrohepatic hyper ammonemia (OMIM#312750) is a neurodevelopmental disorder that occurs predominantly in girls [1,2]. The frequency is about 1

in 15000-20000 children.

Mutation in MECP2 gene caused this disease, a transcription factor that binds to methylated CpG islands and silences transcription.[2,3,4]. This syndrome was identified by Dr Andreas Rett, an Australian doctors who described it for first time in 1960 and then in 1983 second case reported by Swedish researcher Dr. Benget Hagberg[5,6].

Classic Rett syndrome occurs in girls with normal prenatal and perinatal history, normal birth sizes, and normal psycho-motor development during first 6-12 months.[7] and then regressed motor milestone. bilateral hand washing movement are hallmark of this syndrome. In addition to especially in hand movement, individuals with Rett syndrome also have a variety of other rhythmic movement such as hair pulling, bruxism, and cervical retropulsion that occur more frequently in individual that are mutation positive for MECP2[8].

Case reports

First case

8 year-old girl referred to our center because of developmental regression from about 8 month-old age. She is second child of healthy and unrelated parents. There was no similar case in her family. She was born by cesarean section at term gestational age. Birth weight, length and head circumference was in normal range. Pregnancy and delivery were uneventful.Growth and development was normal up to 8 month-old of age. She had crawling, speaking (4-5 word) and sitting(from6-7 moth-old). At 8 month-old she had 1 episode of convulsion that had not good control and then gradually had developmental regression. Positive finding on exam: weight:11.5 kg (<3%), length:105cm (<3%) and head circumference44.5cm (<3%) She had stereotype movement and tremor in hands, flexion deformity of leg, upward plantar reflex, DTR: hyper (figure 1-1 . 1-2) all lab test: including metabolic screening, aminoacid chromatography, urine for reducing agent, urine for organic acid, thyroid test were normal . ammonia mildly elevated.

EEG: abnormal Molecular analysis was done and she had c.763C>T(p.R255X) mutation in exon 4 in hetero-zygous form.

Figure 1-1

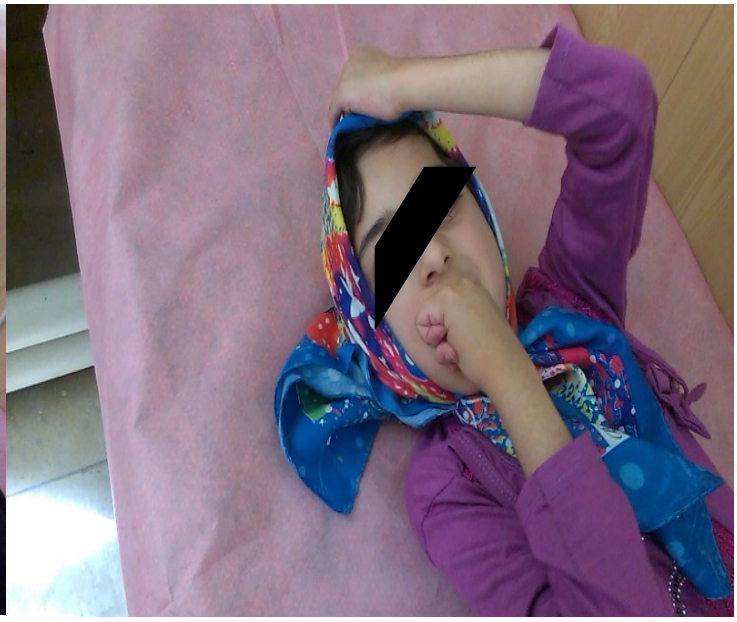


figure1-2

Second case

9 year-old girl that referred to us because of mental retardation. She is a second child of healthyand unrelated parents. There is not similar case in her family. she was born by normal vaginal delivery(NVD) at term gestational age. Birth weight, head circumference and height were in normal range. her mother had history of UTI during pregnancy that received antibiotic. Natal and perinatal history were normal. Growth and development was normal up to 1 year-old of age when motor milestone regress gradually and head growth stopped then repetitive move-ement in hands developed.

Positive finding on exam: -asymmetric facies

-microcephaly

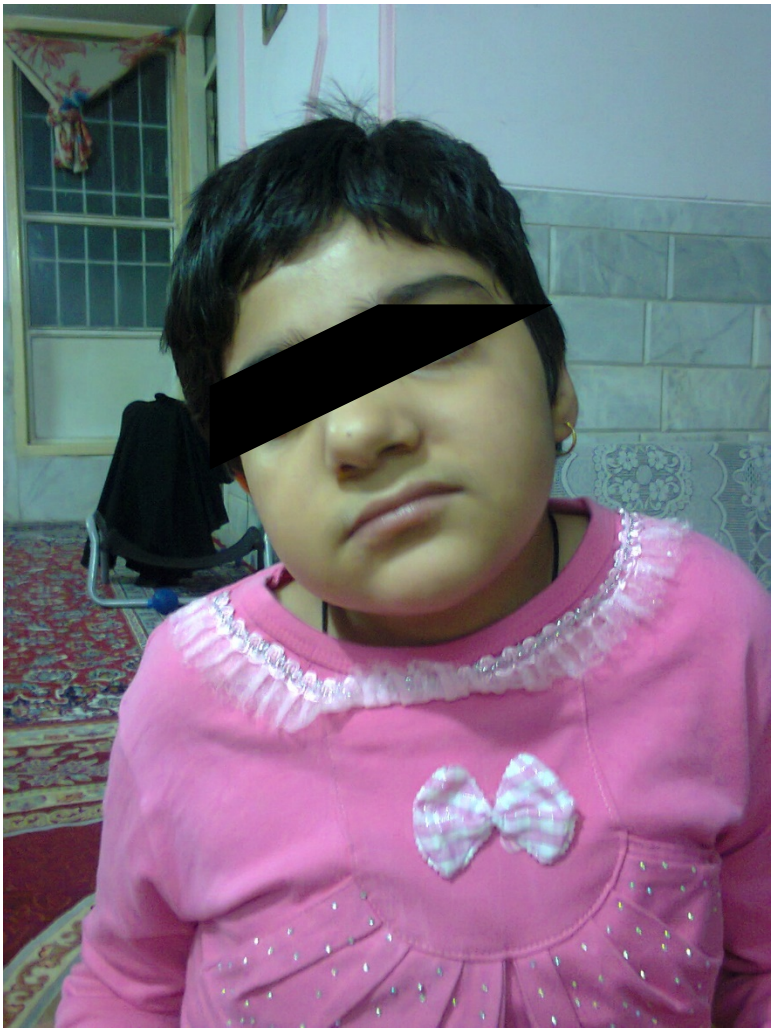
-stereotype movement in hands

-heart murmur

- DTR: hyper

Lab test: metabolic test was normal except ammonia that was in upper limit

Thyroid test: normal, EEG: abnormal, and echocardiography showed ASD 2nd



Discussion

Rett syndrome is a rare but severe regressive brain disorder that affects girls. It is

usually discovered in the first 2 year of life and commonly divided into 4 stage:[9,10,11,14,15]

1- Developmental arrest: sign and symptoms are subtle(at first may be flaccid or mildly Hypotonic) and can last for a few months or a year[1,7]. In this stage the child had not eye contact, there is no interest in toys and may have delay in sitting or crawling. Differential diagnosis in this stage include benign congenital hypotonia, cerebral palsy, praderwilli, angelman, and some of the metabolic disorders.

2- Rapid deterioration : start between 1-4 year of age. In this stage children have not ability to perform skills that they previously had. This loss can be rapid or more gradual and occurring over weeks or months that included decreased head growth, stereotype hand movement including washing motion, hand rubbing, hand-to-mouth licking grasping of hair or clothing and hyper ventilation, abnormal screaming or crying , problem with coordination and loss of social interaction and communication. Differential diagnosis in this stage include: autism, angelman,encephalitis, laundu kleffler, OTC deficiency, PKU, psychosis and infantile neuronal ceroid lipofuschinosis.

3- Pseudostationary(plateau): begins between 2-10 years and can last for many years. Although problem with movement continue, but some improvement in behavior with less crying and irritability and some improvement in hand use and social interaction can be seen.. Seizure may begin in this stage. Differential diagnosis in this stage include cerebral palsy, spinocerebellar degeneration , leukodystrophy, angelman, lennox gastaut.

4- Late motor deterioration: this stage usually begins after age of 10 and can last for years or decades. It is marked by reduced mobility, muscle weakness, joint contracture and scoliosis. They may need wheelchair. All of other degenerative disorders may be in differential diagnosis in this stages.

Most of Rett syndrome cases are caused by identifiable mutation of the MECP2 gene on

Chromosome, a transcription factor that binds to methylated CpG islands and silence transcription and epigenetic regulation of methylated DNA that can arise sporadically or because of germ line mutation.

More than 200 different mutation have been detected up to now. In less than 10% of Rett cases mutation in the genes CDKL5 or FOXG1 have also be found. One of our patient developed symptoms at first stage and another one in second stage that their Parents notice to it. First case with delay in development and regression in motor milestone that had at that time such as sitting and few word speaking, and seizure developed earlier than whatever mention in the literature (stage 3) and in second case her parents note to regression of motor milestones after 1-2 year-old of age. But in both of them definite diagnosis was done atstage 4 by molecular diagnosis and after rule out other possible diagnosis. So I think high index of suspiciousness to this disease in any children with developmental regression and repetitive hand movement lead to earlier diagnosis. Although there is no cure for Rett syndrome up to now but some studies have shown that restoring MECP2 function may lead to cure. Use of IGF1 has been shown to partially reverse signs in MECP2 mutation in mice. Another therapeutic intervention is to counter the neuroexcitotoxic effect of increased spinal fluid level of a neurotr-ansmitter called glutamate and increased NMDA receptor in brain of young Rett girls by the use of dextromethorphan which is antagonist of the NMDA receptor in child below 10 years[12,13].

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