

Abnormalities on the Neurological Examination and EEG in Young Children with Pervasive Developmental Disorders

Natacha Akshoomoff · Nikdokht Farid ·
Eric Courchesne · Richard Haas

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Abstract This study examined the nature and frequency of neurological and EEG abnormalities in 60 young children (ages 2–6 years) with pervasive developmental disorders. A number of standard neurological functions could not be adequately assessed due to the young age of the children and/or limited comprehension and cooperation. The most common neurological deficits were hyporeflexia, stereotypies, and hypotonia. EEG abnormalities were identified in 32% of the children while only two children were known to have clinical seizures. The frequency of cases with hypotonia or hyporeflexia was more common than in older children with this diagnosis. Results also indicate that EEG abnormalities are common in this young population but clinical seizures are rare, confirming other studies.

Keywords Neurology · Seizures · EEG

Introduction

Children with pervasive developmental disorders (PDD) exhibit significant deficits in social interaction, verbal and nonverbal communication, and abnormal repetitive and restricted patterns of behaviors. Age of first diagnosis has been decreasing in recent years due to several factors, including increased awareness of the early signs of autism, improved diagnostic techniques, and the availability of early intervention services (Baird et al., 2001; Charman & Baird, 2002; Rogers, 2001). The first signs that raise concerns among parents and professionals are typically delays in speech and communication skills, limited social responsiveness, and slow development (Charman & Baird, 2002; Filipek et al., 2000).

While concerns about motor development or neurological symptoms are less common, motor abnormalities do appear to be associated with PDD (Bauman, 1992; Minshew, Sweeney, Bauman, & Webb, 2005). Sensory and motor difficulties are reported for many young children with autism, although much of the data is limited to parent report (Baranek, 2002). Studies of home movies from infants later diagnosed with autism have found that these children could be differentiated from typical infants on the basis of abnormal muscle tone, posture, and inactive or disorganized movement patterns (Adrien et al., 1993; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998).

Rapin (1996) performed a standard neurological examination as part of a large study that included 176 children with Autistic Disorder. The children in the

N. Akshoomoff
Department of Psychiatry, University of California,
San Diego, La Jolla, CA, USA

N. Farid
School of Medicine, University of California, San Diego,
La Jolla, CA, USA

E. Courchesne · R. Haas
Department of Neurosciences, University of California,
San Diego, La Jolla, CA, USA

R. Haas
Department of Pediatrics, University of California,
San Diego, La Jolla, CA, USA

N. Akshoomoff (✉)
Child and Adolescent Services Research Center, 3020
Children's Way, MC 5033, San Diego, CA 92123-4282, USA
e-mail: natacha@ucsd.edu

study ranged in age from 3 years to 6 years 11 months. The main purpose of the neurological examination was to define the extent and type of neurological dysfunction present in these children. Children with evidence of lateralized or diagnosable diffuse brain dysfunction were excluded from the study a priori. Hypotonia (decreased muscle tone) was reported for approximately 25% of the children with autistic disorder (both those with and without mental retardation), and 33% of the 110 nonautistic mentally retarded children. As would be expected, motor stereotypies were more common among children in the autistic disorder group, particularly among those with lower IQs (65%). Motor stereotypies were also less commonly observed during the examination than based on parent report. Stereotypies were observed for only 13% of the nonautistic mentally retarded children.

The prevalence of epilepsy among preschoolers with autistic disorder is estimated at 7% (Rapin, 1996) and increases to approximately 20–35% by adulthood (Giovanardi Rossi, Posar, & Parmeggiani, 2000; Minshew et al., 2005). The likelihood of epilepsy is dependent on several factors, such as diagnostic classification, age of subjects, level of cognitive function, and severity and type of language disturbance (Ballaban-Gil & Tuchman, 2000; Tuchman & Rapin, 1997). Epileptiform EEG abnormalities (e.g., spikes, spike wave complexes or sharp waves) are also reported for individuals with autism without clinical seizure disorders. The prevalence of EEG abnormalities in individuals with autism is more difficult to estimate, due to the potential referral biases, the various types of EEGs performed, and standards used to evaluate the EEGs. Studies performed to date have reported that 15–20% of individuals with autism across a large age range exhibited epileptiform EEG abnormalities (Giovanardi Rossi, Parmeggiani, Bach, Santucci, & Visconti, 1995; Tuchman & Rapin, 1997). In a study of 585 children, adolescents, and young adults with autism (age 19 months to 28 years, mean age at study 6 years), 30% had a history of regression and 11% a history of epilepsy (Tuchman & Rapin, 1997). Among the children with available EEGs, 15% of the 335 children without epilepsy had an epileptiform EEG. Although 50% of the children in the entire sample were less than 5 years of age, it is not known if this rate of epileptiform activity differed as a function of age in this sample.

In the current study, we utilized the standardized neurological examination protocol from our previous study of children with autistic disorder who were between 6 and 18 years of age (Haas et al., 1996). This examination is very similar in format and in item type

to that used by Rapin (1996). We sought to determine the nature and degree of neurological dysfunction in younger children with PDD. These children were prescreened to exclude individuals with evidence of an acquired brain injury or comorbid medical conditions that may affect the nervous system. Clinical EEG information from the participants in the current study was utilized to provide an estimate of the frequency of EEG abnormalities in young children with PDD.

Method

Participants

Sixty children between the ages of 2 years 4 months and 5 years 11 months ($M = 3$ years 11 months) participated in this study. All of these children were examined as part of their participation in an MRI study of young children with PDD and/or a study of genetic markers in children with PDD (Akshoomoff et al., 2004; Courchesne et al., 2001; Kim et al., 2002). The Institutional Review Board of Children's Hospital San Diego approved the study. Informed consent was obtained from each participant's parents after the study procedures were explained. Following the diagnostic procedures listed below, 49 of the children received a diagnosis of Autistic Disorder (41 males and 8 females) and 11 (9 males and 2 females) received a diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). The characteristics of the children are listed in Table 1.

Prospective Diagnosis Procedure

Children were initially recruited for the PDD group if they had a clinical presentation consistent with autistic disorder or PDD-NOS. Any child who had a diagnosable medical condition that might affect brain development, such as fragile X, a known brain lesion, an infectious or metabolic disorder, or tuberous sclerosis, was not included in the study. At the time of the initial evaluation, each child was administered at least one diagnostic test (the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Rochen Renner, 1988), the Pre-Linguistic Autism Diagnostic Observation Scale (DiLavore, Lord, & Rutter, 1995), or the Autism Diagnostic Observation Schedule-Generic (ADOS; Lord et al., 2000)) and a parent interview (the Autism Diagnostic Interview (ADI; Le Couteur et al., 1989) or the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994)), or a developmental history. Differences in the diagnostic measures

Table 1 Participant characteristics (Means with standard deviations in parentheses)

Group	N	Age at Exam	Nonverbal IQ	Verbal IQ
Low Functioning Autism	29 males	3 y 11 m	73.2	–
	7 females	(11 m)	(23.66)	
High Functioning Autism	12 males	3 y 10 m	97.46	78.85
	1 female	(6 m)	(15.24)	(5.87)
PDD-NOS	9 males	4 y 2 m	93.82	85.18
	2 females	(8 m)	(12.33)	(15.71)

used were contingent on the availability of appropriate tests at the time of data collection.

While clinically significant signs of PDD are present by the second or third year of life, a specific diagnosis within the DSM-IV category of PDD (American Psychiatric Association, 1994) is considered most reliable when a child is at least 4 years old (Lord & Risi, 2000). All the participants in this study were recruited before the age of 5 and therefore all were reevaluated after age 5 to determine the most accurate diagnosis. The reevaluation battery consisted of the ADI-R, ADOS, CARS, and the appropriate standardized psychological tests for each child's functional level. The ADI-R and the CARS were completed for each child by at least one clinical psychologist from the laboratory. If a child had achieved at least three-word phrase speech at the time of the final ADI-R, algorithm items for both nonverbal and verbal communication were used to compute the communication domain score (Lord et al., 1994). Level of functioning was evaluated using one or more standardized tests including the Leiter International Performance Scale (Arthur, 1980), the Stanford-Binet-IV (Thorndike, Hagen, & Sattler, 1986), the Wechsler Intelligence Scale for Children-III (Wechsler, 1991), the Mullen Scales of Early Learning (Mullen, 1995), the Peabody Picture Vocabulary Test-Revised (Dunn, 1981), and the Vineland Scales of Adaptive Behavior (Sparrow, Balla, & Cicchetti, 1984). The specific tests administered were selected on a case-by-case basis depending on the child's age and level of ability. Dr. Catherine Lord, who was blind to all previous information other than the child's expressive language level, administered the appropriate module of the ADOS to each child. The appropriate ADOS module was selected based on the child's age and/or expressive language level (preverbal or single words, phrase speech, fluent speech/adolescent, fluent speech/adult).

Based on these test data, the clinical psychologists reached a *final best estimate diagnostic decision*. To be diagnosed with autistic disorder, a child had to meet ADI-R, ADOS, and DSM-IV criteria for autistic disorder. Children identified to have intellectual and

adaptive abilities in the severe to profound level of mental retardation (IQ < 35 or mental age < 18 months) were not included in the study. As previously described (Akshoomoff et al., 2004), children who did not meet both ADOS and ADI-R cutoffs for autism but had enough positive symptoms to meet the DSM-IV criteria for PDD-NOS received a diagnosis of PDD-NOS. If ADI-R criteria for autism were not met in all three domains, a diagnosis of PDD-NOS was considered if a child obtained a score within 2 points of the cutoff on the ADI-R reciprocal social interaction domain and within 1 point of the cutoff on either the communication or repetitive behaviors and stereotyped patterns domain. If ADOS criteria for autism were not met, a diagnosis of PDD-NOS was considered if a child at least met ASD criteria in the social domain on the ADOS. If a child obtained scores on the ADI-R and ADOS in the autism range, the clinicians used a final best estimate diagnostic decision to determine if other factors may have inflated the scores and a diagnosis of PDD-NOS was more appropriate. The 13 children in the "Higher Functioning" autistic disorder (HFA) group were those who obtained a nonverbal IQ of 70 or above and a Verbal IQ of 70 or above; nonverbal IQs ranged from 72 to 122 and Verbal IQs ranged from 73 to 90. The 36 children in the "Lower Functioning" autistic disorder (LFA) group had nonverbal IQs that ranged from 35 to 128. The proportion of low functioning children in the present study (75%) was comparable to our previous study (64%) with older children and adolescents (Haas et al., 1996). The 11 children in the PDD-NOS group had nonverbal IQs that ranged from 75 to 115 and Verbal IQs that ranged from 63 to 104.

Neurological Examination

A standard history form was used to obtain information on the medical history, pregnancy, developmental milestones, and family history. Medical records were studied when available. Each child received a comprehensive medical and neurological examination by a pediatric neurologist (R.H.). The nature of the study design did not include an opportunity to examine

reliability of the examination process for the neurologist or reliability of the examination within participants.

The standardized neurological exam consisted of 101 items divided into the following categories: general findings, cranial nerves, facial movements, oral motor function, sensory exam, gross motor, fine motor, and involuntary movements (Haas et al., 1996). The children were rated on each item of the exam using a 3-point scale (0 = normal, 1 = abnormal, 2 = severely abnormal). In addition, a score of “9” indicated that the child was either too young, too low functioning or too uncooperative to understand and/or perform the task.

The examination was developed for this age group to be as objective as possible as these young children typically have limited language and limited ability to cooperate. While similar to a routine neurological examination, it differs in terms of level of detail and stereotyped protocol nature. In regular practice, parts of this examination may not be administered to individual patients. Administration of all items to all participants allows for identification of the areas of the examination that may warrant particular focus in standard clinical practice and in research studies with this population that include a neurological examination.

Items were excluded from the analyses if less than 5% of the children obtained an “abnormal” score or if >50% of the children received a score of “9”. Three items were not included in the analyses because they are not administered to children under the age of 5 years: tandem gait, balance on one foot, and apposing fingers to thumb sequentially.

In 56 of the participants (93%), at least 1 EEG was performed. Routine 16–20 channel EEGs were carried out in 52 children, 6 children underwent prolonged video-EEG recordings, and 1 had a Digitrace ambulatory recording performed. In the vast majority of routine EEGs, sleep EEG was assessed under chloral hydrate sedation.

Results

Ten of the neurologic exam variables were not included in the analyses because 50% or more of participants obtained a score of “9” (percentage with missing scores: position sense: 63.3%; stereognosis: 63.3%; two point stimulation discrimination: 63.3%; graphesthesia: 67%; walking on toes: 51.7%; walking on heels: 71.7%; pronator drift: 71.7%; heel to shin: 61.7%; wrist pronation: 75%; apposing finger to thumb: 65%). In the majority of cases where a score of “9” was obtained, the child was unable to understand the instructions or unable to cooperate with the task demands.

Based on previous studies, six variables of interest were analyzed across the three groups (see Table 2). Of the 49 children who were later diagnosed with Autistic Disorder, 65% were hypotonic (decreased muscle tone in both arms and legs) and 71% were hyporeflexic (decreased deep tendon reflexes). Of the 11 children later diagnosed with PDD-NOS, 45% were hypotonic and 64% were hyporeflexic. Stereotyped and repetitive behaviors were observed among 58% of the children with LFA and 31% of the children with HFA, but significantly less often in the PDD-NOS group ($\chi^2(2) = 9.4$, $P < .05$). Abnormalities in gait while walking were observed in approximately 20% of children. A large proportion of children did not provide sufficient data to rate finger/nose coordination and patting. Abnormalities on these tests were observed in less than 20% of the children who were successfully tested. Consistent with other studies, other items on the neurological test were found to be normal across all or nearly all of the children examined. There was no evidence of cranial nerve abnormalities, spasticity, rigidity, weakness, tremor, choreoathetosis, dystonia, or tics.

Eighteen children (32%) had abnormal EEG records. Thirteen of the children were in the LFA group (72%), 4 (22%) were in the HFA group, and 1 (5%) was in the PDD-NOS group. At the time of the neurological exam, only two children who were later diagnosed with autistic disorder had suffered at least

Table 2 Types of neurological deficits (percentage of subjects in each group)

	Group					
	LFA (N = 36)		HFA (N = 13)		PDD-NOS (N = 11)	
	Abnormal	Missing data	Abnormal	Missing data	Abnormal	Missing data
Hyporeflexia	67%	3%	77%	0%	64%	0%
Stereotypies	56%	3%	31%	0%	9%	0%
Hypotonia	61%	0%	77%	0%	46%	0%
Gait (walking)	22%	3%	8%	8%	27%	0%
Finger/nose coordination	6%	47%	8%	46%	0%	36%
Patting	17%	53%	8%	62%	27%	18%

LFA = Low Functioning Autism; HFA = High Functioning Autism

one known seizure. Two children (1 LFA and 1 HFA) were later given a clinical diagnosis of Landau-Kleffner syndrome by their regular pediatric neurologist, with normalization of the EEG on steroid treatment. Neither of these children had suffered a known seizure. A total of 31 EEGs were recorded on the 18 participants with EEG abnormalities. Fourteen (78%) of the records contained epileptiform abnormalities and 4 (22%) had only focal slowing. EEG abnormalities were reported as epileptiform or non-specific as follows:

- 4 with unifocal epileptiform discharges (sleep).
- 9 with 2 foci epileptiform discharges (6 during sleep).
- 10 with multifocal epileptiform discharges (9 in sleep; 1 both sleep and waking).
- 10 with focal slowing (9 in sleep; 1 both sleep and waking).
- 2 with background slowing.
- 5 with background beta rhythms (1 in sleep; 1 in both sleep and waking).

Discussion

Over 60% of the young children with autistic disorder or PDD-NOS in the present study exhibited hypotonia and/or hyporeflexia. In our previous study of 6–18 year-old children with autistic disorder (Haas et al., 1996), 33% of the children were hypotonic and none of the children exhibited hyporeflexia. These results suggest that muscle tone and reflexes are affected in young children with PDD (both with and without mental retardation), and improve with age. Our finding that young children with autistic disorder more commonly display stereotypies during clinical exam than young children with PDD-NOS affirms that stereotypies are a more common feature of autistic disorder and appear to be related to severity of symptoms.

The observed rate of hypotonia (65%) is also higher than described in the Rapin (1996) study (i.e., approximately 25% of the children with autistic disorder). While that was a slightly older sample of preschoolers, this discrepancy may also be related to differences in identification of hypotonia. The assessment of hypotonia is fairly subjective. We do have the advantage of having results from the same neurologist in both of our studies, but we do not have data on the reliability of identification of hypotonia across observations within a child or across participants within or across examiners.

It is difficult to localize hypotonia or apraxia to one particular brain area because these neurological signs can be associated with more diffuse abnormalities. The

presence of more prominent motor dysfunction at the younger ages is interesting in the light of our previously reported cerebral and cerebellar anatomic abnormalities and more prominent involvement of frontal brain regions in these same children (Akshoomoff et al., 2004; Carper & Courchesne, 2005; Courchesne et al., 2001). Some motor abnormalities in autism appear to be associated with involvement of the basal ganglia, supplementary motor, and anterior cingulate regions (Hardan, Kilpatrick, Keshavan, & Minshew, 2003; Minshew, Sung, Jones, & Furman, 2006). FMRI studies of motor task performance suggest activity patterns of cerebral and cerebellar systems are atypical in high functioning individuals with autism, despite normal task performance (Muller, Kleinmans, Kemmotsu, Pierce, & Courchesne, 2003; Muller, Pierce, Ambrose, Allen, & Courchesne, 2001).

Several of the tasks in the neurological exam could not be administered to the young children in this study due to their young age, lack of understanding or limited cooperation. This included several of the tasks that were found to be abnormal in the previous study of older autistic children, such as tests of graphesthesia, stereognosis, alternating movements, and sequential movements (Haas et al., 1996). In the study by Rapin (1996), the limited ability to perform skilled, purposive limb movements was more common among mentally retarded children with autistic disorder (75%) than children with autistic disorder who had IQs in the normal range (30%). “Limb apraxia” was also reported for 57% of the nonautistic mentally retarded children. Whilst these skills may be delayed in the young children with PDD in our study, we found it difficult to confirm during the neurological examination.

In the present study, we found 32% of young children had an abnormal EEG but there were only 2 subjects (3%) with reported clinical seizure activity. As ours is a young population, this finding highlights the fact that epilepsy tends to develop in later years in autistic individuals. This rate of EEG abnormality is higher than the 15–20% reported previously (Giovannardi Rossi et al., 1995; Tuchman & Rapin, 1997). Since these previous studies were limited to or included a large proportion of older individuals, these results suggest that a proportion of young children with EEG abnormalities will eventually develop epilepsy. Our study did not show any correlation between the level of neurological dysfunction observed and the severity of the autism or presence of EEG abnormality, a finding in keeping with other published studies (McVicar & Shinnar, 2004).

The main aim of conducting a neurological examination in a young child who appears to have autistic

features is to rule out other potential neurological disorders and/or comorbid medical conditions (Filipek et al., 1999, 2000). Our results indicate that while many aspects of the neurological examination may be normal in the young child with PDD who has no known history of neurological injury or dysfunction, subtle neurological deficits may be present upon examination. The results indicate that neurological findings of hypotonia and poor coordination are detectable in a large proportion of young children with PDD but may diminish over time for many children. Nevertheless, some children with PDD continue to exhibit hypotonia as well as motor skills deficits (Haas et al., 1996; Klin, Sparrow, Marans, Carter, & Volkmar, 2000; Rapin, 1996).

Our results also indicate that a sizeable proportion of young children with PDD have an abnormal EEG in the absence of any clinical seizure activity. As we only conducted prolonged sleep EEG recordings (Digitrace or video EEG) in 7 of our 60 cases (12%) we cannot state the true incidence of EEG abnormality in our study population, as prolonged sleep recordings may be needed to identify epileptiform abnormalities in this population (Shinnar et al., 2001; Tuchman & Rapin, 2002). It is also important to note that it may be very difficult for clinicians to recognize clinical seizures in children with PDD. Some of the characteristics of seizure activity may be interpreted as autistic behavior (Minshew et al., 2005). It is certainly important for clinicians to consider the possibility of seizures or seizure activity for children who have a history of regression at any age. There are currently no guidelines on medical treatment for epileptiform EEG without clinical seizures, with the exception of treatment for Landau-Kleffner syndrome (Tuchman and Rapin, 2002). It seems prudent to re-evaluate young children who appear to have PDD and EEG abnormalities, particularly if they demonstrate limited clinical benefit from early intervention programs and have limited language and cognitive development.

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