Case report

Clinical profile of a male with Rett syndrome

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Abstract

We describe a clinical profile of a male with Rett syndrome who presented initially with significant axial and peripheral hypotonia, head and truncal titubation and global delay. He is non-ambulatory, lost the few words he had learned and gradually developed hand stereotypes, breathing difficulties, seizures, scoliosis and has osteoporosis sleep problems and sludging in his gall bladder. Prior to diagnosis he underwent comprehensive neurological, metabolic and genetic investigations. After his older sister was diagnosed with atypical Rett syndrome; MECP2 mutation studies on him revealed a pathogenic mutation. His mother is a Rett carrier with a skewed inactivation of chromosome X. Clinical signs and symptoms required to meet the criteria for diagnosis of Rett syndrome have gradually evolved over time. This case demonstrates an unusual family history for Rett syndrome and alerts readers to the utility of screening males for Rett syndrome.

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1. Introduction

Rett syndrome is an X-linked dominant condition that occurs predominantly in females [1]. It was formerly presumed to be lethal in the hemizygous state accounting for the relative lack of reported affected males. Clinical characteristics have been well documented in females with classic Rett syndrome who have MECP2 mutations. Currently there are very few reported males with MECP2 mutations ranging in severity from early neonatal encephalopathy [2] to young adults with mental retardation and neurological signs [3]. Clinical characteristics and criteria have been well described for females with Rett Syndrome to assist in the diagnosis [4], however, there is a paucity of this information for males with MECP2 mutations.

2. Case report

This boy is the second child born to a 30 year old mother. Alpha-feto-protein screen was abnormal but karyotype was 46, XY. Delivery was at term and uncomplicated. Birth length was 51 cm (50%) birth weight was 3.6 kg (50%) and head circumference 34 cm (25%). Family reported normal early development for the first 6 months, however, review of home videos revealed an alert child who was hypotonic. He commando crawled at 10 months. Following this period he made no progress and was referred at 15 months to the developmental clinic for poor weight gain, hypotonia and truncal unsteadiness. Parents reported that he had never made attempts at four-point kneeling or coordinated crawling. At 9 months he had been able to clap his hands but was not doing this when evaluated although he would reach for toys and bring them to his mouth. He had not acquired a pincer grasp. He did have a few vocalizations but no specific words. If held he could bear weight but was unable to pull to sit or stand.
Comprehensive neurological, metabolic and genetic investigations were non-diagnostic.

At 18 months his left eye was turning in, he had more drooling and feeding problems with symptoms of gastroesophageal reflux. He had central hypotonia with brisk deep tendon reflexes, clonus, a planter flexor response on the Babinski, axial and peripheral ataxia. By 2 years and 6 months he was much more tremulous and showed growth failure with deceleration of head circumference. His grasp was random and uncoordinated. He spoke an occasional phrase and he had made no progress in his gross motor development. He was referred to the neurometabolic clinic and had additional extensive diagnostic investigations including a repeat MRI, EEG, urine and blood studies for genetic metabolic and progressive neurological conditions such as Pelizaeus-Merzbacher, Ataxia telengectasia, Friedreich's ataxia, Spino-cerebellar ataxia, leukodystrophies, peroxisomal and mitochondrial disorders. Repeat genetic studies ruled out Fragile X, Angelman's and Prader-Willi syndromes.

At 5 years of age he started having seizures and had epileptiform activity on EEG. He takes anticonvulsants. Six months later he fractured his left femur, which healed. Osteoporosis was diagnosed and confirmed by DEXA. He developed mild ptosis of the right eye; his breathing pattern changed and he lost his ability to use his hands consistently, with onset of hand stereotypes, such as bringing hands together in midline. He developed increasing rigidity of his lower extremities and some rigidity of his arms. Sleep and constipation became major problems. [Fig. 1]

This boy's older sister had developed normally until 25 months of age. She was then reported to have speech and language delays and ataxia, but ambulated freely and paced frequently. She used stairs, was able to use her hands to self-feed, scribble, and manipulated toys and puzzles. She had developmental issues and had been diagnosed with autism. She had been investigated with her brother and all studies were normal. By parental report she started having hand stereotypes at 8 years, although home videos showed subtle hand abnormalities to be present by age 3 years. She was referred for diagnosis of possible Rett syndrome. Her MECP2 mutation studies were positive for the S134C mutation. Her mother’s and brother’s studies were subsequently positive for the same mutation. The mother’s parents were tested and were negative suggesting that mother represents the de-novo mutation within the family. She is a college graduate but reported having had difficulty with speed and dexterity. Her mild clinical course is likely attributed to her skewed X-inactivation favoring the normal X chromosome in 98% of her cells.

By age 10 years our patient had developed scoliosis following subluxation of his left hip which was surgically corrected. His seizures persist, and feeding has become a major problem requiring the use of a gastrostomy. Due to abdominal discomfort he had an abdominal ultrasound which revealed an enlarged gall bladder with sludging of bile.

3. Discussion

Rett syndrome has a more variable clinical course than previously recognized [5]. Identification of the MECP2 mutations allows diagnostic confirmation in approximately 70–80% of clinically suspected cases [6]. Recognition of Rett syndrome in males has been based on their clinical profile. Since there have been few reports of Rett males confirmed by mutation analysis the spectrum of clinical symptoms is not fully known. There have been fewer families with a mother who carries a Rett mutation and who has an affected son and daughter.

The first report in 1990 [3] described two males in their thirties with some of the features of RS but the genetic confirmation was not possible then. Another report postulated that two males with neonatal encephalopathies in families with Rett syndrome possibly carried the locus on the X chromosome [2]. In 1999 another male patient was described who met all the supportive criteria for RS but without the genetic confirmation [7]. A three generational family with RS is reported with two affected males with severe mental retardation and progressive spasticity [8]. More recent descriptions of MECP2 mutations in males with RS and clinical information have provided additional information on the Rett phenotype in males. [9,10].
The finding of a MECP2 mutation in the sister of this boy who carried the diagnosis of autism led to testing him and his mother. This raises the importance of thorough neurological assessment of females with autism to differentiate atypical or milder forms of RS from autism spectrum disorders. The S134C mutation is a missense mutation and occurs in the methyl-cytosine binding domain of the MECP-2 gene. Mutations in this region are thought to interfere with MECP-2's ability to bind to methylated CpGs. Review of the literature identified four reported cases of S134C mutation [11–14]. They all occurred as de novo mutations in females described as having classic Rett Syndrome. Additional cases are reported in the RettBase data base (http://mecp2.chw.edu.au), however clinical information regarding severity of the condition is not available. It is unclear why the sister in this family shows a milder atypical course than those previously described in the literature. She did not show skewed X-inactivation, so the likely explanation is some unidentified genetic influence. The brother who is more severely affected developed all the necessary diagnostic criteria for Rett syndrome.

4. Conclusions

We stress the usefulness of testing for MECP2 mutations in males with unspecified mental retardation and severe progressive neurological problems. Perhaps this will soon become a more widespread screening test as has the study for Fragile X Syndrome. We also suggest need for a neurological assessment of all girls with autism and careful consideration for testing for MECP2 mutations analysis.

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References