Case Report

A Female with Severe Developmental Delay, Aggressive Behaviour, Hyperphagia, and Obesity: An Atypical Phenotype of a MECP2 Mutation

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Introduction

Rett syndrome (RTT; OMIM 312710) is a neurodevelopmental disorder characterized by language and motor regression, loss of purposeful hand movements, and the development of stereotypical hand movements.[1,2] RTT is known to be caused by mutations in the X-linked gene, *Methyl-CpG-Binding Protein 2 (MECP2)* (OMIM 300005). Interestingly, *MECP2* mutations have also been implicated in other neurodevelopmental conditions such as autism, non-specific intellectual disability, and neonatal encephalopathy.[3-5] Here we describe a female, with a previously reported *MECP2* mutation, who displayed none of the features of typical or atypical RTT. Rather, the patient presented with severe developmental delay, prominent aggressive behaviour, hyperphagia, and obesity. In this report, we aim to broaden the phenotypic spectrum of *MECP2* mutations. We suggest that these mutations should be considered more broadly in patients with severe behavioural disturbances with or without intellectual disability. Overall, a precise genetic diagnosis can have important ramifications for anticipatory guidance and a patient's ability to access adequate social support services.

Case Presentation

We report a female with severe developmental delay and behavioural issues whom we followed in our genetics clinic from the age of 4 until the age of 19. She was the first child born to healthy, non-consanguineous Filipino parents. The pregnancy, delivery, and neonatal course were uncomplicated. Her birth weight was 2800 g (15th to 50th percentile, WHO growth chart). Apart from mild episodes of wheezing, treated with fluticasone and salbutamol puffers as needed, the patient was healthy and was on no other medications.

At present, the patient remains severely delayed in all developmental domains. She was hypotonic as an infant and only began walking at 23 months. Her fine motor skills are impaired as well; she finger feeds but uses utensils poorly. She is able to use scissors and scribble. She is unable to dress independently and has never been toilet trained.

She uttered her first words at 18 months, but presently still only speaks a few words. As a result, she communicates via pointing, grunting, gestures, and picture exchange; she often leads a caregiver's hand towards a desired object. Overall, she can follow simple 1-2 step commands. Socially, she has always been very affectionate with her parents and workers, has always had good eye contact, and has never exhibited any autistic features. In particular, she has never developed perseverations, hand stereotypies, or loss of purposeful hand movements.

At present, most concerning for her parents is her extremely aggressive behaviour. She has exhibited this behaviour all her life, but it has worsened when she started menstruating at the age of 9. The aggression is directed against both her parents and other people, and consists of pinching, hitting, biting, and throwing objects. She underwent behaviour therapy and was tried on multiple psychiatric medications, eventually showing mild improvement on risperidone. Her behaviour becomes particularly difficult about one week prior to her menstrual period until about one week after it. Furthermore, several attempts at hormonal suppression did not improve her aggressive behaviour.

The patient has never experienced feeding difficulties, but by the age of 7 developed hyperphagia and gained a significant amount of weight. Her weight increased from the 75th percentile at 4 years, to the 90th percentile at 7 years. At 19 years, she weighs 75.8 kg (97th percentile, WHO growth chart). She does not wake up at night to eat but does take other people's food. She also becomes interested in eating anytime she sees someone else having a meal.

She has also had impaired growth velocity. Her height dropped from the 50th percentile at 4 years, to the 10th percentile at 7 years, and to below the 3rd percentile (145 cm) at 19 years. Her head circumference has remained steady at around the 50th percentile.

The patient has had generalized seizures between 4 and 6 years of age; several anti-epileptics were tried until they were

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controlled with carbamazepine. She remained on carbamazepine until the age of 12, and has not had seizures since.

On family history, the patient has a younger sister who is healthy. Her mother has a first cousin and a first cousin once-removed who both have developmental delay, and another first cousin once-removed with Down Syndrome. The family history is otherwise negative for any known childhood illnesses or genetic conditions.

On examination, the patient has facial features in keeping with her Filipino background and is not grossly dysmorphic. She has a central hair whorl, mild synophrys, epicanthal folds, a broad nose with a flat nasal bridge, a well-formed philtrum, full lips, a normal palate, and ears of normal shape and set. She has mild clinodactyly. Her feet are flat with calloused arches. The rest of her physical examination has been unremarkable except for a red reticular birthmark on her left leg. Generalized hypotonia was noted during infancy and childhood, but at 19 years her tone is grossly normal.

Investigations and Diagnosis

Initial investigations at the age of 4 revealed a normal female karyotype and were negative for a Fragile X mutation. Complete blood count, thyroid stimulating hormone, ferritin, plasma amino acids, urine organic acids, and urine oligosaccharide and mucopolysaccharide screen were normal. At the age of 7, her symptoms of aggression, hyperphagia, and weight gain prompted a suspicion of Smith Magenis Syndrome, Prader Willi Syndrome, or Angelman Syndrome; genetic testing for all three conditions was negative. A waking electroencephalogram at 7 years was abnormal, showing intermittent slow waves over the bilateral fontal and central head regions.

At the age of 19, a single nucleotide polymorphism microarray and a comprehensive intellectual disability (ID) genetic panel were performed. The microarray was normal, but the ID panel revealed a truncation mutation in *MECP2*: c.1164_1207del (p.389*). Information on RettBASE[6] showed that this is a known *MECP2* mutation, previously reported in 45 individuals in association with classic and atypical RTT as well as non-RTT phenotypes. Several variants of uncertain significance were found in other genes, but no other pathogenic mutation was identified.

Discussion

In addition to severe developmental delay, this female presented with prominent aggressive behaviour, hyperphagia, and obesity, which are features typically associated with other neurodevelopmental syndromes, most notably Smith-Magenis Syndrome and Prader-Willi Syndrome.[7-8] Aggression and obesity have emerged in a small number of reports, however, in association with *MECP2* mutations in individuals presenting with both RTT and non-RTT phenotypes.

Prominent aggression has been reported in two female patients with *MECP2* mutations and skewed peripheral X chromosome inactivation. One of these patients also exhibited typical features of RTT, including stereotypical hand movements and developmental regression.[9] The other, who carried the same *MECP2* deletion as our patient, had normal development but exhibited mild learning difficulty, occasional hand stereotypies, hyperventilation when under stress, and episodes of uncontrolled aggression.[10] Another recent report discusses a female with typical RTT, severe irritability and aggression, successfully treated with lithium.[11] On the other hand, a small study comparing behavioural characteristics in adults with typical RTT and autism identified elopement and mouthing/swallowing objects, but not aggression towards others, as prominent features of RTT.[12]

Obesity has been reported in various studies among both males and females with *MECP2* mutations and milder phenotypes.[13-14] In one report, a familial *MECP2* mutation was identified in four related males with moderate intellectual disability, resting tremors, and obesity, one of whom also displayed aggressive behaviour.[15] In another report, a novel *MECP2* missense mutation was found in a father and daughter both affected with obesity and various behavioural disturbances. The daughter exhibited aggressive outbursts and mild autistic traits, mild intellectual disability, and fine motor impairments. The father's difficulties included behavioural dysregulation, ADHD traits, a learning disability, low average intellectual functioning, and perceptual-motor difficulties.[16]

It has been proposed that much of the phenotypic variability of individuals with *MECP2* mutations can be attributed to variations in X chromosome inactivation patterns in different regions of the brain.[17] In fact, in an interesting mouse study, conditional knockout of *MECP2* from Sim1-expressing neurons in the hypothalamus resulted in behaviours similar to those manifested by our patient – namely, aggression, hyperphagia, and obesity – but not the typical RTT features of motor incoordination and learning and memory deficits.[18] Peripheral X chromosome inactivation patterns were not measured in our patient, as it is unclear to what extent peripheral patterns can predict X chromosome inactivation patterns in the brain.[19]

Conclusion

In summary, this case illustrates that the phenotypic spectrum of *MECP2* mutations is broader than often considered, and that *MECP2* mutations should be considered in the differential diagnosis even for patients presenting with predominantly behavioural disturbances.

References

1. Amir RE, Van den Veyver IB, Wan M, et al. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 1999;23:185-8.
2. Christodoulou J, Ho G. MECP2-Related Disorders. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Seattle: University of Washington; 2012. Available: http://www.genetests.org (accessed 2016 Aug. 31).
3. Zahorakova D, Lelkova P, Gregor V, et al. MECP2 mutations in Czech patients with Rett syndrome and Rett-like phenotypes: novel mutations, genotype–phenotype correlations and validation of high-resolution melting analysis for mutation scanning. J Hum Gen 2016;61:617-25.
4. Carney RM, Wolpert CM, Ravan SA, et al. Identification of MECP2 mutations in a series of females with autistic disorder. Pediatr Neurol 2003;28:205-11.
5. Harvey CG, Menon SD, Stachowiak B, et al. Sequence variants within exon 1 of MECP2 occur in females with mental retardation. Am J Med Genet B Neuropsychiatric Genet 2007;144B:355-60.
6. Christodoulou J, Grimm A, Maher T, et al. RettBASE: the IRSA MECP2 variation database – a new mutation database in evolution. Hum Mut 2003;21:466-72.
7. Powis L, Oliver C. The prevalence of aggression in genetic syndromes: a review. Res Dev Disabil 2014;35:1051-71.
8. Alaimo JT, Barton LV, Mullegama SV, et al. Individuals with Smith-Magenis syndrome display profound neurodevelopmental behavioral deficiencies and exhibit food-related behaviors equivalent to Prader-Willi syndrome. Res Dev Disabil 2015;47:27-38.
9. Suter B, Treadwell-Deering D, Zoghbi HY, et al. Brief report: MECP2 mutations in people without Rett syndrome. J Autism Dev Disord 2014;44:703-11.
10. Huppke P, Maier EM, Warnke A, et al. Very mild cases of Rett syndrome with skewed X inactivation. J Med Genet 2006;43:814-6.
11. Kinay D, Kaya I, Soyata AZ, et al. Beneficial effects of lithium on severe irritability in a patient with Rett syndrome. J Child Adol Psychop 2016 (Epub ahead of print).
12. Matson JL, Dempsey T, Wilkins J. Rett syndrome in adults with severe intellectual disability: exploration of behavioral characteristics. Eur Psychiat 2008;23:460-5.
13. Zappella M, Meloni I, Longo I, et al. Preserved speech variants of the Rett syndrome: molecular and clinical analysis. Am J Med Genet 2001;104:14-22.
14. Kleefstra T, Yntema HG, Oudakker AR, et al. De novo MECP2 frameshift mutation in a boy with moderate mental retardation, obesity and gynaecomastia. Clin Genet 2002;61:359-62.
15. Couvert P, Bienvenu T, Aquaviva C, et al. MECP2 is highly mutated in X-linked mental retardation. Hum Mol Genet 2001;10:941-6.
16. Adegbola AA, Gonzales ML, Chess A, et al. A novel hypomorphic MECP2 point mutation is associated with a neuropsychiatric phenotype. Hum Genet 2009;124:615-23.
17. Wan M, Lee SS, Zhang X, et al. Rett syndrome and beyond: recurrent spontaneous and familial MECP2 mutations at CpG hotspots. Am J Med Genet 1999;65:1520-9.
18. Fyffe SL, Neul JL, Samaco RC, et al. Deletion of MECP2 in Sim1-expressing neurons reveals a critical role for MECP2 in feeding behavior, aggression, and the response to stress. Neuron 2008;59:947-58.
19. Takagi N. The role of X-chromosome inactivation in the manifestation of Rett syndrome. Brain Dev 2001;23:S182-5.