Pediatric Neurology 90 (2019) 37–43

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Articles

Volumetric Analysis of the Basal Ganglia and Cerebellar Structures in Patients with Phelan-McDermid Syndrome

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ARTICLE INFO

Article history:
Received 13 June 2018
Accepted 16 September 2018

Keywords:
22q13.3 Deletion
SHANK3
Repetitive behaviors
MRI
Autism

ABSTRACT

OBJECTIVE: Phelan-McDermid syndrome is caused by haploinsufficiency of *SHANK3* on terminal chromosome 22. Knowledge about altered neuroanatomic circuitry in Phelan-McDermid syndrome comes from mouse models showing striatal hypertrophy in the basal ganglia, and from humans with evidence of cerebellar atrophy. To date, no studies have performed volumetric analysis on Phelan-McDermid syndrome patients.
METHODS: We performed volumetric analysis of baseline brain MRIs of Phelan-McDermid syndrome patients (ages three to 21 years) enrolled in a prospective natural history study (ClinicalTrials.gov NCT02461420). Using MRI segmentations carried out with PSTAPLE algorithm, we measured relative volumes (volume of the structure divided by the volume of the brain parenchyma) of basal ganglia and cerebellar structures. We compared these measurements to those of age- and sex-matched healthy controls part of another study. Among the patients, we performed linear regression of each relative volume using Repetitive Behavior Scale-Revised total score and Aberrant Behavior Checklist

Conflicts of Interest: None.

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https://doi.org/10.1016/j.pediatrneurol.2018.09.008
0887-8994/

stereotypy score. Eleven patients with Phelan-McDermid syndrome (six females, five males) and 11 healthy controls were in this analysis.
RESULTS: At time of MRI, the mean age of the patients and controls was 9.24 (5.29) years and 9.00 (4.49) years, respectively (P = 0.66). Compared to controls, patients had decreased caudate ($P \leq 0.013$), putamen ($P \leq 0.026$), and left pallidum ($P = 0.033$) relative volumes. Relative volume of cerebellar vermal lobules I to V (beta coefficient = −17119, $P = 0.017$) decreased with increasing Repetitive Behavior Scale-Revised total score.
CONCLUSIONS: The volumes of the striatum and left pallidum are decreased in individuals with Phelan-McDermid syndrome. Cerebellar vermis volume may predict repetitive behavior severity in Phelan-McDermid syndrome. These findings warrant further investigation in larger samples.

Introduction

Phelan-McDermid syndrome (PMS) is a disorder of synaptic transmission caused by loss of function of SHANK3 protein, occurring through deletion of terminal chromosome 22 encompassing the *SHANK3* gene, or through intragenic mutations.[1-3] SHANK3 is a postsynaptic density scaffolding protein that plays several important roles in the central nervous system (CNS), including dendritic spine maturation and synapse formation.[4] Affected patients present variably with somatic and neurobehavioral features, including minor facial and systemic anomalies, normal to advanced growth, global developmental delay/intellectual disability, absent or delayed speech, autism spectrum disorder (ASD), and generalized hypotonia.[2,5,3]

Animal models of PMS have recapitulated some of these clinical features and revealed neuropathologic and circuitry changes in the basal ganglia. Mice with *Shank3* deletions have striatal (caudate/putamen) hypertrophy and abnormally shaped striatal neurons. In addition, their striatal postsynaptic densities show reduced expression of scaffolding proteins and glutamate receptor subunits.[6-8] There is also evidence of abnormalities in the basal ganglia circuitry in *Shank3*-deficient mice.[6,7] *Shank3*-deficient mice have defects in the synaptic properties of striatopallidal medium spiny neurons.[7,9] Input to the striatum of the basal ganglia comes from the cortex and thalamus, while output from the striatum takes the form of either the direct projection pathway, comprising striatonigral neurons, or the indirect pathway, comprising striatopallidal neurons. A balance in the activity of the two pathways facilitates motor behaviors. In Wang et al., administration of an agent designed to upregulate striatopallidal medium spiny neuron activity ameliorated repetitive grooming, suggesting that preferential involvement of the indirect striatal pathway may be implicated in the development of repetitive behaviors in *Shank3*-deficient mice.[9]

Neuroimaging studies and case reports/case series of individuals with PMS have highlighted abnormalities in CNS structures other than the basal ganglia. In affected patients, radiographic findings have included corpus callosum thinning, ventriculomegaly, and cerebellar vermis hypoplasia.[10-14] To date, no studies have performed volumetric analysis on magnetic resonance imaging (MRI) data in humans with PMS, in order to evaluate the basal ganglia or cerebellum for evidence of pathology.

In this study, we performed volumetric analysis in 11 subjects, ages three to 21 years, with PMS as well as 11 age- and sex-matched controls. We focused on the basal ganglia and cerebellum. We hypothesized that, compared to controls, patients with PMS have larger striatal volumes, concordant with animal model data. We also hypothesized that decreased cerebellar volumes is predictive of more severe repetitive behaviors, given that cerebellar vermal hypoplasia is a common finding in PMS and that defects in cerebellar circuitry are associated with ASD symptoms.[15]

Methods

Study participants

We performed volumetric analysis on baseline brain MRIs of patients (ages three to 21 years) with PMS enrolled in a multisite, prospective, observational cohort study evaluating the genotype, phenotype, and natural history of PMS (ClinicalTrial NCT02461420). English speaking males or females, ages three to 21 years, with pathogenic deletions or mutations affecting the *SHANK3* gene were eligible for inclusion in the natural history study; brain MRIs were part of the evaluation if clinically indicated. Clinical indications for MRI included (but were not limited to): (a) no previous MRI (given that current practice recommendations for PMS suggest a baseline brain MRI to assess for cysts and other structural abnormalities)[16]; (b) change in developmental progress (e.g., regression); (c) new neurological sign (e.g., motor finding, asymmetry); (d) new onset of seizures or worsening of previous seizure pattern.

Behavioral assessments

Individuals received a diagnosis of ASD based on clinical consensus using the Diagnostic and Statistical Manual for Mental Disorders Fifth Edition (DSM-5),[17] and informed by evaluation with the Autism Diagnostic Observation Schedule[18] and Autism Diagnostic Interview-Revised.[19]

In addition, individuals underwent evaluation with a battery of assessments, including the Repetitive Behavior Scale-Revised (RBS-R),[20] Vineland Adaptive Behaviors Scales II (VABS-II),[21] and Aberrant Behavior Checklist (ABC).[22] The RBS-R is a questionnaire containing 43 items pertaining to restricted and repetitive behaviors across six categories: stereotyped behavior, self-injurious behavior, compulsive behavior, ritualistic behavior, sameness behavior, and restricted

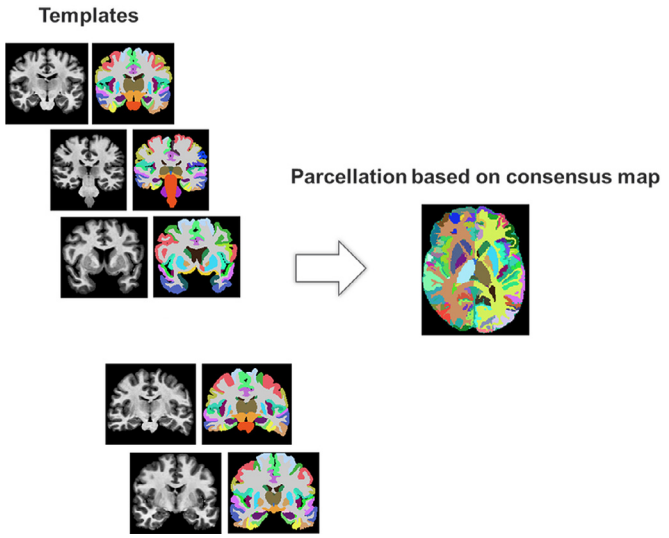

FIGURE 1.
Illustration of multitemplate parcellation. All the templates are first nonlinearly aligned to a target patient. A consensus map is then computed for each patient, providing a fully-automatic, robust to interindividual variability parcellation of each patient's brain.

behavior. Each item is coded with an integer score from zero to three corresponding to the severity of the behavior. Each of the six subscales has two corresponding scores: one for the sum of all the scores within the subscale, and one for the total number of subscale items endorsed. For the entire instrument, there are overall scores for the sum of all the item scores (overall total score) and the total number of items endorsed.

The VABS-II assesses adaptive behavior with respect to communication, socialization, daily living skills, and motor skills.[21] Each domain has an associated standard score, and domain scores generate an overall adaptive behavior composite standard score.

The ABC is a 58-item caregiver checklist evaluating problem behaviors in the following five domains: (a) irritability (mood lability, self-injury, and aggression); (b) lethargy/social withdrawal (isolation from others, little interaction); (c) stereotypies; (d) hyperactivity; and (e) abnormal speech (odd use of speech). Each item is scored from zero to three corresponding to the severity of the behavior. For this analysis, we included the ABC stereotypy domain.

MRI processing

We performed MRI processing and analysis with the Computational Radiology Kit (http://crl.med.harvard.edu/). This toolkit aligns the T2w image to the T1w image using rigid registration with mutual information metric; creates an intracranial cavity (ICC) segmentation using a previously validated multispectral ICC segmentation method[23]; and parcellates each MRI into regions of interest using a previously validated multitemplate fusion segmentation algorithm.[24] The template library consisted of 15 T1w, T2w, and FLAIR healthy control MRIs [nine male; mean age 9.1 (3.3) years; age range five to 15 years], which were hand labeled by expert neuroanatomists using well-established MRI brain labeling protocols[25,26] to create anatomic boundary definitions, with test-retest reproducibility quantified. Each T1w template was non-rigidly aligned to the patient T1w image and multitemplate fusion was carried out using the local MAP PSTAPLE (PSTAPLE) algorithm.[24] PSTAPLE uses both the label images and intensity profiles of the T1w templates to compute probability maps for each target structure, ultimately leading to an automatic consensus labeling of each patient brain. See Figure 1. The automatic parcellations were carefully reviewed to ensure accuracy with respect to basal ganglia and thalamus regions of interest, performing editing as needed.

Using these segmentations of the MRI, we computed left and right relative volumes pertaining to four anatomic structures: left/right caudate, left/right putamen, left/right globus pallidus, left/right thalamus, left/right cerebellar white matter, left/right cerebellar exterior, cerebellar vermal lobules I to V, cerebellar vermal lobules VI to VII, and cerebellar vermal lobules VIII to X. In this study, we did not analyze other brain regions. Each relative volume was computed as the volume of the structure divided by the volume of the brain parenchyma (ICC subtracted by ventricular volume and extracerebral CSF volume) given reports of ventriculomegaly in PMS. We compared relative volumes to those of age- and sex-matched healthy controls.

Statistical analysis

We used Pearson's chi-squared test to compare gender between subject categories. We used Wilcoxon signed-rank test to compare age and relative volumes between patients and controls. We used Wilcoxon rank-sum test to compare relative volumes between patients with ASD versus patients without ASD. We employed Benjamini-Hochberg false discovery rate procedure to control for multiple comparisons, setting acceptable value of false discovery rate to 0.20 for our current sample size.

Results

Eleven patients with PMS (six females, five males) and 11 healthy, age- and sex-matched controls were analyzed. At the time of brain MRI, the mean age of the patients and controls was 9.24 years [range 3.43 to 20.87 years] and 9.00 years [range 3.11 to 16.70 years], respectively (P = 0.66). Among the 11 patients, enlarged ventricles were present in three, a thin corpus callosum was present in two, and arachnoid cysts were present in two. In terms of genotype, 11/11 (100%) had a pathogenic 22q13 deletion, ranging in size from 78kb to 8230kb, that included *SHANK3*. One participant also had a 206.3kb de novo pathogenic 16p11 deletion in addition to 22q13 deletion. 6/11 (54.55%) had a diagnosis of ASD. For the patients, the mean VABS-II adaptive behavior composite was 54.72, the mean RBS-R overall score was 10.82, and the mean ABC stereotypy score was 2.91 (Table 1).

There was no difference in ICC volume (P = 0.33) or total volume of the brain parenchyma (P = 0.66) between patients and controls. Relative volumes of the right caudate (P = 0.0076), left caudate (P = 0.013), right putamen (P = 0.026), left putamen (P = 0.016), and left pallidum (P = 0.033) were decreased in patients versus controls, and these were statistically significant after accounting for multiple comparisons. There was no statistically significant difference in relative volume of any of the cerebellar structures between patients and controls (Table 2).

When comparing relative volumes of each of the structures in patients with ASD (PMS + ASD) versus patients without ASD (PMS − ASD), no structures showed a statistically significant difference between groups (Table 3).

For the patients, linear regressions of each relative volume with RBS-R overall total score showed that with increasing RBS-R total score, there was decreased relative volume of the cerebellar vermal lobules I to V (beta coefficient = −17119, P = 0.017), though separate regressions for individuals with and without ASD were not

TABLE 1.
Demographics and Baseline Characteristics of the Patients and Controls

	Patients (n = 11)	Controls (n = 11)	*P* value
Gender (% male)	45.45% (n = 5)	45.45% (n = 5)	*P* = 1.00
Age at brain MRI [years (SD)]	9.24 (5.29)	9.00 (4.49)	*P* = 0.66
Autism diagnosis (%)	54.54% (n = 6)	N/A	N/A
Vineland Adaptive Behavior Scales-II (VABS-II) adaptive behavior composite standard score [score (SD)]	54.72 (18.97)	N/A	N/A
Repetitive Behavior Scale-Revised (RBS-R) overall score [score (SD)]	10.82 (10.31)	N/A	N/A
Aberrant Behavior Checklist (ABC) stereotypy score [score (SD)]	2.91 (4.83)	N/A	N/A

N/A = not applicable.

TABLE 2.
Relative Volumes of Basal Ganglia and Cerebellar Structures for the Patients and Controls

	Patients (n = 11)	Controls (n = 11)	*P* value	Significant after false discovery rate procedure
Right Pallidum [mean (SD)]	0.00113 (0.00014)	0.00119 (0.00017)	0.15	No
Left Pallidum [mean (SD)]	0.00112 (0.000097)	0.00122 (0.00017)	0.033	Yes
Right Putamen [mean (SD)]	0.00412 (0.00062)	0.00468 (0.00044)	0.026	Yes
Left Putamen [mean (SD)]	0.00410 (0.00063)	0.00472 (0.00045)	0.016	Yes
Right Caudate [mean (SD)]	0.00307 (0.00022)	0.00358 (0.00041)	0.0076	Yes
Left Caudate [mean (SD)]	0.00309 (0.00023)	0.00345 (0.00038)	0.013	Yes
Right Cerebellum White Matter [mean (SD)]	0.0106 (0.0015)	0.0106 (0.0020)	0.86	No
Left Cerebellum White Matter [mean (SD)]	0.0109 (0.0015)	0.0108 (0.0019)	0.79	No
Cerebellar Vermal Lobules I-V [mean (SD)]	0.00339 (0.00042)	0.00365 (0.00045)	0.13	No
Cerebellar Vermal Lobules VI-VII [mean (SD)]	0.00128 (0.00023)	0.00144 (0.00025)	0.21	No
Cerebellar Vermal Lobules VIII-X [mean (SD)]	0.00203 (0.00032)	0.00212 (0.00021)	0.53	No
Right Cerebellum Exterior [mean (SD)]	0.0392 (0.0044)	0.0401 (0.0031)	0.66	No
Left Cerebellum Exterior [mean (SD)]	0.0392 (0.0043)	0.0398 (0.0029)	0.66	No

statistically significant. See Figure 2. The regressions of relative volumes of striatal structures with RBS-R overall total scores were not statistically significant. There was not a statistically significant regression between RBS-R total score and 22q13 deletion size. There was no statistically significant regression between ABC stereotypy score and relative volume of any of the structures.

The statistical significance of these aforementioned findings (including Table 2, Table 3, and linear regressions of each relative volume with RBS-R overall total score) remained true even when the participant with dual diagnoses was excluded from analysis.

Discussion

The main finding in this report is that the volumes of the striatum and left pallidum were decreased in our cohort of 11 patients with PMS compared to healthy controls. However, the volumes of the cerebellar structures were not significantly different in patients versus controls. Finally, cerebellar vermal lobules I to V relative volume increased with decreasing RBS-R total score.

Our study is first to examine volumetric differences in the basal ganglia and cerebellum in human subjects with PMS. Prior reports have implicated a variety of gross structural abnormalities in this syndrome. In one study examining brain MRIs of 10 patients with 22q13 deletions, the following radiographic features were present: thin corpus callosum (90%), thin white matter (70%), ventriculomegaly (80%), definite or subtle cerebellar vermis hypoplasia (60%), and definite or subtle mega cisterna magna (50%, including two patients who also had definite cerebellar vermis hypoplasia).[10] Similarly, in a separate cohort of eight patients with 22q13 deletions who underwent brain imaging with MRI and positron emission tomography scans, the two most common imaging abnormalities were a thin/morphologically atypical corpus callosum and ventricular dilatation. Collectively, these patients also demonstrated hypoperfusion in the left temporal-polar lobe and amygdala.[14] Multiple other reports have corroborated the presence of features such as corpus callosum thinning,[12,13] delayed myelination[12] or other white matter abnormalities,[11] and ventricular enlargement[11] in PMS.

Our findings suggest dysfunction in basal ganglia circuitry as one of the possible mechanisms underlying disease in PMS. In support of this notion, expression of *Shank3* is

TABLE 3.
Relative Volumes of Basal Ganglia and Cerebellar Structures for the Patients Stratified by Diagnosis of Autism

	Patients + ASD (n = 6)	Patients no ASD (n = 5)	*P* value	Significant after false discovery rate procedure
Right Pallidum [mean (SD)]	0.00113 (0.00013)	0.00112 (0.00017)	0.855	No
Left Pallidum [mean (SD)]	0.00115 (0.00011)	0.00109 (0.000070)	0.273	No
Right Putamen [mean (SD)]	0.00403 (0.00084)	0.00422 (0.00026)	1.00	No
Left Putamen [mean (SD)]	0.00395 (0.00084)	0.00428 (0.00023)	0.715	No
Right Caudate [mean (SD)]	0.00305 (0.00030)	0.00309 (0.00011)	1.00	No
Left Caudate [mean (SD)]	0.00316 (0.00025)	0.00300 (0.00019)	0.361	No
Right Cerebellum White Matter [mean (SD)]	0.0108 (0.0016)	0.0104 (0.0014)	0.715	No
Left Cerebellum White Matter [mean (SD)]	0.0112 (0.0016)	0.01050 (0.0015)	0.465	No
Cerebellar Vermal Lobules I-V [mean (SD)]	0.00334 (0.00040)	0.00344 (0.00048)	0.715	No
Cerebellar Vermal Lobules VI-VII [mean (SD)]	0.00122 (0.00030)	0.00134 (0.00010)	0.361	No
Cerebellar Vermal Lobules VIII-X [mean (SD)]	0.00190 (0.00033)	0.00219 (0.00027)	0.144	No
Right Cerebellum Exterior [mean (SD)]	0.0391 (0.0055)	0.0392 (0.0032)	0.584	No
Left Cerebellum Exterior [mean (SD)]	0.0388 (0.0052)	0.0396 (0.0035)	0.584	No

particularly high in the striatum and thalamus compared to other regions in the CNS.[27,8] Moreover, *Shank3* deficient mice exhibit obsessive, self-injurious grooming in conjunction with evidence of impaired neurotransmission at striatal and cortico-striatal synapses.[6-8] The basal ganglia have a number of important functions in the brain, including sensory control, motor programming, and reward-driven behaviors. Striatal dysfunction is an example of one of the final common pathways that may lead to the emergence of autism symptoms, in particular repetitive behaviors[28]— features which are prominent in PMS.[5,3] Interestingly, RBS scores did not correlate with striatal volumes in the patient group, perhaps reflecting that this cohort had relatively mild repetitive behaviors (mean RBS overall total score 10.82), and/or that this cohort had relatively small numbers.

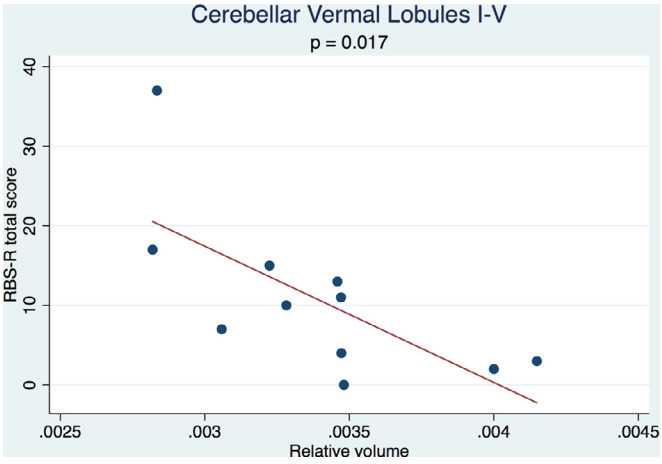

FIGURE 2.
Scatter plots and fitted lines of RBS-R total score versus relative volumes of cerebellar vermal lobules I to V showing an inverse relationship between the relative volume and RBS-R total score. RBS-R, repetitive behavior scale-revised.

Surprisingly, among our patients, the finding of comparatively decreased caudate and putamen size was contrary to our hypothesis regarding striatal volume. We had speculated that striatal volume would be greater in patients, based on the fact that *Shank3B*$^{-/-}$ mice have evidence of caudate hypertrophy.[8] One possible explanation for this discrepancy is that the PMS mouse model may not completely recapitulate the phenotype seen in humans. This notion of face validity[29] poses a challenge for animal models across multiple genetic disorders. Of note, in light of this conflict with animal model data, our findings may not be generalizable as of yet and warrant confirmation with a larger number of patients. The lack of a correlation between basal ganglia volume and stereotypy score in our cohort also seems surprising, though this may be consistent with the mixed nature of data about whether increased or decreased basal ganglia volumes are associated with repetitive behavior severity.[30] For example, in one study, in young children with ASD, decreased basal ganglia and thalamus volumes were associated with increased levels of repetitive and stereotyped behavior.[31] However, in another study, increased right caudate and total putamen volume were associated with greater repetitive behaviors.[32] In fragile X syndrome, a monogenic disorder associated with a high prevalence of ASD, researchers have shown that left and right caudate volumes are positively correlated with severity of self-injurious behaviors and number of self-injurious behavior topographies.[33]

Underdevelopment of the cerebellar vermis is a known finding in humans with PMS,[10] but in our cohort relative

volumes of cerebellar structures were not significantly different compared to controls. The factors that influence development of cerebellar vermis hypoplasia in PMS are unclear. For example, in the aforementioned study, there was not a clear-cut relationship between 22q13 deletion size and degree of cerebellar vermis hypoplasia, suggesting that there could be genetic modifiers influencing this phenotype. It could also be that our sample may be disproportionately skewed in terms of patients not being affected by cerebellar hypoplasia. Given that MRI studies on PMS, including this one, have involved small numbers of participants, a large scale study may be necessary to fully understand the prevalence of cerebellar hypoplasia within the disorder.

Though relative volumes of cerebellar structures were not significantly different compared to controls, patients with larger relative volume of cerebellar vermal lobules I to V had lower (i.e., less impaired) RBS-R total scores. Cerebellar vermis malformations have been implicated in ASD symptoms.[34] Therefore, one possible mechanism for our findings is that reduced cerebellar vermal volumes, perhaps reflecting degree of Purkinje cell loss, could mediate some aspects of the behavioral phenotype of PMS.

The major caveat to our study is that the overall sample size of our study was small with only n = 11 subjects. This small number may explain why there was not a statistically significant difference in relative volumes of any of the studied structures between PMS+ASD and PMS−no ASD. Moreover, due to the varying cognitive abilities within this group, we were not able to obtain a full scale IQ score for all participants; nonetheless we included VABS data (adaptive functioning) as a proxy for overall cognitive ability. Given the relative paucity of detailed MRI studies on this patient population, our results are noteworthy and point to further avenues of investigation. Specifically, it will be important to demonstrate replicability of our findings with larger numbers of patients. Nonetheless, this study highlights the basal ganglia and cerebellum as intriguing targets for further investigation in PMS.

This study is supported by the Developmental Synaptopathies Consortium (U54NS092090), which is a part of the National Center for Advancing Translational Sciences Rare Diseases Clinical Research Network. The Rare Diseases Clinical Research Network is an initiative of the Office of Rare Diseases Research of the National Center for Advancing Translational Sciences, and Developmental Synaptopathies Consortium is funded through collaboration between the National Center for Advancing Translational Sciences, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. We are sincerely indebted to the generosity of the families and patients in PMS clinics across the United States who contributed their time and effort to this study. We would also like to thank the Phelan-McDermid Syndrome Foundation for their continued support in PMS research.

APPENDIX

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