Rett Syndrome: An Overlooked Diagnosis in Women with Stereotypic Hand Movements, Psychomotor Retardation, Parkinsonism, and Dystonia?

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Abstract: Rett syndrome is an X-linked neurodevelopmental disorder resulting in profound psychomotor retardation. It is usually diagnosed by a pediatrician or pediatric neurologist. Adult neurologists may, therefore, overlook the possibility of Rett syndrome in women with psychomotor retardation of unknown etiology. We report the case of a woman diagnosed with Rett syndrome at age 49 years. This report emphasizes the diagnostic value of movement disorders, including hand stereotypes, Parkinsonism, and dystonia, in adults with Rett syndrome. © 2007 Movement Disorder Society

Key words: Rett syndrome; motor stereotypes; Parkinsonism; dystonia, psychomotor retardation

CASE REPORT

This 49-year-old woman was the only child of unrelated French parents. She had no familial history of neurologic or psychiatric disease. The pregnancy and delivery were normal. The neonatal period was uneventful. Physical examination was normal at age 15 months. She smiled, brought biscuits to her mouth, and manipulated toys. She sat alone unsupported and stood up unaided. She used a few words and enjoyed jargoning. From this age her condition gradually deteriorated. During a 4-month period, she cried inconsolably and her parents said she seemed to be "in another world." She lost all her acquired language and other communication skills and was no longer able to make purposeful movements with her hands. At the same time, she started to have abnormal hand movements. She walked unsupported, with an unsteady broad-based gait, and had difficulties in gait initiation (see video Segment 1). She had almost continuous stereotypic hand patting and rubbing movements. She also had generalized akineto-rigid Parkinsonism with dystonic postures of the
distal part of the four limbs. Deep tendon reflexes were brisk without Babinski’s sign. There was no clear sensory impairment. In addition to her severe neurological disturbances, she had marked fixed kyphoscoliosis. Her mother reported she had no sleep abnormalities. She also showed features of premature aging, and had the aspect of an older woman, owing to global muscular atrophy, thin and wrinkled skin, gray hair, and a stooping posture. Genetic studies showed a heterozygous frameshift mutation c.1163del35 in the exon 4 of MECP2 gene, supporting the clinical diagnosis of RTT. Levodopa therapy (750 mg/day) failed to improve dystonia or Parkinsonism as well as treatment with trihexyphenidyl (2 mg/day), which was discontinued due to daytime sedation.

**DISCUSSION**

We describe the 49-year clinical course of a patient with RTT due to a mutation in the MECP2 gene. The diagnosis was made 48 years after clinical onset, based on hand stereotypies, Parkinsonism, and dystonia associated with profound psychomotor retardation.

Andreas Rett published the first description of RTT in 1966, but worldwide recognition of RTT did not occur until Hagberg and colleagues published a full description of 35 cases in 1983. At this time, our patient was 27 years old and was, therefore, no longer being seen by pediatricians or pediatric neurologists. The additional delay in diagnosis might have been due in part to an unawareness of RTT among adult neurologists.

Hand stereotypies in a woman with psychomotor retardation should raise the possibility of RTT, as they are an early and specific manifestation and often persist throughout the disease course. Motor stereotypes are involuntary, coordinated, patterned, repetitive, rhythmic, nonreflex movements with predictable form, amplitude, and location. They can occur in children with sensory deprivation, autistic disorders, mental retardation, and numerous neurogenetic disorders, including RTT. In these settings, motor stereotypies may be a compensatory activity aimed at maintaining an optimal level of arousal despite a lack of external stimuli.

Our patient also had akineto-rigid Parkinsonism and dystonia. Although clinical descriptions of adult RTT are rare, these two features seem to become more frequent with aging and have been reported to occur in more than 50% of RTT patients after age 8 years. Stereotypies, Parkinsonism, and dystonia are consistently present in RTT and may be associated with nigrostriatal–dopaminergic pathway dysfunction. Indeed, necropsy studies of RTT brains have shown neuropathological and neurochemical abnormalities compatible with degenerative changes of the substantia nigra, and also a selective reduction in the number and activity of dopamine terminals in the caudate nucleus and putamen. Recently, positron emission tomography scan studies of RTT patients have suggested a presynaptic deficit of nigrostriatal activity.

The diagnosis of RTT in adulthood might be further hindered by a lack of detailed information on early childhood. Although hand stereotypies can be encountered in other conditions, they are highly suggestive of RTT in adults with psychomotor retardation, especially when Parkinsonism and dystonic features are also present. Other features of RTT include fixed kyphoscoliosis, which is found in 80% to 90% of patients after age 20 years. There are few reports on the long-term outcome of RTT patients, and it is difficult to determine whether the premature aging seen in our patient is a common feature. Some previous reports mention premature muscle aging. Our patient looked older than her real age, primarily because of changes to her hair, skin, and muscle mass. MeCP2 is a transcriptional repressor and splicing regulator, but it is not known exactly how its dysfunction leads to central nervous system damage. The premature aging of some RTT patients may provide new insights into the function of MeCP2; several genes under the transcriptional control of MeCP2 might be involved in the normal aging process.

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**LEGENDS TO THE VIDEO**

**Segment 1.** The patient walked with an akinetically unsteady, broad-based gait. She had hand rubbing and patting stereotypies, which persist when walking. She also had akineto-rigid Parkinsonism.

**REFERENCES**


Pathogenicity of the Lrrk2 R1514Q Substitution in Parkinson’s Disease

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Abstract: An increasing number of nonsynonymous LRRK2 variants are being reported as putative pathogenic mutations. We identified one large kindred harboring the Lrrk2 R1514Q substitution; however, the variant did not segregate fully with disease. Combined analyses of three case–control series demonstrate that the R1514Q substitution is not associated with increased risk of disease (OR: 1.3; 95% CI: 0.6–2.8; \( P = 0.45 \)). These findings highlight the importance of using family-based studies and multiple population screenings when examining the association of these polymorphic LRRK2 gene variants with Parkinson’s disease.

Key words: Lrrk2; R1514Q; pathogenicity; genetic testing

A number of mutations in the LRRK2 gene have been associated with autosomal dominant Parkinsonism and some variants in this gene have also been found in patients with apparent sporadic Parkinson’s disease (PD). Segregation analyses within families provide st-