Original Article

Autonomic Dysfunction in Mental Retardation and Spastic Paraparesis With *MECP2* Mutation

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ABSTRACT

Autonomic nervous system involvement in female patients with classic Rett syndrome usually manifests as breathing abnormalities, peripheral vasomotor disturbances, and cardiac sympathetic imbalance, the latter a possible cause of sudden death. *MECP2* gene mutations responsible for Rett syndrome have also been found in male patients with mental retardation, sometimes associated with different neurologic abnormalities. However, autonomic nervous system functions have never been investigated in male patients with X-linked mental retardation owing to *MECP2* mutations. We studied heart rate variability, a marker of autonomic activity, in a family with the *MECP2* mutation in male patients, one of whom had died suddenly. Cardiovascular features similar to those observed in a Rett syndrome variant with preserved speech were found, suggesting sympathetic imbalance. (*J Child Neurol* 2004;19:964–966).

Mutations in the X-linked gene encoding methyl-CpG binding protein 2 (MeCP2) cause Rett syndrome, a childhood neurologic disorder accounting for a large proportion of mental retardation in females.[1] Classic Rett syndrome has a peculiar phenotype and progressive clinical course, with stabilization and survival possible into middle and old age. However, there have been cases of sudden death, possibly owing to progressive cardiac dysfunction caused by abnormalities in autonomic nervous system activity.[2–6]

We first described an A140V mutation in the *MECP2* gene[7] (subsequently proved to be a hot spot for mutation causing mental retardation in males[8–10]) in four severely mentally retarded brothers with progressive spastic paraparesis and in their mildly affected sister and mother.[11] The oldest brother (MR48) died suddenly at age 39 years. To investigate the possibility of heart dysfunction in this family, we studied heart rate variability, a marker of autonomic activity.

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MATERIALS, METHODS, AND RESULTS

Heart rate variability and corrected Q–T intervals were studied in three members of the family with nonspecific X-linked mental retardation and progressive motor impairment, the clinical features of which have recently been reported in detail.[11] The family pedigree is shown in Figure 1. The mother and the oldest living son (X307, aged 42 years), who is now bedridden owing to progressive gait deterioration, were not available for study. We examined two affected males (cases MR50 and X308, age 34 and 29 years, respectively) and the sister (MR49, age 44 years). Neurologic findings were substantially unchanged since a previous report.[11] All had cold blue extremities and distal trophic changes of the lower limbs.

Heart rate variability was measured using a commercially available system (Remco Cardioline delta 612, Milan, Italy).[12] A spectral method (fast Fourier transform) was used for the analysis. Three main spectral components were distinguished in a spectrum calculated from 5-minute recordings: a very low-frequency component (< 0.04 Hz), a low-frequency component (range 0.04–0.15 Hz), and a high-frequency component (range 0.15–0.4 Hz). Very low-frequency, low-frequency, and high-frequency power components and total power were expressed in absolute units of power (millisecond squared). The range of normality of total power is 3466 ± 1018 milliseconds^2. The ratio of high to low frequency was calculated as an index of sympatovagal balance (normal values 1.5–2). Q–Tc (Q–T interval corrected for heart rate by the Bazett method) was considered abnormal if greater than 0.44 seconds. Q–Tc dispersion was defined as the difference between the minimum and

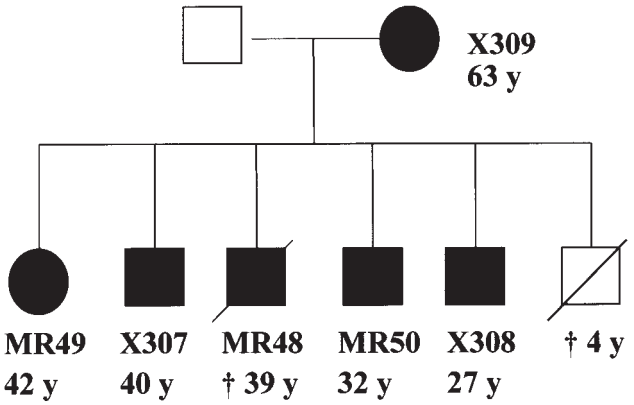

Figure 1. Pedigree of a family with X-linked mental retardation and the *MECP2* mutation. † = deceased.

maximum heart rate–corrected Q–T intervals from the 12 electrocardiographic leads, which were simultaneously recorded.[13]

Heart rate variability was normal in all patients. Analysis of spectral components of heart rate variability showed significant imbalance in sympathetic tone (Table 1). Analysis of ventricular repolarization showed an increase in the Q–Tc interval in patients MR50 and X308 and Q–Tc dispersion in MR49.

DISCUSSION

Autonomic nervous system involvement in female patients with classic Rett syndrome usually manifests as constipation, breathing abnormalities, peripheral vasomotor disturbances with cold extremities, and cardiac sympathetic imbalance, the latter a possible cause of sudden death.[14,15] Our previous studies suggested that reduced heart rate variability, an imbalance in sympathetic tone, and ventricular repolarization anomalies might favor the onset of ventricular arrhythmias in classic Rett syndrome.[13] The Rett syndrome phenotype spectrum has significantly broadened since *MECP2* mutations were found, not only in patients with classic Rett syndrome but also in a wider range of phenotypes than previously suspected, including a group of female patients with preserved speech and less severe neurologic involvement.[16–19] In this subtype of girls with Rett syndrome, abnormalities in autonomic function, similar to those found in classic Rett syndrome but with a lower frequency, have been described.[13] Male patients with Rett syndrome are extremely rare because the Rett syndrome–causing mutations lead to severe neonatal encephalopathy, which is usually lethal before 1 year of age in hemizygous male children.[20–22] However, mutations of the *MECP2* gene, different from those reported in patients with Rett syndrome and possibly with less deleterious effects on MeCP2 functions, have been found in less severely affected female patients and longer surviving male patients with moderate to severe mental retardation, associated or otherwise with neurologic impairment, such as gait disturbances, movement disorders, seizures, and speech impairment.[8,9,23] These patients usually lack the most characteristic clinical features of the Rett syndrome phenotype, including loss of acquired purposeful hand skill, stereotypic "hand-washing" movements, acquired microcephaly, autistic features, and breathing abnormalities. The latter, however, have recently been reported in a 21-year-old male with severe mental retardation and spastic tetraparesis carrying a C674T de novo *MECP2* mutation.[24] Moreover, unlike classic Rett syndrome, no cases of sudden death have been reported among X-linked mental retardation families carrying an *MECP2* mutation, except patient MR48 of the present family. Autonomic nervous system function has never been investigated in sporadic or familial patients with X-linked mental retardation owing to *MECP2* mutations. The present study suggests that: (1) male and female patients of the first family with an A140V *MECP2* mutation have clinical and laboratory signs suggesting autonomic dysfunction; (2) cardiovascular features are similar to those found in a Rett syndrome variant with preserved speech;[13] (3) sympathetic imbalance might have had a role in the pathogenesis of sudden death in case MR48; (4) an A140V *MECP2* mutation can be associated with cardiac dysautonomia; and (5) clinical signs of autonomic dysfunction can be a further indication for screening *MECP2* gene mutations in mentally retarded males with neurologic signs.

Recent studies in animal models have shown that MeCP2 deficiency in mice causes a less severe phenotype than in humans because hemizygous mutant males develop symptoms and die in early adulthood.[25] Moreover, mutant

Table 1. Heart Rate Variability Parameters

	Heart Rate Variability						
	Total Power	*VLF*	*LF*	*HF*		*Q–Tc*	*Q–TcD*
Patient	*(ms^2)*	*(ms^2)*	*(ms^2)*	*(ms^2)*	*LF/HF*	*($s^{1/2}$)*	*($s^{1/2}$)*
MR49	6408	1068	4664	644	7	0.46	0.04
MR50	2580	234	2117	209	10	0.47	0.06
X308	2974	1064	1599	266	6	0.44	0.05
Normal values	3466 ± 1018	1170 ± 416		975 ± 203	1.5–2.0	< 0.44	< 0.05

Q–Tc and Q–Tc dispersion in patients with an A140V *MECP2* mutation and normal values obtained from the Task Force for the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[12]
LF = low frequency; HF = high frequency; VLF = very low frequency.

mice frequently display breathing abnormalities and cold extremities, indicating autonomic dysfunction. Animal models have provided important insights into MeCP2 expression in different tissues, showing that MeCP2 protein is present not only in the brain but also in peripheral tissues, such as lung and heart.[26] This observation also suggests that certain cardiac anomalies, such as a prolonged corrected Q–T interval, might result from MeCP2 dysfunction in the heart rather than the central nervous system. Further clinical and experimental studies are necessary to clarify this point.

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