Hand Stereotypies Distinguish Rett Syndrome from Autism Disorder

Sylvie Goldman, PhD,[1,2,3]* and Teresa Temudo, MD, PhD[4,5]

[1]Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, USA; [2]Department of Pediatrics, Albert Einstein College of Medicine, Bronx, New York, USA; [3]Rose F. Kennedy Center for Research in Mental Retardation and Human Development, Albert Einstein College of Medicine, Bronx, New York, USA; [4]Serviço de Neuropediatria, Departamento da Criança e Adolescente, Centro Hospitalar do Porto, Porto, Portugal; [5]Instituto de Ciências Biomédicas Abel Salazar, Porto, Portugal

ABSTRACT

Background: Rett syndrome (RTT) and autism disorder (AD) are 2 neurodevelopmental disorders of early life that share phenotypic features, one being hand stereotypies. Distinguishing RTT from AD often represents a challenge, and given their distinct long-term prognoses, this issue may have far-reaching implications. With the advances in genetic testing, the contribution of clinical manifestations in distinguishing RTT from AD has been overlooked.

Methods: A comparison of hand stereotypies in 20 children with RTT and 20 with AD was performed using detailed analyses of videotaped standardized observations.

Results: Striking differences are observed between RTT and AD children. In RTT, hand stereotypies are predominantly complex, continuous, localized to the body midline, and involving mouthing. Conversely, in AD children, hand stereotypies are simple, bilateral, intermittent, and often involving objects.

Conclusions: These results provide important clinical signs useful to the differential diagnosis of RTT versus AD, especially when genetic testing for RTT is not an option.

Key Words: stereotypies; hand stereotypies; Rett syndrome; autism

Rett syndrome (RTT) and autism disorder (AD) are 2 sporadic neurodevelopmental disorders of early life; even though 75%–95% of RTT cases are linked to *MECP2* mutations[1,2] and AD has a strong polygenetic basis. Although they represent 2 distinct neurological conditions, RTT and AD, especially in severely affected children, share clinical features such as poor sociability and lack of communication, along with irritability and anxiety.[3] Furthermore, in addition to their signature "hand-washing" stereotypies, girls with RTT have many other stereotypies, like flapping and pacing, which are also observed in children with AD.[4] Conversely, hand stereotypies are, in fact, far from specific to RTT, as they can be observed rather often in children with AD.[5] These observations sometimes render the distinction between RTT and AD quite challenging for practitioners, and because RTT is ultimately fatal whereas AD is not, such a differential diagnosis is critically important.

Here, we report striking differences in the characteristics of hand stereotypies in children with RTT compared with those of matched cognitively impaired children with AD. We posit that these differences afford invaluable clues to distinguishing between RTT and AD on a clinical ground, especially in those situations where *MECP2* genetic testing is not readily accessible.

Patients and Methods

Subjects

The 20 girls with RTT fulfilled revised criteria for RTT[6] and were examined and videotaped by the same child neurologist in Portugal. All children were carriers of an *MECP2* mutation and had a NVIQ < 50; 9 walked independently. Ten were medicated with an antiepileptic (sodium valproate or carbamazepine). Their mean and median chronological age was 60 months (range, 36–96 months).

The 20 low-functioning children (11 boys, 9 girls) from the United States had a preschool diagnosis of

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The 2 authors contributed equally to this article.

***Correspondence to:** Sylvie Goldman, Albert Einstein College of Medicine, Kennedy Center, Room 807, 1300 Morris Park Avenue, Bronx, NY 10461, USA; sylviegold@aol.com

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autistic disorder based on DSM-III-R criteria. The number of available autistic girls who met criteria for this study was insufficient to limit selection to girls, but our previous study[5] and that of another group[7] showed no sex differences in stereotypies. The children were participants in a large multicenter longitudinal study of developmental disorders recruited between 1985 and 1988.[8] They were selected randomly from those in our previous study[5] who presented stereotypies and were matched pairwise on chronological age (mean, 68 months; range, 33–98 months) and NVIQ (<70; mean, 31; median, 27) with the girls with RTT. All were ambulatory, and none had a frank sensorimotor deficit or known neurological disorder; none was receiving high doses of anticonvulsant or psychotropic medication.

The parents of all the children signed an informed consent for participation and videotaping. The parents of the children presented here signed an additional consent for publication of their child's video and photograph.

Scoring

We independently scored a 5-minute consecutive video segment selected to be most representative of the child's overall behavior. We focused on hand stereotypies and developed a coding system to record the type of hand movement (eg, clapping, clenching), the position of the hand (joined or apart), their localization (eg, midline or away from the body), their laterality (eg, bilateral or unilateral), and their complexity[9] (simple stereotypies were defined as single movement involving 1 group of muscles [eg, handclapping], whereas complex stereotypies were defined as clusters of different coordinated movements performed in the same sequence and involving a group of muscles [eg, opening and closing the hands with finger extension]).[10] To be counted, a stereotypy had to be seen at least twice in order to be able to document its repetitiveness. The characterization and scoring of each stereotypy are presented in Table 1. The inconsistent filming of the face because of the fixed camera or the focus on the whole body did not allow for reliable scoring of associated facial movements. However, the videotapes provided enough details to allow for the coding of hand movements directed toward the mouth (ie, mouthing). The 2 trained authors coded each child's videos in both groups independently, with an interrater reliability kappa $\geq$0.8. A third coder, blinded to diagnoses, scored 70% of the entire sample, with an interrater reliability kappa ranging from 0.8 to 1.0 for the 9 variables. Scores in the 2 groups were compared using chi-square analysis.

Table 1. Characteristics and scoring of hand stereotypies in autism disorder and Rett syndrome

	Scoring		
	AD (n = 20)	RTT (n = 20)	
Descriptors	Number of subject (%)		Chi-square, $P < .05$
Frequency			AD < RTT
Rare	7 (35%)	1 (5%)	
Frequent	10 (50%)	9 (45%)	
Continuous	3 (15%)	10 (50%)	
Topography			AD ≪ RTT
Midline	6 (30%)	20 (100%)	
Not midline:	14 (70%)	0 (0%)	
Complexity			AD = RTT
Simple	7 (35%)	11 (55%)	
Complex	13 (65%0	9 (45%)	
Laterality			AD < RTT
Unilateral	3 (15%)	9 (45%)	
Bilateral	17 (85%)	11 (55%)	
Amplitude			AD > RTT
Small	15 (75%)	5 (25%)	
Large	5 (25%)	15 (75%)	
Dystonic features			AD = RTT
Yes	9 (45%)	5 (25%)	
No	11 (55%)	15 (75%)	
Rhythmic			AD < RTT
Yes	10 (50%)	16 (80%)	
No	10 (50%)	4 (20%)	
Use of object			AD > RTT
Yes	12 (60%)	6 (20%)	
No	8 (40%)	14 (80%)	
Variety			AD = RTT
One single type of stereotypy	8 (40%)	6 (20%)	
More than 1 type of stereotypy	12 (60%)	14 (80%)	

Results

In the present study, 40 children with hand stereotypies are surveyed using videotape analyses. Among these, 20 had a confirmed diagnosis of RTT, and 20 had a definite diagnosis of AD. In this cohort of 40, hand stereotypies were associated with rocking, pacing, and skipping in 25% of AD children and in none of RTT children. All 40 children exhibited more than 1 type of hand stereotypy, yet RTT children typically displayed a much greater variety of hand stereotypies than did AD children (see Table 1). With respect to the complexity of the stereotypies, in the AD group, they appeared as simple hyperkinetic movements such as finger wiggling (40%) and hand flapping (30%). Complex hand stereotypies were observed in both groups, but with some salient differences. For instance, hand washing was only observed in RTT children, whereas shaking or tapping objects was only observed in AD. Furthermore, even when RTT and AD children exhibited the same type of complex hand stereotypies, they often differed in quality and frequency. In particular, clapping in RTT appears slow and monotonic, with forceful holding of hands together, whereas in AD children, clapping appears rapid and variable in its presentation, and when the hands are together, they touch briefly and lightly (see Video 1). Our videotape scoring revealed other striking and distinct features. During the selected 5-minute observation that started with the

Table 2. Characteristics of hand stereotypies

Characteristic	RETT syndrome	Autism disorder
Duration	Continuous	Intermittent
Position	Midline predominantly, proximal with mouthing	Varied, more distal
Object	Does not involve object	Involves objects and their properties
Visual behavior	No hand gaze	Visual inspection and peripheral fingers flickering

occurrence of hand stereotypies, all the RTT children had continuous hand movements, whereas all the AD children had intermittent clusters of repetitive hand movements (see Table 2). Furthermore, hand stereotypies in RTT children were localized predominantly in front of and at a close distance to the midline of the chest. In 60%, they were accompanied by mouthing, and in 70%, hands were joined or close to each other (see Video 2). Conversely, in the AD group, the repetitive patterned movements occurred in 75% away from the body with hands apart. Unilateral hand stereotypy was 2.5-fold more frequent in RTT than in AD children, whereas bilateral hand stereotypy occurred equally in both groups. Hand gaze was never observed in this RTT group, whereas 20% of children with AD exhibited close inspection of fingers or objects (see Video 3).

Discussion

Our video scoring revealed prominent differences in the phenomenology of stereotypies between RTT and AD. In RTT, hand stereotypies were continuous and predominated at the midline, whereas in AD, these stereotypies were intermittent and away from the body. In addition, when stereotypy episodes involved objects or hand gaze, the child always belonged to the AD group, never to the RTT group. Our observation is consistent with the findings from a recent study of 144 individuals with RTT.[11] In this study using family videos—a less systematic method—the authors also reported that repetitive movements in RTT were often continuous, localized in the midline of the body, and bilateral.

The phenotypic overlap between RTT and AD has long been recognized.[12] However, findings such as neurodevelopmental regression after a normal period of development, a loss of hand skills along with the appearance of stereotypies, deceleration of head growth, and progressive motor deterioration help to support the diagnosis of RTT. Our study has demonstrated that a fine clinical examination of hand stereotypies can reveal straightforward features that may further strengthen the diagnosis of RTT, hence helping in the differentiation of RTT from AD. Although the differential diagnosis of RTT versus AD can be achieved by genetic testing for *MECP2* mutations, when such testing is either not available or not affordable, the clinical characteristics discussed above may be indispensable in distinguishing RTT from AD.

Thus far, little is known about the pathophysiology of hand stereotypies. However, that these repetitive movements occur in both RTT and AD suggests they may share a common neurophysiological basis, even if, as discussed above, their frequency and topology differ. Hyperkinetic movement disorders consistently point toward dysregulation in the basal ganglia circuitry, but the actual neuronal pathways implicated in motor stereotypies in general, and in hand stereotypies in particular, remain to be established. However, at the cellular level, we know that the timing of the regression period in RTT parallels the period of intense synaptic development.[13] Furthermore, neuropathological findings in RTT show selective reduction of dendritic spines in the pyramidal cells of the brain; this has also been reported in autism.[14] Thus, it may be suggested that the shared occurrence of stereotypies in RTT and AD results from comparable impaired integration of the basal ganglia/motor thalamus input to the upper motor neurons because of failure of synaptic maintenance.

It is also worth mentioning that stereotypies in children have been suggested to be part of normal development[15,16] and that a developmental "arrest" might leave these children in a state where they are (physiologically) prone to stereotypic behavior. Although provocative at this point, this concept is important to consider but remains to be experimentally proven. Nonetheless, in our particular study, the repetitive movements we are reporting here are phenotypically dissimilar to those previously reported in normally developing children.[17,18]

Legends to the Videos

Video 1: Segment 1: A 5-year-old girl with Rett syndrome exhibiting continuous forceful clapping close to her body. **Segment 2:** A 3-year-old girl with autism disorder showing light rapid clapping.

Video 2: A four-year-old girl with Rett syndrome sitting on her mother's lap presenting with complex hand stereotypies associated with mouthing.

Video 3: A six-year-old boy with autism disorder scrutinizing toys. ■

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