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Cornelia de Lange Syndrome: Correlation of Brain MRI Findings With Behavioral Assessment

TAMANNA R. ROSHAN LAL,
Pediatrician and Medical Genetic Resident at McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine

MARK A. KLIEWER,
Professor of Radiology and Medical Physics, University of Wisconsin-Madison. He is a member of the Clinical Advisory Board of the Cornelia de Lange Syndrome Foundation

THELMA LOPES,
Pediatric Neuro-radiologist at Sinai Hospital of Baltimore

SUSAN L. REBSAMEN,
Pediatric Neuro-radiologist at University of Wisconsin-Madison

JULIA O'CONNOR,
Assistant Professor, Behavioral Psychology at Kennedy Krieger Institute of Johns Hopkins University School of Medicine. She is a member of the Clinical Advisory Board of the Cornelia de Lange Syndrome Foundation and a member of the Board of Directors for the Foundation

MARCO A. GRADOS,
Associate Professor, Division of Child and Adolescent Psychiatry, Johns Hopkins University School of Medicine. He is also a member of the Clinical Advisory Board of the Cornelia de Lange Syndrome Foundation

AMY KIMBALL,
Genetic counselor at the Harvey Institute for Human Genetics at Greater Baltimore Medical Center, also a member of the Clinical Advisory Board of the Cornelia de Lange Syndrome Foundation

JULIA CLEMENS, and
College senior at Wesleyan University, premedical student. She has acted in a volunteer capacity for the Cornelia de Lange Syndrome Foundation for many years

ANTONIE D. KLINE*
Director of Pediatric Genetics at the Harvey Institute for Human Genetics at Greater Baltimore Medical Center, also the medical director for the Cornelia de Lange Syndrome Foundation, and chair of the Clinical Advisory Board

Abstract

*Correspondence to: Antonie D. Kline, Harvey Institute for Human Genetics, Greater Baltimore Medical Center, 6701 N. Charles St Suite 2326, Baltimore, MD 21204. akline@gbmc.org.

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Neurobehavioral and developmental issues with a broad range of deficits are prominent features of Cornelia de Lange syndrome (CdLS), a disorder due to disruption of the cohesin protein complex. The etiologic relationship of these clinical findings to anatomic abnormalities on neuro-imaging studies has not, however, been established. Anatomic abnormalities in the brain and central nervous system specific to CdLS have been observed, including changes in the white matter, brainstem, and cerebellum. We hypothesize that location and severity of brain abnormalities correlate with clinical phenotype in CdLS, as seen in other developmental disorders. In this study, we retrospectively evaluated brain MRI studies of 15 individuals with CdLS and compared these findings to behavior at the time of the scan. Behavior was assessed using the Aberrant Behavior Checklist (ABC), a validated behavioral assessment tool with several clinical features. Ten of fifteen (67%) of CdLS patients had abnormal findings on brain MRI, including cerebral atrophy, white matter changes, cerebellar hypoplasia, and enlarged ventricles. Other findings included pituitary tumors or cysts, Chiari I malformation and gliosis. Abnormal behavioral scores in more than one behavioral area were seen in all but one patient. All 5 of the 15 (33%) patients with normal structural MRI studies had abnormal ABC scores. All normal ABC scores were noted in only one patient and this was correlated with moderately abnormal MRI changes. Although our cohort is small, our results suggest that abnormal behaviors can exist in individuals with CdLS in the setting of relatively normal structural brain findings.

Keywords

MRI; brain; Cornelia de Lange syndrome; behavior; Aberrant Behavior Checklist

INTRODUCTION

Cornelia de Lange syndrome (CdLS; OMIM #122470, #300590, #610759, #614701, and #300882) is a cohesinopathy disorder caused by single mutations in cohesin complex genes [Krantz et al., 2004; Tonkin et al., 2004; Musio et al., 2006; Deardorff et al., 2007, 2012a,b]. Among cohesin genes, mutations in *NIPBL* (5p13) account for over 60% of cases, while those in *SMC3* (10q25) and *SMC1A* (Xp11), and, more recently, in the genes *Rad21* (8q24.11) and *HDAC8* (Xq13.1), account for about 5–7% of affected individuals [Deardorff et al., 2012b]. These genetic mutations result in a developmental malformation syndrome characterized by small stature, microcephaly, limb abnormalities (oligodactyly, 2,3 toe-syndactyly), distinctive facial features (arched eyebrows, synophrys, short nose, down-turned mouth), hirsutism, developmental delays, multiple organ system defects (central nervous system, gastrointestinal, genitourinary, and cardiac), and behavioral issues [Jackson et al., 1993]. Within CdLS, there is a wide spectrum of severity, from severe involvement with global impairment to mild involvement with normal intelligence [Kline et al., 2007a]. Mutational data analysis has demonstrated a genotype-phenotype correlation only in NIPBL. Nonsense, splice site and frame shift mutations leading to a truncated and presumably non-functional NIPBL protein are associated with a more severe phenotype characterized by typical facial features, severe to profound developmental and cognitive delay with poor communication, severe growth retardation, and structural abnormalities of the limbs and other organs. Missense mutations are, in general, associated with a milder phenotype characterized by absent limb abnormalities and with less severe developmental and growth

involvement. Furthermore, some splice site mutations have been identified in probands with a moderate phenotype with typical characteristics but with reduced developmental and cognitive abilities [Mannini et al., 2013]. The other genes have had less of a genotype–phenotype correlation, partially because of less total number of patients identified; in general, mutations in *SMC1A*, *SMC3*, and *Rad21* have a milder phenotype [Mannini et al., 2013]. Both diagnostic criteria and a scoring system to characterize severity have been developed to confirm clinical diagnoses [Kline et al., 2007b].

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The prevalence of specific abnormalities within different organ systems in CdLS is not well established. Given the prominence of neurodevelopmental abnormalities both in the clinical phenotype of the syndrome and on neuro-imaging studies, it seems probable that anatomic abnormalities might correlate with development and behavior. For example, seizures occur in slightly over 20% of individuals [Kline et al., 2007b] and sleep disturbance is common [Stavinoha et al., 2011]. The behavioral profile of CdLS includes self-injury, aggression, hand posturing, obsessive-compulsive traits, attention deficit disorder with or without hyperactivity, short attention span, depression, and autism or autistic behaviors [Jackson et al., 1993; Basile et al., 2007; Oliver et al., 2008; Srivastava et al., 2014]. Intellectual disability is common and neurologic exams are typically normal other than hyperreflexia [Kline et al., 2007a]. Although the prevalence of autism spectrum disorder in CdLS is relatively high, the presentation of autism symptoms is subtly different when compared to idiopathic autism [Moss et al., 2012].

A few reports of brain findings have been published. Autopsies have revealed specific changes: hypoplastic corpus callosum, cerebellar vermis, septum pellucidum with septo-optic dysplasia and commissural dysplasia [Hayashi et al., 1996]; immature cerebral gyri, thickened leptomeninges, and hypo-plastic thalamic nuclei, pons and cerebellar cells [Yamaguchi and Ishitobi, 1999]; and lack of myelination in temporal cortex, frontal lobe hypoplasia and neurofibrillary tangles [Vuilleumier et al., 2002]. Some patterns of brain changes on computed tomography (CT) scans and magnetic resonance imaging (MRI) studies have been reported, including enlarged ventricles, thinning of white matter, gyral simplification, and brainstem and cerebellar hypoplasia [Ozkinay et al., 1998; Kline et al., 2007b; Whitehead et al., 2015]. There have been no reports of brain study findings compared with either IQ or mutation analysis results in CdLS.

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Correlation between neuroanatomical findings and behavior has been found in other genetic conditions, including Down syndrome, fragile X syndrome, and Rett syndrome [Pinter et al.,

2001; Gothelf et al., 2008; Mahmood et al., 2010]. Specifically, in fragile X syndrome, Gothelf et al. [2008] found a positive correlation between the size of the caudate nucleus and behavior as measured by the Aberrant Behavior Checklist and the stereotypy scale of the Autism Behavior Checklist. Specific brain differences have been documented in individuals with autism spectrum disorder, including symmetry differences [Knaus et al., 2012] and on functional MRI studies compared to severity of autistic traits [Gothelf et al., 2008; Cerliani et al., 2015]. Functional MRI studies also have been done in Down syndrome looking at adaptive behavior [Pujol et al., 2015], but in very few other genetic conditions. It would not be likely that a single major change in the brain would be noted which would correspond to behavioral subscales on the ABC in CdLS, but small correlations might be expected. The purpose of our overall study is to document a range of CNS abnormalities found on brain MRI studies, and test for correlation between these findings and the neurobehavioral issues in patients with CdLS. This phase of the study compared MRI findings to some clinical findings and behavior based on the Aberrant Behavior Checklist.

METHODS

Patients with CdLS who had a brain MRI were recruited through community advertisements via the CdLS newsletter, online advertisements (http://www.cdlsusa.org), and by direct personal communication (AK) to patients seen at the Harvey Institute for Human Genetics at the Greater Baltimore Medical Center (GBMC). Interested families with affected individuals made contact via telephone or e-mail to learn more about the study and the informed consent process. Written informed consent from all parents, guardians or higher functioning patients over 18 years of age was obtained. The protocol of this study was prospectively reviewed and approved by the GBMC Institutional Review Board.

Diagnosis of CdLS was confirmed clinically (ADK). Brain MRI scans were interpreted independently by three neuro-radiologists (TL, MK, SR), who were blinded to the behavioral assessments of the patients. The Aberrant Behavior Checklist—Community (ABC), a behavioral questionnaire, was completed via phone or in person by the parents or caregivers of individuals with CdLS. This interview was conducted by a pediatrician (TR) or an experienced behavioral psychologist (JO). Parents or caregivers were asked to recall the behavior exhibited by their child during the time period that the MRI was done. The questionnaires initially scored by the pediatrician were re-confirmed by the behavioral psychologist.

Inclusion criteria included children with a clinical diagnosis of CdLS, brain MRI obtained at 5 years of age or older, and a parent or guardian willing to complete the behavioral questionnaire.

Study Measures

The MRI scans were reviewed for completeness and diagnostic quality, and were compared to known normal brain MRI results. Based on prior literature, specific neurologic abnormalities previously described were intentionally sought. These included: hypoplasia of the cerebellum, corpus callosum, septum pellucidum, and brainstem; brachycephaly; microcephaly; ventriculomegaly; colpocephaly; and cerebral atrophy. Record was also made

for any evidence of focal or regional cortical atrophy; migrational abnormality; convolutional maldevelopment; supratentorial midline abnormality (optic nerve, corpus callosum, pituitary axis); infratentorial midline abnormality (vermis, cerebellum, brain-stem); temporal lobe gliosis; white matter abnormality; facial abnormality (palate, maxilla, mandible, sinuses, mastoids); cerebral spinal fluid (CSF) space enlargement; tumors; gliosis; diffusion abnormality; bleed; stoke; or surgical changes. In addition, close inspection was directed at these anatomic features: temporal bone and middle ear; cranial base; temporal lobes; cerebral cortex; and white matter. Abnormalities were described and rated as to severity, extent, and chronicity. A score was assigned based on findings in different anatomical areas (cerebrum, temporal lobe, corpus callosum, pituitary axis, cerebellum, brainstem, ventricles, CSF spaces, and flair sequence) with higher numbers associated with more severe changes.

The Aberrant Behavior Checklist (ABC) is a symptom checklist for assessing problem behaviors of children and adults with intellectual disability and is a widely used scale to assess behavior in this population, particularly when assessing treatment effects. It has been validated for ages 5 years and above. The checklist is a 58-item questionnaire, which covers five subscales [Aman et al., 1986] and includes five clinical history questions. The behavior sub-scales are: (I) Irritability/Agitation (mood lability, self-injury, aggression); (II) Lethargy/Social Withdrawal (isolation from others, minimal interaction); (III) Stereotypic Behavior (repetitive movements); (IV) Hyperactivity; and (V) Inappropriate speech (increased or unusual use of speech). The checklist can be completed by parents, special educators, psychologists, direct caregivers, nurses, and others with knowledge of the person being assessed.

Data Analysis

A scoring system for the MRI results was devised for comparison purposes. Scores of 1, 3, and 5 were used depending on level of involvement. Each of the following findings was given a scaled score of 1, 3, or 5 depending on severity: generalized atrophy, lobar atrophy, temporal lobe/hippocampal findings, migrational abnormalities, white matter changes, corpus callosum findings, cerebellar hypoplasia, brainstem changes, ventricular dilation, and gliosis. Additional scores were given for specific changes, including: a score of 1 for enlarged pituitary/pituitary cyst or microadenoma of pituitary, a score of 1 for an acquired Chiari I malformation, a score of 1 for enlarged cistern magna, a score of 3 for microcephaly and/or brachycephaly, a score of 1 for a schwannoma/cyst or diverticulum of CSF space, a score of 3 for subcortical gliosis, a score of 3 for dilated CSF spaces, a score of 1 for unusually bright fluid on flair sequence, a score of 3 for gliosis seen on flair sequence and a score of 1 for bony fusion of upper cervical vertebrae, mild foramen magnum stenosis or shortened clivus.

On the ABC, the sums of item severity ratings (from 0 for “not at all” to 3 for “severe”) for each subscale are used to obtain an average score for each of the five domains [Srivastava et al., 2014]. Based on the scores, each subscale behavior is categorized as Normal (N), Elevated (E), or Clinically Significant (CS). The questionnaire scores were compared to the

findings of the MRI scans using the Fisher's Exact test. Statistical significance was confirmed at *P* values of 0.05 or less.

RESULTS

Initially, 56 patients were recruited who had MRI scans of the brain. However 41 patients had the MRI scans done as an infant or before 5 years of age. Therefore only 15 patients met the inclusion criteria and were included in this phase of the study (Table I), as the ABC is validated for people ages 5 years and above. The patients' ages ranged from 5 to 28 years, and 87% were female. Clinical presentations varied, as assessed by the ABC (Table I), although this was incomplete for several patients. The majority of the patients were ambulatory, six of those reported (46%) had seizures, four (31%) had deafness, one was blind and none had cerebral palsy. Eleven (79%) were in some degree of special education because of development or behavior or both.

Ten of the 15 (67%) MRI scans were abnormal, including 40% with generalized cerebral or lobar atrophy, 27% with white matter changes, 33% with cerebellar vermal hypoplasia, 13% with temporal lobe hypoplasia, 47% with findings in the CSF space and 20% with mildly dilated ventricles (Fig. 1). Twenty percent had abnormal or thin corpus callosum. Thirty-three percent had enlarged or mega cisterna magna. One patient had migrational abnormalities. Simplified gyral pattern can be seen in Figure 1. Pituitary abnormalities were found in four subjects, including Rathke cleft cysts in two, pituitary microadenoma in one, and small pituitary gland in one. White matter changes were found in five cases (gliosis in three, occipital thinning in one, and a tiny cyst in one). Two patients (13%) had Chiari I malformation. Head shape was normal in 11 patients (73%), and there was microbrachycephaly in three, microcephaly in one, and frontal bossing in one. Sixty percent had lower facial changes including high arched palate in six cases (40%), micrognathia in three and hypoplastic mandibular condylar heads in three. Mastoid and sinus disease was found in eight of the 16 patients (50%). Additional details can be found in Table I.

The families were called to complete the ABC via telephone or questioned in person. The time between having the MRI scan and the parents/caregivers answering the ABC questions ranged from 0 days to up to 10 years. On the ABC score ratings, 8/15 (53%) of the patients had some clinically significant scores and all but one (14/15, 93%) also had some elevated scores. Overall, 8 of 15 (53%) of the patients were found to have irritability/agitation. Eight of 15 (53%) had lethargy/social withdrawal, 3 of 15 (20%) had stereotypic behavior, 7 of 15 (47%) of the patients were hyperactive and 10 of 15 (67%) had inappropriate speech (Table I). The Fisher exact test looked at the correlation between the ABC scores and brain MRI studies, but there were no statistically significant results (Fig. 2). Ten of 15 (67%) of the patients had abnormal changes on their MRI studies. Cerebral and cerebellar atrophy do not appear to correlate with level of behavior severity. Four of seven (57%) of the patients with only normal or elevated ABC scores had abnormal MRIs, and only a single patient of the ten (10%) had all normal ABC scores with a moderate to severe MRI. Four of ten (40%) patients with abnormal MRI findings had only normal or elevated ABC scores. A single patient of five (20%, but 7% of the total cohort) with a normal MRI study had all areas of behavior involved on the ABC, with all scores clinically significant except the lethargy

subscale, which was elevated. There were more clinically significant ABC scores in those with moderately severe or severe MRI findings than in those with mild or moderate MRI findings (Fig. 2), but this did not reach statistical significance. Four of five (80%) of the patients with normal MRI studies had abnormal ABC scores (27% of the total cohort). Elevated scores on irritability and on lethargy appear to be associated with cerebral atrophy and/or more severe MRI changes but this was not found to be statistically significant. There was also no significant correlation between clinical findings as listed on the ABC (e.g., seizures, deafness) with MRI changes or behavior scores.

DISCUSSION

No prior longitudinal study has attempted to correlate specific brain findings with behavior and other clinical features in CdLS. Neuroimaging should be able to provide a better understanding of the precise nature and evolution of brain changes, and when compared to behavior could provide prognostic information for families and providers. If such correlation was evident, then it might be possible to recommend specific medical interventions or preventative measures. Such information would be particularly valuable in this syndrome because difficult behaviors are common in CdLS and are often problematic to manage, and ultimately detrimental to families and to the CdLS individual's quality of life [Kline et al., 2015]. Brain changes are assumed to be congenital, although it is unclear whether any are progressive, although unlikely. None of our patients had serial brain MRI scans, as there was no indication for this.

The Aberrant Behavior Checklist (ABC) has validated psychometric properties, with motivation for completion by the caregiver being the main variable determining reliability [Aman et al., 1987]. Extensive psychometric assessment of the ABC has indicated that its subscales have high internal consistency, adequate reliability, and established validity [Aman et al., 1985]. There is precedent for having measured behavior via telephone administration of the ABC [Siegel et al., 2013], but we are not aware of another study using this tool recalling behavior during an event with a lag in time. The ABC has been used in other assessments of behavior in CdLS [Moss et al., 2012; Srivastava et al., 2014]. Many behavioral differences were noted in our cohort. The majority of our patients had irritability, which assesses mood differences and tantrums, but also includes self-injurious behaviors. A majority also had inappropriate speech, which includes repetitive and/or excessive speech. Half had lethargy which assesses for activity level, but also for signs of depression, withdrawal, preoccupation, poor communication, and negative response to personal interactions, much of which can be seen in autism. Of the four individuals with clinically significant scores in the lethargy subscale, the MRI scores were all categorized as severe or moderate-severe, and three of the four had at least mild cerebral atrophy and mildly dilated ventricles. Other findings in these four patients include mega cisterna magna in three of four, inferior vermal hypoplasia in half and pons or hippocampal hypoplasia in three-quarters. In general, the lethargy scores appear elevated in those with more severe MRI's (Fig. 2). A minority of the whole cohort demonstrated stereotypy, but 40% had evidence for hyperactivity, including impulsivity, difficult to control, and disruptive behaviors. Our findings were consistent with previous reports of maladaptive behaviors found in CdLS

associated with autistic traits [Nakanishi et al., 2012; Srivastava et al., 2014], and with less repetitive behaviors [Moss et al., 2012].

Unfortunately, we found no statistically significant correlation between neuro-anatomic abnormality and behavioral problems. That said, our data are retrospective and the cohort is small. We did, however, find intriguing trends. Unexpectedly, more severe structural brain changes were present in individuals with milder behavioral involvement as rated by the ABC. On the other hand, there was more ABC hyperactivity evident in those individuals with milder structural MRI changes. Inappropriate speech and irritability, which includes items for aggression and self-injury, did not appear to correlate with any MRI findings. It must be noted, however, that deeper brain structures such as the basal ganglia are not readily assessed through standard structural MRI. Ratings for stereotypical behavior in our cohort were low, impeding analyses. Although again not statistically significant, those with clinically significant lethargy subscale scores appeared to have more abnormal findings on brain MRI, which suggests that these neuroanatomic findings could correlate with some features of social isolation, depression and/or autistic features in CdLS. An additional facet of this project, comparing MRI findings and behavior to more extensive clinical findings, is ongoing and may provide further interpretation.

Our results suggest that abnormal behaviors can exist in individuals with CdLS in the setting of relatively normal structural brain findings.

There are several limitations to this study. The first limitation is that the patient cohort was small. Most of the affected individuals who have had brain MRI scans had to be excluded from this study, as they did not meet the age criteria. These patients had brain scans done at birth or below the age of five years, due to various clinical symptoms which include microcephaly, seizures, hypotonia and trauma. A smaller number of individuals had brain MRI studies done as children or adults, some for abnormal behaviors and others for neurologic findings or seizures. A second limitation is that there was a variable period between the time of the MRI scan and the time that the ABC checklist was completed; parents/caregivers may have had difficulty recalling their child’s behavior at the time when the MRI was done. The time between having the MRI scan and the parents/caregivers answering the questionnaire ranged from 0 days to up to 10 years. An inaccurate recollection of behavior might skew behavior questionnaire scores as well as the data analysis. A third limitation pertaining to this study is that the ABC does not measure anxiety or other prominent behavioral disorders that can be typically seen in patients with CdLS [Kline et al., 2007a]. Thus, this study is unable to accurately correlate the changes in the brain MRI studies to the full range of abnormal behaviors seen in CdLS, although trends can be noted.

There is evidence in animal models of cohesinopathy that milder structural brain malformations appear to have more severe behaviors. Learning and memory defects in Drosophila have been noted to accompany morphologic brain structure differences [Wu et al., 2015]. Cohesin disruption is known to affect the nervous system in other organisms, and differential expression of cohesin in the cortex vastly influences many other genes in mice [Cuadrado et al., 2015]. The mechanisms that lead to the abnormal behaviors may therefore stem not from gross brain malformation but from changes on a molecular level. Alternatively, it is feasible that individuals with CdLS and with higher cognitive function

experience greater frustration and anxiety in their daily lives. If so, then more normal brain structure may lead to greater behavioral issues for the affected individual. In any case, further and larger clinical studies might establish patterns of correlation.

A remarkable five (30%) of our 15 cases had some degree of vermian hypoplasia, and two of these five cases also had underdevelopment of the frontal lobe cortex (Fig. 1). This combination of findings is particularly intriguing given the more recent understanding of the anatomic and developmental connectedness of the cerebellum and the prefrontal cortex [Basson and Wingate, 2013]. It has been speculated that defects in this connectivity may result in abnormal behaviors, such as disorders of executive function (planning and reasoning), language, emotional control, social interaction, time construction, and learning. Such behavioral alterations have been collectively referred to as “cerebellar cognitive affective syndrome” and have been linked to a range of neurodevelopmental disorders like autism, attention deficit hyperactivity disorder and schizophrenia. There appears to be a regulatory role of the cerebellum, as seen in mouse models for genetic conditions with autism such as tuberous sclerosis and fragile X syndrome [Hampson and Blatt, 2015], and the mechanism in CdLS may be similar.

A second planned phase of this project is ongoing to collect more detailed clinical information and compare expanded phenotype and level of severity to the MRI findings. Ideally, a larger prospective study would more comprehensively assess the behaviors of affected patients, and follow those behaviors longitudinally over the course of a few years. Perhaps then a stronger correlation between behavior, particularly autism, and anatomic abnormality as revealed by MRI studies could be discerned.

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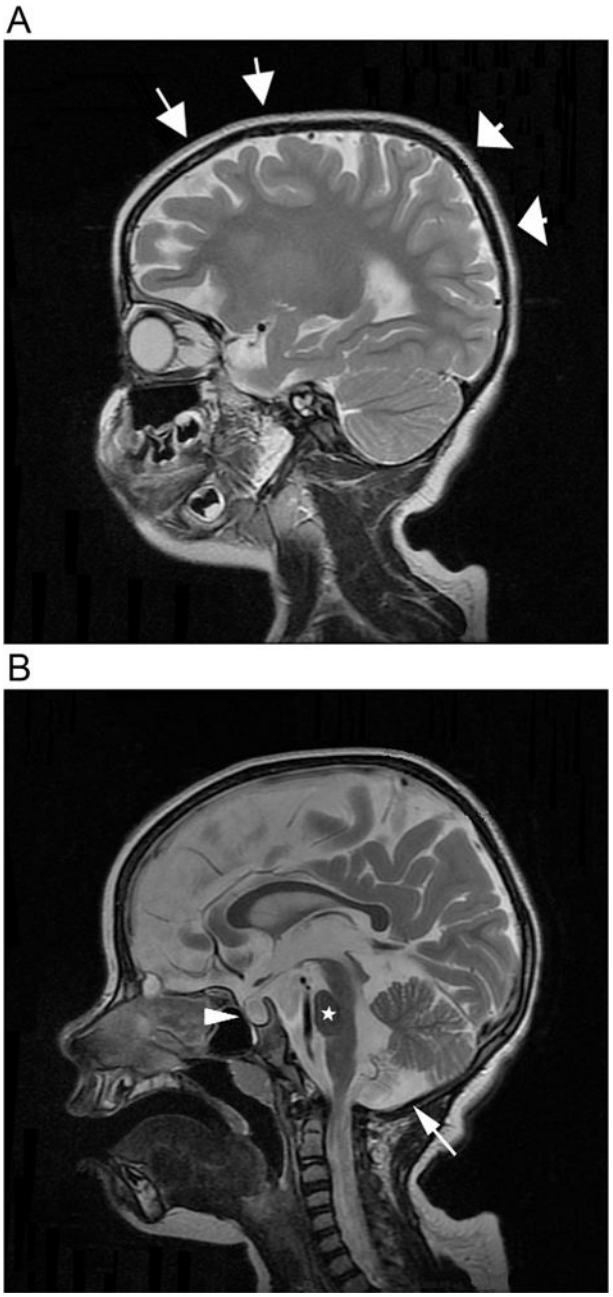

Figure 1.

MRI findings. (A) Sagittal T2 weighted MR image of a 6-year-old subject demonstrates a simplified sulcation of the frontal lobe (arrows) relative to the parietal lobe (arrowheads). (B) Midline sagittal T2 weighted MR image in the same patient demonstrates a mega cisterna magna (arrow), mild vermian hypoplasia (V), small pons (star), and cystic sellar mass, likely a Rathke's cyst (arrowhead).

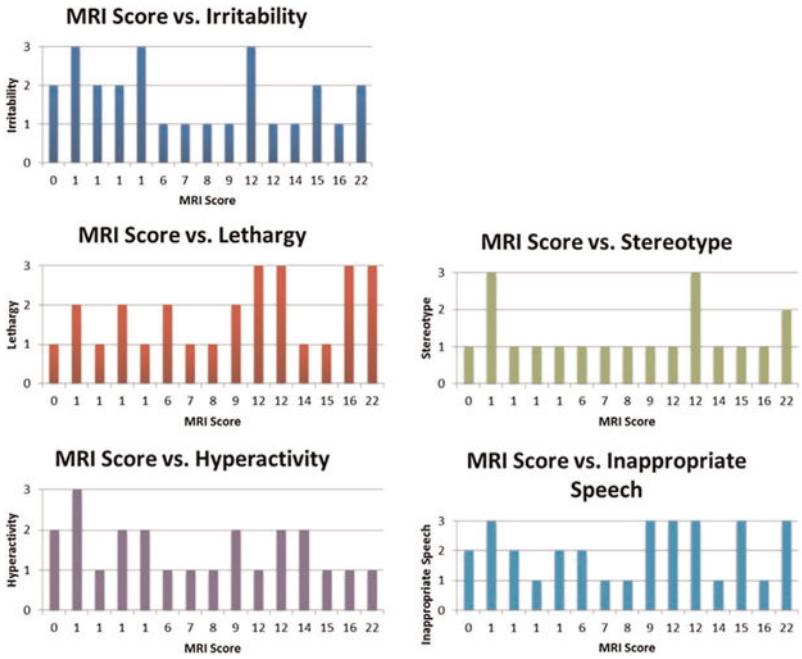

Figure 2.

MRI score v ABC findings. Graphs of total MRI severity score v. individual subscale ratings from the Aberrant Behavior Checklist for each of the 15 individuals in this study. For the subscale ratings on the left, a “1” is normal, a “2” is elevated, and a “3” is clinically significant.

TABLE I

Table Showing the 15 Individuals With CdLS, Demographics, Results of Clinical History Questions and Scoring in Each of the Five Subscales on the ABC, MRI Scores, Category of Severity of MRI, and Specific Findings on MRI

	Demogrphics		Clinical history from ABC					ABC subscale scores[a]					MRI evaluation		MRI findings								
Pt. #	Gender	Age	Special Ed	Deafness	Blindness	Epilepsy	CP[a]	I	II	III	IV	V	Score	Category	Cerebral atrophy	Lobar atrophy	Corpus callosum[c]	Cerebellum vermis[c]	Brainstem, temporal lobe[c]	Ventricles	Cisterna magna[d]	White matter[e]	Pituitay[f]	CSF spaces[g]	Head shape[h]
1	F	28	−	−	−	−	−	N	N	N	N	N	8	Moderate	Mild	Mild	N	Mild vermian hypo	N	N	N	Occ thinning	Microademona	Small cyst	N
2	M	14	−	−	−	−	−	E	N	N	N	E	1	Mild	N	N	N	N	N	N	N	N	Slightly small	N	N
3	M	22	+	+	+			N	N	N	E	N	14	Severe	N	Moderate	Small thin ant comm	Mild inf vermian hypo	N	N	N	N	N	Prominent left MC	Micro, mild brachy
4	F	13	+	−	−	+	−	N	E	N	N	E	6	Moderate	N	N	N	N	Temporal lobe hypo	N	N	N	N	N	Frontal bossing
5	F	6	+					E	CS	E	N	CS	19	Severe	Mild[1]	N	N	Mild inf vermian hypo	Small pons	Mildly dilated	Mild mega	Hyperfocus	RCC v cystic sellar mass	Enlarged SA spaces	N
6	F	24	+	−	−	−	−	E	N	N	E	E	0	Mild	N	N	N	N	N	N	N	N	N	N	N
7	F	15	+	−	−	−	−	CS	E	CS	CS	CS	1	Mild	N	N	N	N	N	N	N	N	RCC v CP	N	N
8	F	7	+			+		N	CS	N	N	N	16	Severe	Mild-moderate global	Mild global	Short, hypo	N	Small pons	Mildly dilated	Mega	N	N	Large CSF, ventr spaces	Micro, brachy
9	F	21	−	−	−	+	-	CS	N	N	E	E	1	Mild	Bifrontal mild	N	N	N	N	N	N	N	N	N	N
10	F	7	+	−	−	+	−	N	N	N	N	N	7	Moderate	N	N	N	N	N	N	Mega	Gliosis	N	Gliosis	N
11	F	15	+	+	−	+	−	CS	CS	N	N	CS	12	Moderate-severe	N	N	Slightly thin	N	Hippocampus hypo	N	N	Gliosis	N	Marked subcortical gliosis	N
12	F	8	+	+	−	−	−	E	N	N	N	CS	15	Severe	N	N	N	N	N	N	N	Early	N	N	Micro,
13	F	5						N	E	N	E	CS	9	Moderate	N	N	N	Mild vermian hypo	Mild pons hypo	N	N	N	N	N	Micro
14	M	16	+					E	E	N	E	N	1	Mild	N	N		N	N	N	Mega v. AC	N	N	N	Obscured
15	F	10	+	+	−	+	−	N	CS	CS	E	CS	12	Moderate-severe	Mild left frontal	N	N	Mild inf vermian hypo	N	Mildly dilated	Mega	N	N	Dilated left FH spaces	N

+, present; −, not present; N, normal; E, elevated; CS, clinically significant.

[a]Subscales: I, irritability/agitation; II, lethargy/social withdrawal; III, stereotypic behavior; IV, hyperactivity; V, inappropriate speech; N, Normal; E, Elevated; CS, Clinically Significant; CP, Cerebral palsy.

[b]Mild generalized atrophy v communicating (external) hydrocephalus.

[c]Hypo, hypoplasia; comm, commissure; inf, inferior; ant, anterior.

[d]AC, arachnoid cyst.

[e]Occ, occipital; Hyperfocus, 3mm T2 hyperfocus left temporal subcortical white matter.

[f]RCC, Rathke cleft cyst; CP, craniopharyngoma.

[g]CSF, cerebrospinal fluid; MC, Meckel's cave (cyst v diverticulum v schwannoma/dural ectasia), SA, subarachnoid; ventr, ventricular; FH, frontal hemisphere.

[h]Head shape: Micro, microcephaly; Brachy, brachycephaly.

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