ORIGINAL ARTICLE

The Incidence and Evolution of Parkinsonian Rigidity in Rett Syndrome: A Pilot Study

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ABSTRACT: ***Background:*** Patients with Rett syndrome (RTT) may demonstrate parkinsonian features. Here, we report a preliminary cross-sectional and prospective evaluation of the evolution, regional distribution, and eventual incidence of rigid tone in a cohort of *MECP2* mutation-positive patients. ***Methods:*** In 51 participants, muscle tone rigidity in extremity regions and neck plus hypomimia were quantified using an RTT rigidity distribution (RTTRD) score with a range of 0 to 15. RTTRD scores were correlated with age, ability to walk and speak, mutation type, and, in a small subgroup (n = 9), cerebrospinal fluid (CSF) homovanillic acid (HVA) and 5-hydroxyindole-acetic acid levels. ***Results:*** Participant ages ranged from 2 years and 5 months, to 54 years. Rigidity was found in 43/51 (84.3%); it appeared as early as age 3, increased in extent with age, and was present in all participants aged ≥ 13. Ankle region rigidity appeared first, followed by proximal legs, arms, neck, and face. Ambulatory participants (n = 21) had lower RTTRD scores than nonambulatory (n = 30; p = 0.003). We found a trend to lower scores in participants with retained speech (n = 13) versus those with none (n = 38; p = 0.074), and no difference in scores for those with truncating (n = 25) versus missense mutations (n = 22; p = 0.387). RTTRD scores correlated negatively with CSF HVA levels (R = −0.83; p = 0.005), but not with 5-hydroxyindole-acetic acid levels (R = −0.45; p = 0.22). ***Conclusions:*** Although assessment of muscle tone is somewhat subjective and the RTTRD has not been validated, this study nevertheless suggests that parkinsonian rigidity in RTT is common and frequently increases in extent with age; its severity correlates directly with impaired ambulation and inversely with CSF HVA levels.

RÉSUMÉ: Étude pilote portant sur l'incidence et l'évolution de la rigidité parkinsonienne dans le cas du syndrome de Rett. ***Contexte:*** Des patients atteints du syndrome de Rett sont susceptibles de manifester des caractéristiques cliniques parkinsoniennes. Nous voulons ici rendre compte d'une évaluation préliminaire transversale et prospective de l'évolution, de la distribution régionale et de l'incidence éventuelle de la rigidité au sein d'une cohorte de patients porteurs de la mutation du gène MECP2. ***Méthodes:*** La rigidité musculaire des extrémités du corps, du cou ainsi que l'hypomimie ont été quantifiées chez 51 participants au moyen d'une distribution de la rigidité associée au syndrome de Rett, les scores variant de 0 à 15. Ces derniers ont ensuite été corrélés avec des variables telles que l'âge, la capacité de marcher et de parler, le type de mutation et, dans le cas d'un sous-groupe (n = 9), les quantités d'acide vanillique et d'acide 5-hydroxyindolacétique dans le liquide cérébro-spinal (LCS). ***Résultats:*** L'âge des participants variait de 2 ans et 5 mois à 54 ans. Des signes de rigidité ont été observés chez 43 participants sur 51, soit 84,3 %. Ils sont apparus dès l'âge de 3 ans, se sont accrus au fil des années et étaient observables chez tous les participants âgés de 13 ans et plus. Ces signes sont apparus initialement dans la région de la cheville ; ont suivi les portions proximales des jambes, les bras, le cou et le visage. Les participants ambulatoires (n = 21) ont obtenu de plus faibles scores de distribution de la rigidité associée au syndrome de Rett que les patients non-ambulatoires (n = 30; p = 0,003). Nous avons aussi observé de plus faibles scores chez les participants atteints de blocage de la parole (n = 13) par rapport à ceux n'étant pas atteints (n = 38; p = 0,074). Aucune différence dans les scores n'est apparue chez ceux dont les mutations entraînent la synthèse d'une protéine tronquée (n = 25) comparativement à ceux affectés par une mutation faux sens (n = 22; p = 0,387). De plus, les scores de distribution de la rigidité associée au syndrome de Rett ont été corrélés négativement avec des quantités d'acide vanillique dans le LCS (R = -0,83; p = 0,005), mais pas avec des quantités d'acide 5-hydroxyindolacétique (R = - 0,45; p = 0,22). ***Conclusions:*** Bien que l'évaluation de la tonicité musculaire demeure quelque peu subjective et que la distribution de la rigidité associée au syndrome de Rett n'ait pas été validée, cette étude suggère néanmoins qu'une telle rigidité est répandue et que sa sévérité augmente fréquemment avec les années. Cette sévérité est directement corrélée avec des troubles de l'ambulation et indirectement corrélée avec des quantités d'acide vanillique dans le LCS.

Keywords: Dopamine, dystonia, HVA, MECP2, parkinsonism, Rett syndrome

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Rett syndrome (RTT) is a genetic disorder encountered almost exclusively in females, with an incidence rate of 1/10,000 to 1/22,000.[1,2] Typically becoming manifest between the ages of 6 and 18 months, the disorder is characterized by partial or complete loss of acquired hand use and of speech, by either inability to walk or the presence of a dyspraxic gait, and by the development

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of stereotypic movements and postures in the upper limbs.[1] After the initial period of regression, the disorder typically stabilizes after age 3, with some improvement in social skills and in the ability to communicate. In approximately 90% of individuals with a classic RTT phenotype, the cause is a mutation in the *MECP2* gene, coding for methyl-CpG binding protein 2 (MeCP2).[3] The clinical severity of the phenotype correlates to some extent according to mutation type.[4,5]

It is well recognized that, during the first 10 to 20 years of life, many RTT patients demonstrate a gradual evolution in muscle tone from generalized hypotonia to progressive muscle rigidity, often accompanied by dystonic posturing and progressive scoliosis. The gradual appearance of simultaneous hyperactivity in agonist and antagonist muscle groups is typically accompanied by a decline in gross motor abilities that corresponds to the so-called "late motor deterioration stage" of RTT (stage IV), a stage during which, in contrast, social skills often improve.[6] Many teenaged and adult patients with more severe RTT phenotypes eventually evolve to a disabling generalized parkinsonian state with marked rigidity, hypomimia, and, notwithstanding the persistence of hand stereotypies in some individuals, generalized bradykinesia/akinesia.[7,8]

Since the landmark publication by FitzGerald et al[7] more than 20 years ago, and notwithstanding the common occurrence of varying degrees of rigidity and bradykinesia in older individuals with RTT, there are very few published data concerning the evolution, anatomical variability, and eventual incidence of this disabling complication of the disorder. In this preliminary study, we report a cross-sectional and prospective evaluation of the appearance, anatomical distribution, and progression of increased muscle tone and rigidity in a cohort of RTT children, youth, and adults assessed and followed at a neurology clinic dedicated to this disorder.

Patients and Methods

Between 2006 and 2013, all patients seen in the Rett Syndrome Clinic at the Children's Hospital of Eastern Ontario were evaluated using a standardized historical questionnaire and neurological examination protocol. Historical information obtained included data concerning pregnancy, delivery, neonatal course, developmental milestones achieved and lost (where appropriate), age and course of regression and subsequent stabilization, the presence or absence of the currently accepted major and minor diagnostic criteria,[1] age at diagnosis of RTT, mutation type (where known), and the presence or absence of any multisystemic complications of RTT (e.g. seizures, dystonia/parkinsonism, gastrointestinal disorders, scoliosis).

In addition to a detailed problem-oriented neurological examination, the physical assessment of each patient included a simple, standardized survey of the anatomical extent of muscle tone rigidity: the Rett Syndrome Rigidity Distribution score (RTTRD; Table 1). Muscle tone was assessed proximally and distally in all four limbs and in the neck, with the patients relaxed and lying in a supine position. Because tone cannot be readily evaluated in facial muscles, hypomimia served as a surrogate for muscle rigidity in this region. If there was an asymmetry in muscle tone findings in limbs between sides at any level tested, the score assigned was that of the more severely involved limb. As can be seen in Table 1, patients with normal or low muscle tone in all muscle groupings evaluated had a total score of 0; those with increased tone had scores of 1 to 15, with 15 indicating the presence of rigidity in all muscle groupings assessed.

Table 1: RTT rigidity distribution scoring system

Normal or low tone in any region:		0
Upper limb		
1. Shoulder	Increased adductors/rotators	1
2. Elbow	Increased flexors	1
	Increased extensors	1
3. Forearm	Increased pronation	1
	Increased supination	1
4. Wrist/hand	Increased finger/wrist flexors	1
	Increased finger/wrist extensors	1
Lower limb		
1. Hip	Increased adductors/rotators	1
2. Knee	Increased hamstrings	1
	Increased quadriceps	1
3. Ankle/foot	Increased plantar flexors	1
	Increased dorsiflexors	1
	Increased toe flexors	1
Neck	Increased neck extensors/SCM	1
Face	Hypomimia with decreased blinking	1
Maximum score		15

In the assessment of muscle tone, rigidity was defined as increased resistance to passive muscle stretch in both flexor and extensor muscles acting around a given joint, and present throughout the range of movement. To eliminate the possibility of transient increases in tone suggestive of gegenhalten (paratonia), the resistance to stretch had to be persistent during repeated, serial evaluations; when present at any given site, gegenhalten was assigned a score of 0. Spasticity was defined as an initial increase in response to stretch confined to flexor muscles in the upper limbs (e.g. biceps, wrist flexors) and to selected "extensor" muscles in the lower limbs (e.g. hip adductors, knee extensors, plantar flexors). It was anticipated that spastic tone abnormalities would be accompanied by a reduction in tone after the initial resistance (a "spastic catch") and by the presence of extensor plantar responses.

Patients were included in this study if they were known to have an *MECP2* mutation. Where the specific mutation was known, patients were subdivided into those with truncating mutations and those with missense mutations. Patients were also classified as to whether or not they had learned to walk independently, and whether they had any retained spoken language.

Whether individual patients had RTTRDS evaluations on more than one occasion was dependent on where they lived. Nearly half of the patients and their caregivers traveled long distances to seek assessment and counsel in the clinic and, for practical reasons, were only seen once. Those living closer to Ottawa were followed on a more regular basis and were repeatedly assessed over periods of up to 7 years.

The evolution of tone rigidity with increasing age was evaluated for each of the eight anatomical regions by dividing the participants into four age categories: 2 to 5, 6 to 10, 11 to 19, and 20 and older.

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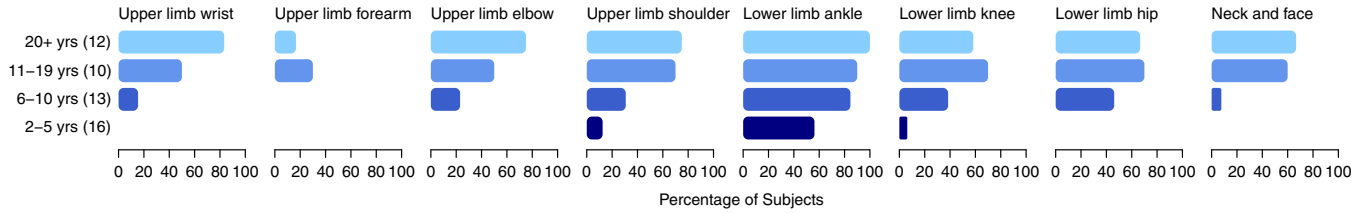

Figure 1: *Regional evolution of rigidity findings. Bar graphs show the percentages of participants in each of the four ascending age groups for each of the eight anatomical regions.*

The percentages of participants with high tone in each anatomical region were calculated for the four age categories. Average RTTRD score comparisons were then made using Welch two-sample *t* tests between those participants who were ambulatory versus those who were not, between those who had retained spoken language versus those who had none, and between those with truncating mutations and those with missense mutations.

A small cohort of the participants (n = 9) had participated in a large (n = 64) study of cerebrospinal fluid (CSF)HVA and 5HIAA levels reported by Samaco et al;[9] these patients had their CSF studies in 2004, 2 years before the opening of the Children's Hospital of Eastern Ontario RTT clinic and the commencement of the present study. Post-hoc Pearson correlations were computed between the CSF neurotransmitter metabolite levels and the first RTTRD scores performed in these patients. At the time of the RTTRD assessments, the person performing them (PH) was blinded to the CSF results. The time lag between the date of the CSF study and the subsequent RTTRD scoring varied between 31 and 48 months.

Results

RTTRD assessments were carried out in 51 patients who ranged in age from 2 years 5 months to 54 years. Of the 51 participants, 26 had more than one assessment (range, 2-5) over periods of up to 7 years; 25 participants were only assessed once. Per the updated diagnostic criteria outlined in the paper by Neul et al,[1] 38 participants had a classic phenotype and 13 an atypical phenotype. Mutation types were known for 47/51 participants; 25 had truncating mutations, whereas 22 had missense mutations.

In all participants, muscle tone was classified as rigid in type, present equally in opposing flexor and extensor muscles; no participants were found to have a spastic catch. Even in young participants in which increased muscle tone was confined to plantar flexor muscles, high tone was present throughout the range of joint movement and was accompanied by the presence of flexor plantar responses. The phenomenon of gegenhalten was sometimes encountered, primarily in younger participants.

Only 8/51 (15.7%) participants had an initial RTTRD score of 0; all were younger than age 13. Of the remaining 43 participants, at the time of the most recent assessment, ten (19.6%) had increased muscle tone confined to one of the eight regions assessed (invariably the ankle region), whereas four (7.8%) had high tone confined to two regions (the oldest at age 21) and 29 (56.9%) increased tone in three or more regions (the youngest by age 9.5). RTTRD scores were very low (average, 0.94 ± 1.00; range, 0-3) during the first 6 years of life – or typically 4 years after initial diagnosis. Although there was considerable variation in scores among patients, there was a subsequent steady rise in overall RTTRD scores: the average score for participants ages 6 to 10 was 3.00 ± 2.16 (range, 0-11), whereas average scores for those aged 11 to 19 and > 20 were 6.70 ± 3.47 (range, 0-13) and 7.67 ± 3.80 (range, 3-14), respectively. After age 5, only two subjects (aged 10 years 6 months and 12 years 8 months) had initial RTTRD scores of 0. Of these, the younger had a classic phenotype with a truncating mutation and progressed to a score of 6 over the next 5 years; the older subject had an atypical phenotype with a missense mutation and was only assessed once.

Three or more serial assessments were made in 15 participants over time periods of 2 to 6 years. Ten of 15 tended to show progression in the severity and extent of muscle rigidity over time, their RTTRD scores increasing by 2 to 6 (mean, 3.9); 8/10 had a classic RTT phenotype. In contrast, the five stable participants (score change, 0-1; mean, 0.4) were more evenly split between classic and atypical phenotypes (3 and 2, respectively). Thus, although average RTTRD scores increased with advancing age, some individual participants demonstrated a gradual worsening of muscle rigidity over the period of observation; others did not. Of the 15 cases, eight were nonambulatory at the time of first assessment, whereas seven were ambulatory. One of the latter (with a classic phenotype and an R294X mutation) lost the ability to walk unaided during a 3.5-year period of observation; her RTTRD score did not increase during that time.

The evolution of rigidity by anatomical region was assessed by calculating percentages of participants having abnormal muscle tone in each of the eight regions for four age groups: 2 to 5 years (n = 16); 6 to 10 years (n = 13); 11 to 19 years (n = 10); and 20 years and older (n = 12) (Figure 1). In the 2- to 5-year age group, increased muscle tone, if present, was confined to those muscles acting around the ankle joint and, to a lesser extent, the shoulder joint. In the 6- to 10-year-old patients, muscle rigidity also began to appear in the knee and hip regions as well as, to a lesser degree, the wrist and elbow regions; hypomimia was seen in only one patient. All anatomical regions were affected in some or all of the patients in the 11 to 19 and 20+ age groups, including the wrist pronators and supinators, the region that was least affected overall. In total, 29 participants (56.9%) had generalized muscle rigidity involving extremities, neck and face by the time of study completion.

The findings of this cross-sectional analysis were confirmed by a region-by-region analysis of muscle rigidity findings in the ten participants with multiple assessments and a progressive course (Table 2). As Table 2 demonstrates, there was considerable variation in the geographic extent of rigidity among participants of approximately the same age at the time of the first assessment (e.g. cases 17, 18, and 22). With subsequent assessments, more anatomical regions became involved, especially in the upper limbs, neck and face.

Average RTTRD scores in ambulatory patients (n = 21; 2.43 ± 2.79; range, 0-8) were lower than those in nonambulatory

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Table 2: Regional evolution of rigidity in participants with increasing RTTRD scores

Part	Age	Pheno	Mut	F/N	W	FA	El	Sh	An	Kn	Hip	Score
2	2-6	C	T									0
	6-6			●●					●			3
	8-9			●●								2
17	6-4	C	T						●●●	●	●	5
	7-4							●	●●●	●●	●	7
	8-4			●●				●	●●	●	●	7
	9-6			●●	●		●	●	●●●	●●	●	11
18	6-6	C	T				●●		●	●		4
	8-6			●			●		●●	●●	●	7
	10			●			●	●	●●	●●	●	8
22	7-5	C	T						●			1
	8								●●			2
	10-6			●	●				●●	●		5
28	10-6	C	T									0
	13-9								●	●	●	3
	15-6			●			●		●●●	●		6
29	10-11	A	M					●			●	2
	12							●				1
	13-11						●●	●	●			4
30	12-2	C	M		●	●	●●	●	●●	●	●	9
	12-8				●	●	●	●	●●●	●●	●	10
	13			●●	●	●	●	●	●●●	●●	●	12
	15-6			●●	●	●	●●	●	●●●	●●	●	13
32	12-6	A	T						●			1
	13-6								●●			2
	15-6			●			●		●●			4
34	13-10	C	T	●●			●●	●	●●	●	●	9
	15-2			●●	●●		●	●	●●●	●	●	11
	17-2			●●	●●	●	●●	●	●●●	●	●	13
42	34	C	M	●●	●		●●	●	●	●●	●	10
	34-8			●●	●		●●	●	●●●	●●	●	12
	36-8			●●	●	●	●	●	●●●	●●	●	12
	37-8			●●	●	●	●	●	●●●	●●	●	12
	38			●●	●●	●	●●	●	●●●	●●	●	14

A, atypical; An, ankle; C, classic; El, elbow; FA, forearm; F/N, face/neck; Kn, knee; M, missense; Mut, mutation type; part, participant number; pheno, phenotype; Sh, shoulder; T, truncating; W, wrist. Participant ages are expressed as years followed by, where appropriate, months.

patients ($n = 30$; 5.40 ± 4.02; range, 0-14; $p = 0.003$). Figure 2 shows a graphic comparison of the distribution of RTTRD scores in the two groups. In the ambulatory group, RTTRD scores varied from 1 to 8, 16/21 (76.2%) having scores of 0 to 3. In contrast, RTTRD scores in the nonambulatory group varied from 0 to 13, with 12/30 (40.0%) having scores of 0 to 3 and 10/30 (33.3%) scores of 9 to 13. In both groups, as mentioned previously, lower scores were predominantly seen in younger participants. As already noted, only one participant became nonambulatory during the period of observation; all of the remaining 29 nonambulatory participants had either never walked or had been able to walk with assistance earlier in life and then lost this ability well before the study period. There was a trend for scores also being lower in patients with retained speech ($n = 13$; 2.69 ± 3.09; range, 0-8) than in those with none ($n = 38$; 4.68 ± 3.96; range, 0-14) but the difference was not statistically significant ($p = .074$).

We found no correlation between RTTRD scores and mutation type: 18/25 (72%) participants with truncating mutations were nonambulatory versus 10/22 (45.5%) of those with missense mutations (3.76 ± 3.57 vs 4.77 ± 4.28; $p = 0.387$).

Figure 3 shows the results of the comparison of RTTRD scores with earlier CSF HVA levels. There was an inverse correlation

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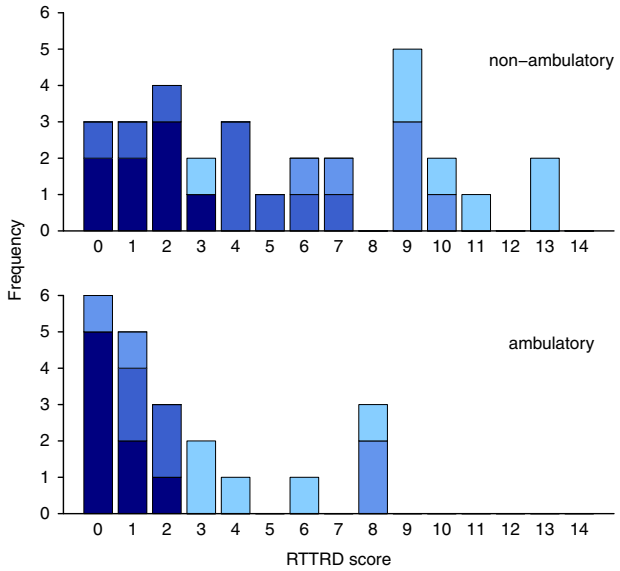

Figure 2: *Comparison of RTTRD scores in ambulatory versus nonambulatory participants. Bar graphs show the frequencies of participants with individual RTTRD scores from 0 to 15; nonambulatory participants are in the upper graph, ambulatory participants in the lower graph. Where appropriate, bars are divided into segments showing the same age groupings as in Figure 1.*

between CSF HVA levels and RTTRD scores such that lower HVA levels were associated with higher subsequent RTTRD scores ($R = -0.83$; $p = 0.005$). In contrast, there was no significant correlation between the CSF 5HIAA levels and the later RTTRD scores ($R = -0.45$; $p = 0.22$).

Discussion

To our knowledge, this study represents the first attempt to evaluate the incidence, evolution, and regional distribution of progressive muscle rigidity in RTT. A total of 84.3% of our 51 patients either already had some degree of muscle rigidity at the time of first clinical assessment or developed increasing

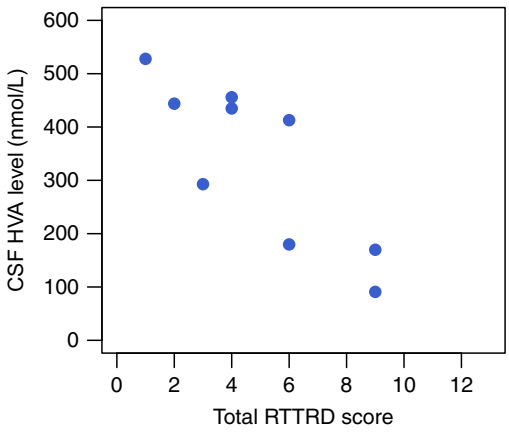

Figure 3: *RTTRD score correlation with CSF dopamine metabolite levels. Scatter plots of CSF HVA levels in the nine participants who had these studies performed. RTTRD scores are on the X axis; neurotransmitter metabolite levels in nmol/L are on the Y axis. HVA levels were associated with higher subsequent RTTRD scores ($R = -0.83$; $p = 0.005$).*

muscle hypertonia over time. This is a much higher percentage than that reported by Temudo et al, with similar participant numbers (48.3% of 60 participants).[8] Overall, the majority of our patients (56.9%) demonstrated generalized rigidity, often severe, by the time of their last assessment; the youngest such patient was only 9.5 years old.

Of the 15 participants with three or more serial assessments, ten (initially aged 2 years 6 months to 34 years) demonstrated increasingly extensive rigidity over the period of observation (33-75 months). Although the other five did not progress over time (24-44 months), the period of observation may well have been too short to exclude the possibility of longer term deterioration.

Although nonambulatory participants had higher RTTRD scores than those who could walk, and were the only participants with scores of 9 or higher, this finding does not necessarily mean that the development of a parkinsonian state plays the most important role in any late decline in gross motor function. Of the seven participants with three or more RTTRD assessments who were ambulatory at the beginning of the study, only one lost the ability to walk during the period of observation—without any change in her RTTRD scores. In contrast, seven of nine nonambulatory participants had increases in their scores from 4 to 6 (mean, 4.6) without, by definition, any major deterioration in gross motor function (Table 2). There may have been deteriorations in some participants' ability to maintain a supported standing position, in residual fine motor abilities, and increases in nursing care requirements, but we did not assess these functional capacities during the present study.

Our results in this respect are similar to those reported in a prospective 3- to 4-year follow-up study of gross motor abilities in 70 ambulatory or partially ambulatory participants with RTT in the Australian Rett Syndrome Database.[10] In this cohort, gross motor skills improved slightly in 31.4%, remained stable in 10.0%, and declined slightly in 52.9%. The findings in this study, and in ours, suggest that much longer periods of follow-up (in terms of decades) may be required to confirm or refute the long-term decline in gross motor function described in earlier studies of RTT cohorts.[6,7]

In short, our results suggest that the RTTRD is a quantifiable expression of an important component of a more severe phenotype in RTT; in the context of a relatively short period of follow-up, it does not appear to predict the subsequent development of late motor deterioration. Longer periods of follow-up may prove otherwise. In like manner, the trend to an association between RTTRD scores and lack of retained speech is probably also a nonspecific indicator of phenotypic severity.

Based on the results of two large RTT genotype/phenotype studies,[4,5] we expected that our participants with truncating mutations would have more motor impairment and higher RTTRD scores than those with missense mutations; instead, we found no differences between the two mutation types. It is possible that our relatively low participant numbers may account for our findings, given that the participant numbers in the Bebbington et al[4] and Cuddapah et al[5] studies were 272 and 1052 respectively. This hypothesis is supported by the fact that a higher percentage of the participants with truncating mutations were nonambulatory in comparison with those having missense mutations.

In this study, we focused on only one of the principal features of the parkinsonian state: rigidity. Other than noting its presence or absence, it is difficult to quantify accurately the severity of

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bradykinesia in RTT patients, in particular because of the pervasive presence of stereotypic hand movements. In our participants, bradykinesia was certainly prominent in older individuals with generalized rigidity. The presence of hypomimia was part of our assessment system and is as much an expression of bradykinesia as it is a surrogate for rigid muscle tone. Hand and foot stereotypies are also barriers to any attempt to quantify resting tremor. Partial or profound postural instability is pervasive in RTT but was not quantified in this preliminary study.

Although the mechanisms responsible for the progressive parkinsonian features in older RTT patients are far from clear, evidence is emerging to suggest that one important factor may be a dysfunction in the nigrostriatal dopaminergic projection system. First, although there have been somewhat conflicting reports in the literature concerning dopamine metabolite levels in CSF in RTT,[11-14] a relatively recent study of 64 RTT participants showed that average HVA levels in these participants were significantly lower than those in >200 control participants; average 5HIAA levels were also significantly reduced in the RTT participants.[9] Twelve of 64 (19%) of the RTT participants had CSF HVA levels below the normal reference range for age; the corresponding figure for 5HIAA levels was 15/64 (23%). In comparison the equivalent figures for the control participants were, respectively, 3/209 and 3/258, both around 1%.[9]

Second, limited pathological studies in RTT patients have shown that substantia nigra pars compacta neurons are smaller and more hypopigmented than normal.[15,16] No evidence has emerged for progressive loss of nigrostriatal neurons in RTT, an observation that may help explain why, having had the initial appearance of muscle tone rigidity with or without symptoms of motor function regression, some RTT patients then appear to plateau and remain relatively stable.

Third, in comparison with wild-type mice, *mecp2*-null mice have lower brain dopamine levels, lower brain tyrosine hydroxylase levels (a marker of dopamine synthesis), and a significantly reduced amount and speed of motoric activity.[9] Brain serotonin and norepinephrine levels are also significantly reduced in *mecp2* knockout mice, speaking to the presence of a pervasive impairment in monoamine transmitter synthesis in the RTT mouse model.[9]

Fourth, Samaco et al[9] have also developed conditional knockout (CKO) mouse models in which *mecp2* was specifically deactivated in tyrosine hydroxylase (TH, dopaminergic) or in tryptophan hydroxylase (TPH, serotonergic) neurons. TH-CKO mice had significantly lower brain dopamine levels than wild-type mice and marked impairment in movement speed and balance. In contrast, TPH-CKO mice had significantly lower brain serotonin levels and normal motor function, but increased aggressivity.[9]

Although the number of participants was small, our post-hoc comparison of RTTRD scores and preceding CSF HVA levels lends support to the presence of symptomatic nigrostriatal dopaminergic dysfunction in RTT in that lower CSF HVA levels were strongly associated with a higher and more extensive degree of muscle rigidity at a later date. Our results suggest that the early identification of low CSF HVA levels in RTT patients may be an important clue to the later onset of a parkinsonian state at an age when targeted therapeutic interventions may be more successful.

The principal limitations of this study are the relatively small number of participants and that, because of restrictions imposed by long travel distances for many of our participants, serial assessments could not be performed in all individuals. A multicenter study involving larger participant numbers and prospective gross and fine motor functional assessments over a longer period would be required to confirm our results. Another potential weakness is the necessarily subjective nature of the clinical assessment of muscle tone. This problem is partially offset by the fact that all tone assessments throughout the study were performed by the same individual (PH). Nevertheless, an inter-observer reliability study of the RTTRD scoring system would be a logical next step.

In our view, the results of this preliminary evaluation of the RTTRD system indicate the need for a more complete assessment tool for the quantification of the parkinsonian state in RTT. In addition to an evaluation of the distribution of muscle rigidity and bradykinesia, the assessment should contain a brief functional domain dealing with postural stability, sitting ability, capacity to transition from sitting to standing, and with gait. Existing parkinsonian rating scales such as the Unified Parkinson's Disease Rating Scale[17] and the Simpson-Angus Scale[18] are largely inappropriate for individuals with RTT because of their marked limitation in communication skills and pervasive movement dyspraxia. There are a few items dealing specifically with parkinsonian features in the RTT Natural History Study Motor-Behavioral Assessment Form.[5] Although very pertinent, these items are a small part of an extensive, global assessment of gross motor, fine motor, speech, and social function in RTT, an assessment that is time-consuming to administer and a tool that has not yet been systematically validated.

In summary, this study confirms that, at an age in which social skills are significantly improving in many RTT patients, a majority is developing a progressive, generalized parkinsonian state that may be partly responsible for eventual gross motor function deterioration that increasingly interferes with the ability to take advantage of any improvement in social ability. More work is required to develop a reliable clinical tool capable of quantifying both the severity of the RTT parkinsonian disorder and the associated degree of functional incapacity. The existence of a validated assessment tool would be an important requirement for the design of targeted treatment trials.

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Disclosures

The authors do not have anything to declare.

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