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Stereotypies in Rett syndrome

Analysis of 83 patients with and without detected MECP2 mutations

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Abstract—Background: Hand stereotypies are considered a hallmark of Rett syndrome (RTT) and are usually described as symmetric movements at the midline. However, related pathologies may show the same type of involuntary movement. Furthermore, patients with RTT also have stereotypies with other localizations that are less well characterized. **Methods:** We analyzed stereotypies in 83 patients with RTT, 53 with and 30 without a mutation detected in the *MECP2* gene. Patients were observed and videotaped always by the same pediatric neurologist. Stereotypies were classified, and data were submitted to statistical analysis for comparison of mutation-positive and -negative patients and analysis of their evolution with the disease. **Results:** All the patients showed hand stereotypies that coincided with or preceded the loss of purposeful hand movements in 62% of the patients with *MECP2* mutations. The hair pulling stereotypy was more frequent in the group with detected mutations, whereas hand washing was not. Hand gaze was absent in all RTT patients with *MECP2* mutations. Patients with *MECP2* mutations also had more varied stereotypies, and the number of stereotypies displayed by each patient decreased significantly with age in this group. In all patients, stereotypies other than manual tended to disappear with the evolution of the disease. **Conclusions:** Although symmetric midline hand stereotypies were not specific to patients with an *MECP2* mutation, some of the other stereotypies seemed to be more characteristic of this group. In patients younger than 10 years and meeting the necessary diagnostic criteria of Rett syndrome, the association of hand stereotypies without hand gaze, bruxism, and two or more of the other stereotypies seemed to be highly indicative of the presence of an *MECP2* mutation.

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Rett syndrome (RTT) was discovered by Andreas Rett who noted that two girls waiting for his consultation presented the same movement disorder: hand stereotypies.

In 1966, Rett¹ published data on 22 girls with progressive cerebral atrophy, stereotyped hand

movements, dementia, alalia, gait apraxia, and a tendency toward epileptic attacks. As the disease is primarily sporadic in nature and familial cases are rare,² it took more than 30 years to determine its genetic basis: mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene.

Stereotypies may be defined as involuntary, rhythmic, patterned, coordinated, repetitive, and seemingly purposeless movements or utterances that are usually continuous, in contrast with mannerisms or tics.³ They can be transient (physiologic)^{4,5} or persistent (pathologic).^{6,7}

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In addition to motor and phonic, stereotypies can be classified as either simple (e.g., tapping, mouthing, clapping) or complex (e.g., a sequence of different movements always performed in the same way and sometimes seeming to have a purpose); they can also be described according to the predominant site involved (e.g., head, trunk, hand, inferior limbs).^{3,6}

Stereotyped hand movements are a hallmark of RTT, and one of its necessary diagnostic criteria.⁸ Usually they are associated with or follow the disappearance of purposeful hand movements, but can also be present before developmental regression begins.⁹ These almost continuous, repetitive, compulsive automatisms disappear during sleep. Environmental manipulation was shown to have a limited effect on their frequency, suggesting that these movements are reinforced through neurochemical processes.¹⁰

Other stereotyped movements and behaviors can also be present in RTT, but are much less well described.¹⁰⁻¹³

We describe the stereotypies that can be present in RTT and their lifelong evolution, based on an observational study of 83 patients with a clinical diagnosis of RTT, all studied for the presence or absence of *MECP2* mutations. We also compare the stereotypies present in patients with and without a positive molecular diagnosis.

Methods. All Portuguese pediatric neurologists were asked to indicate their patients with possible RTT. Patients were always observed and videotaped by the same pediatric neurologist, and a clinical checklist for RTT was completed. A classification of stereotypies was used that was modified from Jankovick³ and Fernandez-Alvarez and Aicardi.⁶ Informed consent was obtained from all parents to collect blood, and to take and use video and photographs.

Blood samples from patients and their parents were received at our laboratory, and genomic DNA was extracted using the Puregene DNA isolation kit (Gentra, Minneapolis, MN). The coding region and exon-intron boundaries of the *MECP2* gene were amplified by PCR and sequenced. The robust dosage PCR method was used, as described,¹⁴ for the detection of large rearrangements in the *MECP2* gene. Primers and PCR conditions are available upon request.

Contingency tables were obtained, and χ^2 and Fisher exact tests were used. Groups were compared with Student's *t* test. The SPSS (v.14) statistical package was used to analyze the data.

Results. We observed 117 cases with possible RTT; 33 were excluded because they did not fulfill the revised diagnostic criteria and one because the patient was a man with a severe encephalopathy who never presented stereotypies.⁸ The mean age at the first observation of the 83 patients who fulfilled the diagnostic criteria was 10.0 years (range, 1 to 31, median, 7 years). Twenty patients were observed and videotaped two or more times at 6-month intervals.

Cases were classified as classic (60.2%) and variant (39.8%) forms of RTT. Mutations were found in 63.9% of all patients (*n* = 53), corresponding to 84.0% of the classic forms and 33.3% of the variants; all were *de novo*. Patients were thus divided into two groups: those with a positive molecular diagnosis (Group I) and those without (Group II).

All cases presented hand stereotypies that appeared

at a mean age of 22.3 months in Group I and 25.4 months in Group II, after decrease or loss of purposeful hand movements (22.2 months in Group I and 17.4 months in Group II), and several months after losing social contact (17.0 months in Group I and 11.1 month in Group II). In 25 cases (23 in Group I and two in Group II), loss of purposeful hand movements and appearance of stereotypies coincided; in 11 cases (10 cases in Group I and one in Group II), stereotypies preceded the loss of purposeful hand movements (mean time, 9.5 months; range, 5.0 to 25).

The most frequent hand movement observed was the compulsive wringing, washing-like movement of both hands, usually at the midline, most often in front of the body (73.26% in Group I and 80.0% in Group II). Other symmetric movements of both hands were also present (table; video E-1 on the *Neurology* Web site at www.neurology.org; figure 1). Stereotypies with separated hands, more often each hand performing a different movement and coexisting or not with midline hand stereotypies, were present in 60.2% of all the patients (60.4% in Group I and, 60.0% in Group II) (table; video E-2; figure 1). Of the Group I patients, 20.4% showed only hands-apart stereotypies. None of the patients in Group I looked at their hands while performing hand stereotypies, whereas 40.0% of those in Group II did (*p* < 0.001).

The second most frequent stereotypy in RTT was bruxism. We found bruxism in 90.4% of 83.0 RTT patients (94.3% in Group I and 83.3% in Group II); in all patients, it occurred while awake and disappeared during sleep.

Stereotypies with other topographies are described in the table (see also videos E-3 and E-4; figure 1). They could be very complex at the beginning of the disease; two girls had a stereotyped dancelike behavior involving many sites of the body, always performed in the same sequence, and seemingly with a purpose (table; video E-5).

Most patients (97.6%) had more than one stereotypy, and 31.7% (*n* = 26) had five or more different ones (38.5% in Group I and 20.0% in Group II). The number of stereotypies per patient was larger in Group I (a mean of 4.8 stereotypies in Group I and 3.7 in Group II), and the patients in this group exhibited a significantly greater number of topographies of stereotypies: 28 different stereotypies were found in Group I, whereas only 19 stereotypies were seen in Group II. Although 54.6% of the patients in Group I performed five stereotypies, only three were performed by 52.7% of the patients in Group II. Patients who acquired independent gait had a significantly larger number of stereotypies, in both groups. Group I (but not Group II) patients with rigidity showed a significantly smaller number of stereotypies.

The most frequent association was that of the hand-washing stereotypy with bruxism (69.1%; 70.6% in Group I, 66.7% in Group II). Among patients with more than one manual stereotypy, mouthing and hand washing were the most frequently associated (43.4%; 39.6% in Group I, 50.0% in Group II).

Significant differences between the mutation-positive (Group I) and mutation-negative groups (Group II) regarding the frequency of specific stereotypies were found (table).

We also found that the number of stereotypies decreased with age (particularly after the age of 10), mainly

Table Stereotypies found in a series of 83 patients with Rett syndrome

	Total, % (n = 83)	Group I, % (n = 53)	Group II, % (n = 30)	χ^2
Motor stereotypy				
Simple				
Head				
Rolling	1.2	1.9	0.0	0.573
Retropulsion	7.2	11.2	0.0	3.661*
Grimacing	8.4	11.2	3.3	1.583
Bruxism	90.4	94.3	83.3	5.956†
Protrusion of the lips	6.0	9.4	0.0	3.012
Repetitive closure of the eyes	7.2	9.4	3.3	1.063
Eye rolling	12.0	15.1	6.7	1.284
Joined hands	80.7	81.1	80.0	0.016
Washing	75.9	73.6	80.0	0.431
Clapping	14.5	15.1	13.3	0.048
Mouthing	21.7	22.6	20.0	0.079
Separated hands	60.2	60.4	60.0	0.001
Mouthing	36.1	37.7	33.3	0.161
Hair pulling	10.8	17.0	0.0	5.714†
Pill rolling	8.4	3.8	16.7	4.124*
One hand behind the neck	4.8	5.7	3.3	0.226
Castanets	1.2	1.9	0.0	0.573
Twisting two or three fingers	3.6	3.8	3.3	0.011
Flapping	2.4	1.9	3.3	0.170
Tapping	30.1	28.3	33.3	0.230
"Sevillana"	2.4	3.8	0.0	1.160
Hand twirling	8.4	9.4	6.7	0.190
Hand gaze	14.5	0.0	40.0	24.783‡
Arms				
Repetitive and rhythmic flexion of the arms	4.8	5.7	3.3	0.226
Legs				
Intermittent leg elevation and tapping of the floor	10.8	11.3	10.0	0.035
Toe walking	15.7	17.0	13.3	0.193
Jumping	1.2	1.9	0.0	0.573
Feet				
Feet twirling	3.6	5.7	0.0	1.762
Whole body				
Trunk rocking	21.7	22.6	20.0	0.079
Shifting weight from one leg to the other	20.5	24.5	13.3	1.474
Complex	2.4	3.8	0.0	1.160
Phonic stereotypy				
Repetitive sounds	4.8	5.7	3.3	0.226
Repetitive words or phrases	1.2	1.9	0.0	0.573

* $p < 0.1$.† $p < 0.05$.‡ $p < 0.010$.

in Group I (figure 2): a difference was observed between patients younger and older than 10 years of age ($t = 3.749$, $p = 0.001$) in Group I.

In the 20 patients observed various times (15 in Group I and five in Group II), the mean length of follow-up was 3.75 years (range, 1 to 6 years; median, 4

years). All maintained the pattern of manual stereotypies, but there was a change in the pattern of stereotypies with other localizations: new stereotypies might be added to or replace one of previous ones. Stereotypies other than manual ones tended to disappear with evolution of the disease.



Figure 1. Different topographies of stereotypies in Group I Rett syndrome patients. Typical hand washing stereotypies (A to C); mouthing with hands apart (D to G); mouthing with joined hands (H); hair pulling (I, J); cervical retropulsion (K to M) (K and L with simultaneous closure of the eyes); twisting of the fingers with hands apart (N); shifting weight from one leg to the other (O, P).

Discussion. Stereotyped hand movements are considered a hallmark of RTT, and it has been assumed that they are symmetric and at midline.^{10-13,15-19} The aim of this study was to analyze the specificity of the stereotypies in patients with a positive molecular diagnosis of RTT. There are a number of limitations to this study, including the fact that it was a single-rater, cross-sectional, and observational, and, therefore, state-dependent study; however, 24% of the patients were observed several times, and complete video records allowed reanalysis and increased objectivity.

Although washing-like movements of both hands are considered an indicator of RTT, this finding is not specific of the syndrome; remarkably, in this study, this stereotypy was more frequent in the group with no mutation in the *MECP2* gene. In addition,

a significant proportion of the mutation-positive patients showed only hands-apart stereotypies. One of the singularities of *MECP2* mutation-positive RTT patients was that they tended not to look at their hands when performing hand stereotypies, possibly because they have very poor ocular-manual coordination.

Differences were found in the frequency of four stereotypies, and of these, hair pulling, bruxism, and cervical retropulsion were more frequent in the mutation-positive group.

In general, mutation-positive patients had more diverse stereotypies that diminished after the age of 10. These patients also had a larger number of stereotypies per patient. In patients younger than 10 years and with the necessary diagnostic criteria of RTT, the association of hand stereotypies without

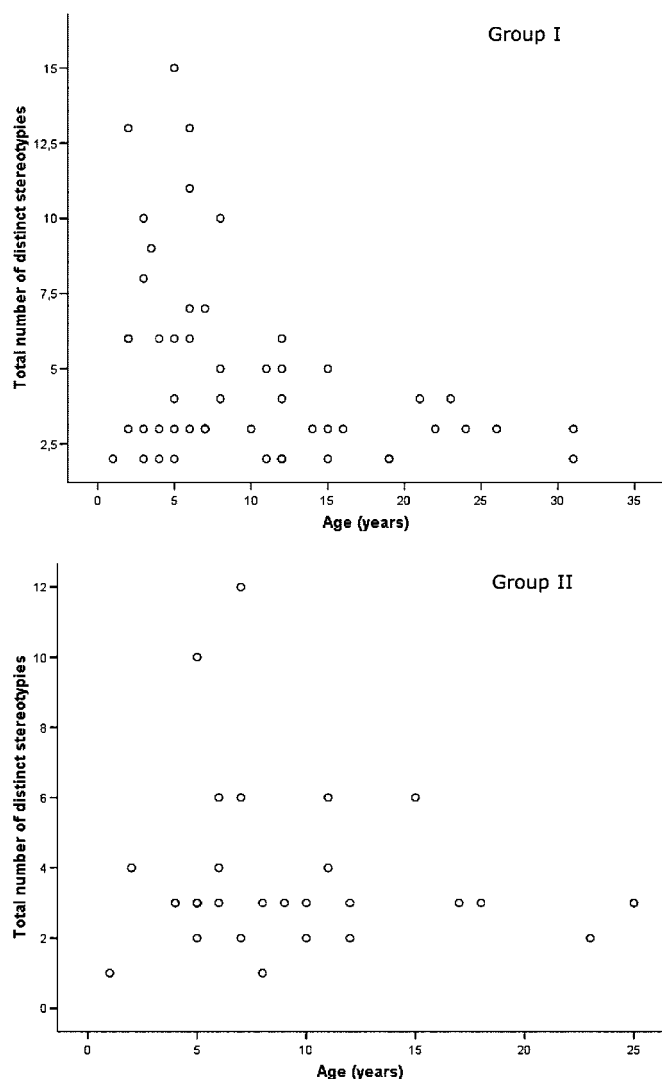


Figure 2. Total number of distinct stereotypies by age (some points in the graph may correspond to several patients). The number of stereotypies decreased with age (particularly after age 10 years), especially in Group I, in which a significant difference was observed between patients younger and older than 10 years ($t = 3.749$, $p = 0.001$).

hand gaze, bruxism, and two or more of the other stereotypies seemed to be highly indicative of the presence of an *MECP2* mutation.

The pathophysiologic basis of stereotypies in RTT remains elusive, and we do not know whether these involuntary movements interfere with motor learning. Most studies stress that hand stereotyped movements coincide with or follow the disappearance of purposeful prehension in RTT; however, a video analysis of 22 patients in the first 6 months of life, before the beginning of regression, showed stereotyped hand movements in 42% of cases.⁹ In our series, in the group with *MECP2* mutations, stereotypies were also described by the parents as coinciding with the loss of purposeful hand movements in 43.3% and preceding it in 18.8%. We thus

believe that the particularly compulsive behavior of stereotypies in patients with RTT may have a role in the complex process of loss or reduction of hand use.

Like other authors,^{12,13} we found that manual stereotypies became simpler and slower with the progress of the disease, as patients become hypokinetic and rigid; however, each patient maintained the same type of hand movements throughout the period of observation. Other stereotypies tended to disappear and behaved like tics, with one stereotyped movement replacing another. This allows us to speculate that the physiopathology of hand stereotypies may be different from that of other topographies.

We conclude that stereotypies in RTT can be pleomorphic, mainly in the first decade of life. Nevertheless, the pattern of some repetitive movements associated with this disorder suggests that they have underlying monotonous motor programming, the basis of which should be investigated.

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