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A case report of precocious puberty related to Rett syndrome and a literature review

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Rett syndrome is an X-linked dominant disorder, and the typical phenotype includes intractable epileptic seizures and severe mental retardation, in particular, a rapid regression in language and limited progress in psychomotor development. Premature breast and pubic hair development and advanced bone age are signs of precocious puberty (PP), defined as puberty occurring before 8 years of age in girls. There are rare reports about precious puberty associated with Rett syndrome. Herein, we report the case of a patient with Rett syndrome with precocious puberty. Her first signs of PP occurred 6 months prior to presentation (at 7.5 years old), and the laboratory measurements, including tests of bone age and gonadotropin-releasing hormone stimulation, were positive for PP. PP was controlled after treatment with leuprorelin 3.75 mg for one year. In addition, the genetic and phenotypic spectrum of previously reported cases of Rett syndrome with precocious puberty are reviewed and summarized.

1. Introduction

Rett syndrome is a neurodevelopmental disorder with a prevalence rate in females of 1:8,500. There are two types of clinical manifestations: typical and atypical. Patients with typical Rett syndrome develop normally during early life but demonstrate a significant regression of motor ability and communication skills between the 6th and 18th months of age. Atypical Rett syndrome has various clinical manifestations, and these individuals present with milder and more severe phenotypes. Individuals with partially atypical Rett syndrome have no regular developmental period or have less serious regression and milder manifestations of Rett syndrome. The final diagnosis of Rett syndrome mainly depends on the genetic diagnosis.

To our knowledge, most reported cases of Rett syndrome have been in females, but there are few studies about the pubertal development of individuals with Rett syndrome. In previously reported cases of Rett syndrome, 5 of these individuals had precocious puberty (Xu and Liu 2021; Bernstein et al. 2019; Bas et al. 2013; Huppke et al. 2003; Holm 1985). Here, we report an additional case of Rett syndrome in which the patient had precocious puberty. To reveal the association between Rett syndrome and sexual precocity, we also reviewed the literature to evaluate the genotypic and phenotypic spectrum of this disorder.

2. Case

An 8-year-old girl was referred to our hospital due to premature breast and pubic hair development for 6 months. The girl was diagnosed with Rett syndrome at the age of 4 on the basis of mental retardation and epileptic seizures. The patient was born to a nonconsanguineous couple, and the proband's mother suffered from gestational diabetes. The patient was born at 37 weeks by caesarean section with Apgar scores of 8, 10 and 10 at 1, 5 and 10 min, respectively. Her birth weight was 3000 g, and her height was 51 cm. The developmental milestones were normally achieved before 1 year of age. She could raise her head at 2 months of age, rollover at 4 months of age, sit unaided at 6 months of age, and say papa and mama at 12 months of age. However, the first episode of a loss of consciousness and convulsions occurred at 18 months of age, and she was diagnosed with epilepsy on the basis of abnormal electroencephalograms (EEGs). In the central area, parietal area, middle temporal area and posterior temporal lobe area, bilateral low- to medium-amplitude sharp waves, sharp and slow waves, spike waves, spike and slow waves, and multiple spike and slow waves were discharged individually or continuously and frequently. After epileptic episodes several times a day at 18 months old, the girl could not stand alone, and she lost her ability to speak. She had purposeless hand movements and acquired microcephaly, with no special facial features or abnormal gait. Brain MRI showed bilateral abnormal white matter signals in the frontal and parietal lobes and brain atrophy (Fig. 1).

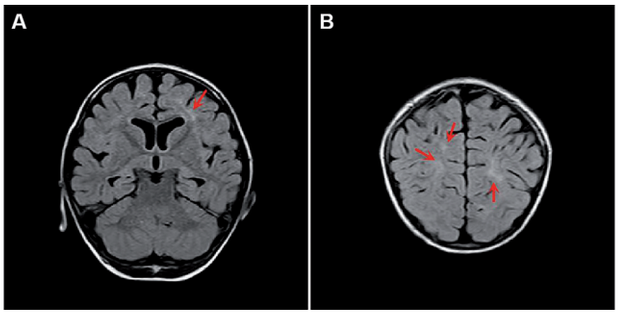

Fig. 1: Brain MRI showing bilateral abnormal white matter signals in the frontal and parietal lobes (red arrows) and brain atrophy.

The *de novo* variant c.1157_1197del (p.L386fs) was identified in our genetic analysis of the patient. This variant is located at the C-terminus and results in a truncation that causes the loss of the last 101 amino acids of the MECP2 protein; these amino acids were replaced by four incorrect amino acids, resulting in abnormal protein function, similar to previously reported cases. However,

this variant was not found in her parents. Finally, she was diagnosed with Rett syndrome at 4 years old. Then, she received topiramate and Keppra treatment, her seizure frequency was reduced (1-2 times in half of a year), and her condition remained stable for approximately 2 years (5-7 years old). However, in the 6 months prior to presentation, seizures occurred several times (5-6 times for a month; i.e., as often as before).

The premature breast development was noticed 6 months prior to presentation (7.5 years old), pubic hair development occurred 4 months prior to presentation (7.6 years old), and pubertal development was rated phase II-III (B3, PH2) according to Tanner stages. Her height was 128 cm, her weight was 18 kg, and her head circumference was 47 cm. The annual growth rate of height was 9 cm for nearly one year, with a lower growth rate before PP (average growth rate was 5 cm per year). Gonadotropin-releasing hormone (GnRH) analysis (by immunochemiluminescence assay, ICMA) showed high luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, which were 11.3 mU/ml and 8.6 mU/ml, respectively, and the LH/FSH ratio was 1.3 (the normal prepubertal LH level is <5 mU/ml, and the normal LH/FSH ratio value is <0.6). The plasma oestradiol level (by ICMA) was 14 pg/ml (normal value <13.6 pg/ml). The FT4 level was 10.1 pmol/L (reference range 11.5-22.7 pmol/L). The levels of the tumour markers ACTH (adrenocorticotropic hormone), plasma cortisol, and HCG (human chorionic gonadotrophin) were normal. Ultrasound showed ovaries of normal volume with numerous follicles (the largest follicle was 0.6 cm), indicating the onset of puberty. The child's bone age was estimated at 9.5 years by the Greulich and Pyle method (Berberoğlu 2009; Partsch et al. 2002). MRI of the *Sella turcica* and ultrasound of the adrenal gland revealed normal findings, while the findings of other parts of the brain were similar to before. These findings were consistent with the diagnosis of idiopathic PP (precocious puberty). Our patient was successfully treated with a GnRH analogue (leuprorelin 3.75 mg every month) and Euthyrox (2 µg/kg/day).

At the one-year follow-up, the seizures of the patient were controlled, occurring 1-2 times yearly. Her height was 134 cm, and her weight was 21 kg, while breast development was graded B2 and PH2. GnRH analysis showed that the peak LH level was 2.8 mU/ml, the FSH level was 3.1 mU/ml, and the LH/FSH ratio was 0.9. The patient's bone age was estimated at 9.5 years.

3. Discussion

According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM5), the diagnostic criteria for Rett syndrome include 4 main diagnostic criteria (a partial or complete loss of acquired purposeful hand skills, a partial or complete loss of acquired spoken language or language skills, gait abnormalities, or stereotypic hand movements) and 11 supportive criteria (e.g., small cold hands and feet, scoliosis, abnormal muscle tone, bruxism when awake, or breathing disturbances). Patients with typical Rett syndrome present with all the diagnostic criteria, while patients with atypical Rett syndrome present with only a subset of the symptom complex, including both milder and more severe phenotypes. Patients diagnosed with atypical Rett syndrome must have 2 of the 4 main diagnostic criteria plus 5 out of the 11 supportive criteria (Bernstein et al. 2019).

Mutations in *MECP2* account for 80%–96% of cases of classic Rett syndrome, while mutations in several other genes, e.g., *CDKL5, CACNA1A, GNAO1, GRIN2B*, and *FOXG1,* have been identified in patients with atypical Rett syndrome (Epperson et al. 2018; Gerald et al. 2018; Harada et al. 2018; Kyriakopoulos et al. 2018; Villard 2007). The *MECP2* gene, located on chromosome Xq28, encodes a chromatin-associated protein that binds methylated CpG dinucleotides in promotors. There are three major functional domains in the MECP2 protein: an amino-terminal methyl-binding domain (MBD), a nuclear localization domain, and a transcription repressor domain. Variants in the MBD tend to be associated with more severe clinical Rett phenotypes (Weaving et al. 2003). MECP2 is widely expressed in the brain and plays an essential role in the process of neuron maturation, and variants in *MECP2* lead to detrimental impacts in different stages of brain development, ranging from mild intellectual disability to severe neonatal encephalopathy, which can even cause death in early infancy (Villard 2007). The *de novo* variant c.1157_1197del was identified in our genetic analysis of the patient. This variant is located at the C-terminus and results in the loss of the last 101 amino acids of the MECP2 protein; these amino acids were replaced by four incorrect amino acids, resulting in abnormal protein function due to the protein truncation. The C-terminal domain of MECP2 is necessary for the inhibition of pre-microRNA processing. An intact C-terminus of MECP2 is required for interaction with microRNAs involved in the transcriptional and translational regulation of other target genes (Cheng et al. 2014). The variant in our patient is also located in exon 4, which is a proline-rich domain. A previous report suggested that nearly 77.7% of classic and atypical Rett patients showed changes within the coding region of exon 4, which suggests that our variant is also a hotspot mutation (Li et al. 2007).

Puberty occurring before the age of 8 years in girls and 9 years in boys is considered precocious. There are central and peripheral precocious puberties that are caused by different pathologies. Central precocious puberty (CPP) is actually true precocious puberty and is due to premature activation of the hypothalamo-pituitary-gonadal (H-P-G) axis, while pseudoprecocious puberty (PPP) is caused by genetic diseases, including McCune-Albright syndrome, familial male-limited precocious puberty (FMPP), congenital adrenal hyperplasia (CAH), or acquired causes, including tumours with human chorionic gonadotropin (HCG), sex steroid-excreting tumours of the adrenal gland, ovary, or testis and exposure to exogenous sex hormones (Berberoğlu 2009). Since Rett syndrome is a complex neurodevelopmental disorder affecting mostly females, research on puberty in those with Rett syndrome is limited. Recent studies revealed that the average age

Table: Clinical features of individuals with Rett syndrome with precocious puberty and *MECP2* mutations reported to date

Phenotype & genotype	Xu et al. (2020)	Bernstein et al. (2019)	Bas et al. (2013)	Huppke et al. (2003)	Holm et al. (1985)	Present study (2021)
Developmental regression	+	+	+	+	+	+
Mental retardation	+	+	+	+	+	+
Stereotyped movements	+		+	+	+	
Microcephaly			+		+	
Seizures	+	+	+			+
Abnormal EEG	+	+	+		+	+
Episodic hyperventilation			+		+	
Precocious puberty	+	+	+	+	+	+
Genotype	c.397C>T	c.1162_1172del	c.455C>G	c.502C>T	No did	c.1157_1197del
Protein	p.R133C	p.Pro388*	p.P152R	p.R168X	No did	p.L386fs

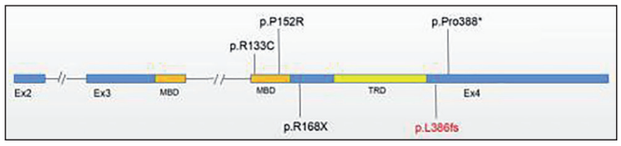

Fig. 2: Map of *MECP2* mutations in patients with Rett syndrome with precocious puberty. MBD, methyl-CpG-binding domain; TRD, transcription repression domain. The *de novo* mutation of the current patient is in red font.

of menarche in females with Rett syndrome was 12.2 years (SD 5.4 years), and the mean age of Tanner stage 2 breast development was 7.1±2.5 (SD) years, which was consistent with rates within the general population (Humphrey et al. 2021). However, some cases of precocious puberty still appear in individuals with Rett syndrome (Xu and Liu 2021; Bernstein et al. 2019; Bas et al. 2013; Huppke et al. 2003; Holm 1985). The cause of precocious puberty in individuals with Rett syndrome is unknown, and the relationship between precocious puberty and Rett syndrome is uncertain. To determine the high-risk factors for precocious puberty in Rett syndrome patients, we evaluated the genotypes and phenotypes of these patients (Table and Fig. 2).

Based on studies of the correlation between hormones and epilepsy, several studies have shown that epileptic activity, especially mediated through the amygdala, alters reproductive function, including changing ovarian cyclicity in females and altering sex steroid hormone levels in both sexes (Zaatreh et al. 2000). Furthermore, there is asymmetric activation of the hypothalamus with unilateral amygdala seizures. This may be the basis for the occurrence of different reproductive endocrine disorders described for patients with left-sided or right-sided temporal lobe epilepsy (Taubøll et al. 2015). Moreover, long-term treatment with some older antiepileptic drugs may lead to dyslipidaemia or thyroid disturbances, which also can affect the hypothalamo-pituitary-gonadal (H-P-G) axis and thereby lead to PP (Berberoğlu 2009). Our patient had intractable epilepsy and convulsions several times after 7 years of age, which may have triggered sexual development mediated by the amygdala. Thyroid dysfunction may aggravate reproductive hormone disorders. We infer that these factors together may have induced PP in our proband. On the other hand, GnRH can suppress epilepsy through the downregulation of high oestrogen levels. Oestrogen increases neuronal excitability through its effect on N-methyl-D-aspartate receptors. The pubertal level of oestrogen in this prepubescent girl may have decreased the neuronal seizure threshold, leading to the development of intractable epilepsy (Govil-Dalela et al. 2016). The convulsions of our patient worsened frequently in the 6 months prior to presentation, without changes in the environment, infection, stress, depression, insomnia or drug interruption syndrome. High levels of reproductive hormones, including oestrogens, LH, and FSH, may have been responsible for the severe epilepsy in the six months prior to presentation. After the initiation of treatment with a GnRH analogue, the oestradiol levels began to fall back to prepubertal levels, the seizures subsided as well.

All of the cases reported in the literature of Rett syndrome with PP, including our case, reported CPP instead of PPP, and the majority of these individuals (5/6) had abnormal EEGs and (4/6) intractable epilepsy. By further analysis of the molecular biological findings, we found that all patients (excluding the patients with no genetic testing results in 1985) had mutations in *MECP2,* similar to our patient; therefore, we infer that the *MECP2* mutation may be a hotspot mutation for Rett syndrome with precocious puberty. However, the association between *MECP2* mutations and CPP still needs more research.

In conclusion, this is an additional case of Rett syndrome with precocious puberty, and we revealed a *de novo* disease-causing variant in *MECP2*. Rett syndrome patients with epilepsy, especially intractable epilepsy, need to be closely evaluated for gonadal development and CPP, and treatment for this condition should be initiated early. The association of precocious puberty and *MECP2* mutations has not been reported before, and further experiments are needed for the clarification of this association.

Ethics approval and consent to participate: All patients were informed and signed informed consent voluntarily. This study was approved by the ethics committee of West China Second University Hospital, Sichuan University and complied with the guidelines outlined in the declaration of Helsinki were followed.

Consent for Publication: The written consent was received from all participants.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest: None declared.

Authors' contributions: LLY and MYJ designed the experiments. LLY and MYJ performed the experiments. YRX and HRL collected and analyzed the data. FX and JRL drafted manuscript. All authors read and approved the final manuscript.

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