

## CLINICAL QUIZ (p184) ANSWER

### What is the diagnosis ?

In view of developmental regression, stereotypic midline hand movement, loss of speech, Rett syndrome (RTT) was suspected. Methyl-CpG-binding protein 2 (*MECP2*) gene was tested that showed a denovo heterozygous missense pathogenic variant c.401C>G. This variant has been reported in the literature to be associated with Rett syndrome, therefore the diagnosis of Rett syndrome in this girl was substantiated.

### What is Rett syndrome?

Rett syndrome is a progressive neurodevelopmental disorder characterised by apparently normal psychomotor development during the first 6 to 18 months of life, followed by a rapid regression in language and motor skills. During the phase of rapid regression, replacement of purposeful hand use by repetitive, stereotypic hand movements is pathognomonic.

### What are the clinical features of *MECP2*-related disorder?

*MECP2*-related disorders in females include classic Rett syndrome, variant Rett syndrome, and mild learning disabilities. It is typically lethal in males but rare surviving males can present with neonatal encephalopathy and intellectual disability.

#### **Classical Rett syndrome**

There is usually apparently normal in psychomotor development during the first 6 to 18 months of life, followed by a rapid regression in language and motor skills. The hallmark is loss of purposeful hand use and replaced by repetitive stereotypical hand movements. Head growth may begin decelerating as early as age three months. Seizures occur in about 90% of females, mostly with generalised tonic-clonic seizures and partial complex seizures.<sup>1</sup> They may have screaming fits and inconsolable crying by age 18-24 months. Additional characteristics include autistic features, panic-like attacks, bruxism, episodic apnoea and/or hyperpnoea, seizures, gait ataxia and apraxia, and tremors. After rapid deterioration, the neurologic manifestations become relatively stable. Other features including failure to thrive, maybe partially related to oropharyngeal and gastroesophageal incoordination resulting in poor dietary intake.<sup>2</sup> Constipation is also very common in Rett syndrome. More than 80% of patients have scoliosis.<sup>3</sup> About 70% of patients also have osteopenia and increases the risk of fractures.<sup>4</sup> One of the most life threatening problem in Rett syndrome is cardiac arrhythmia that included prolonged QT interval, T-wave abnormalities, and reduced heart rate variability which may account for some cases of sudden death in Rett syndrome.<sup>5</sup>

#### **Atypical RTT / Rett syndrome variant<sup>6</sup>**

- Preserved Speech Variant (Zappella Variant): developmental regression at 1-3 years old, with milder reduction of hand skills. There is recovery of language after regression at about mean age of 5 years old. This variant got a lower frequency of epilepsy, and relatively normal head circumference. Mutations in *MECP2* were found in majority of cases.
- Early Seizure Variant (Hanefeld Variant): early onset of seizure, mostly before 5 months of life. *MECP2* mutation is rarely found in this type of variant, instead *CDKL5* mutation maybe found.
- Congenital Variant (Rolando Variant): Grossly abnormal initial development, with severe psychomotor delay and inability to walk. Microcephaly and regression occur much earlier than in classical Rett syndrome, with mostly in the first 4-5 months old. This variant is associated with *FOXG1* mutations.

## What are the diagnostic criteria of Rett syndrome?

The diagnostic criteria was updated and modified in 2010,<sup>6</sup> which shown in table below:

Rett syndrome diagnostic criteria 2010

Consider diagnosis when postnatal deceleration of head growth is observed.

### Required for typical or classic RTT

1. A period of regression followed by recovery or stabilisation
2. All main criteria and all exclusion criteria
3. Supportive criteria are not required, although often present in typical RTT

### Required for atypical or variant RTT

1. A period of regression followed by recovery or stabilisation
2. At least 2 out of the 4 main criteria
3. Five out of 11 supportive criteria

### **Main criteria**

1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of acquired spoken language
3. Gait abnormalities: Impaired (dyspraxia) or absence of ability
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms

### **Exclusion criteria for typical RTT**

1. Brain injury secondary to trauma (peri- or Postnatally), neurometabolic disease, or severe infection that causes neurological problems
2. Grossly abnormal psychomotor development in first 6 months of life

### **Supportive criteria for atypical RTT**

1. Breathing disturbances when awake
2. Bruxism when awake
3. Impaired sleep pattern
4. Abnormal muscle tone
5. Peripheral vasomotor disturbances
6. Scoliosis/kyphosis
7. Growth retardation
8. Small cold hands and feet
9. Inappropriate laughing/screaming spells
10. Diminished response to pain
11. Intense eye communication – "eye pointing"

### What are the genetic abnormalities and inheritance pattern of Rett syndrome?

Rett syndrome is a X-linked dominant disease, due to mutations in *MECP2* gene. It is seen almost exclusively in females, as most males die in utero or shortly after birth. However, there are occasional report of surviving males with 47,XXY<sup>7</sup> or somatic mosaicism.<sup>8</sup> Male carrying *MECP2* mutation can also rarely present as severe neonatal encephalopathy and manic-depressive psychosis, pyramidal signs, Parkinsonism, and macro-orchidism (PPM-X syndrome).<sup>9</sup>

Most cases (>90%) are sporadic. Occasionally reported on asymptomatic female carriers found in familial Rett syndrome. It is mainly due to extreme skewing of their X chromosome inactivation, allowing a normal female phenotype in the carrier.<sup>10</sup>

Mutation in other genes were reported to be associated with atypical Rett syndrome. Mutation of *CDKL5* was found to be associated with early-seizure onset variant of Rett syndrome.<sup>11</sup> Mutations in *FOXG1* is also characterised as having the congenital variant of Rett syndrome.<sup>12</sup> However, there are discussions on whether *CDKL5* and *FOXG1* mutations actually a different disease entities from Rett syndrome.<sup>13,14</sup>

### What is the management strategy of Rett syndrome?

Management is mainly symptomatic using a multidisciplinary approach. Guideline has been developed for the management of scoliosis in Rett syndrome.<sup>15</sup> Low dose risperidone or selective serotonin uptake inhibitors have been shown successful in treating behavioral problem like agitation. Adequate fluid intake and a high-fiber diet may help treating constipation. Prolonged QTc may benefit from the use of  $\beta$ -blockers and avoidance of medication known to prolong the QT interval.

Some ongoing novel therapeutic trials included using Insulin-like Growth Factor 1,<sup>16</sup> and dextromethorphan, an antagonist of the NMDA receptor<sup>17</sup> have been shown partial positive result in Rett syndrome.

### References

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