Etiologic Yield of Autistic Spectrum Disorders: A Prospective Study

AGATINO BATTAGLIA* AND JOHN C. CAREY

Studies addressing etiologic yield in childhood developmental disabilities have mainly looked at individuals with developmental delay/mental retardation. The few studies addressing the question of etiologic yield in patients with pervasive developmental disorders (PDDs) had a major drawback, in that the enrolled subjects were diagnosed as having the autistic spectrum disorders based only on history and clinical examination, and/or on unspecified instruments. In addition, only some of these patients underwent a complete laboratory evaluation. To investigate the etiologic yield of PDDs, we undertook a large prospective study on subjects selected according to very strict criteria and diagnosed as having PDD based on the present “gold standard” (ADI-R and ADOS-G), and a clinical diagnosis made by a child psychiatrist. Eighty-five (85) patients with PDD and their first degree relatives participated in this study. These patients were selected from a sample of 236 subjects who had received a clinical diagnosis of PDD at the Stella Mari Institute between March 2002 and 2005. Selection criteria for entering the study were: (1) a diagnosis of PDD (with exclusion of the Rett syndrome) confirmed after the administration of the ADI-R (autism diagnostic interview-revised) and the ADOS-G (autism diagnostic observation schedule-generic). In addition, a clinical diagnosis was made by the child psychiatrist, on the basis of presence or absence of DSM-IV symptoms of autism; (2) chronological age between 4 and 18 years; (3) IQ > 30; (4) availability of both biologic parents. Patients, 65/85 (76.5%), had autism, 18/85 (21.2%) had PDD-NOS, and the remaining 2/85 (2.3%) had Asperger syndrome. Ages varied between 4 years 2 months and 12 years 5 months (mean 7.6 years), and there was a marked male preponderence (68/85). All subjects underwent various laboratory studies and neuroimaging. With respect to possible etiologic determination, a detailed history and physical examination in this group of patients with PDD was informative in 10.5% (9/85). HRB karyotype was diagnostic in one, and molecular fragile X studies in one child. Brain MRI was informative in two children (2.3%) with relative macrocrania but no neurological features; and EEG was helpful in one child, identifying a Landau–Kleffner disorder. Audiometry and brainstem auditory evoked potentials (BAEPs) showed a bilateral sensorineural loss in another child. Metabolic evaluation gave normal results in all subjects. The results suggest an evaluation paradigm with reference to etiologic determination for individuals with PDDs that does not presently justify metabolic or neuroimaging on a screening basis. Recurrence risk, treatment implications, and significant and long-lasting emotional relief for the parents suggest that serious consideration be given to clinical genetic examination, genetic testing, EEG study during wakefulness and sleep, and audiometry, despite a relatively low yield. © 2006 Wiley-Liss, Inc.

KEY WORDS: autism; autism spectrum disorders; pervasive developmental disorders; comprehensive assessment; diagnostic yield; rational evaluation

INTRODUCTION

Determining the underlying etiology for a child’s developmental disability is of the utmost importance for several reasons. Establishing a diagnosis and etiology may help in predicting the prognosis with relative certainty; establishing an accurate recurrence risk; organizing appropriate laboratory testing; establishing a health maintenance plan; initiating adequate treatment, when feasible; and, in many instances, may be crucial for the therapeutic alliance [Battaglia et al., 1999; Battaglia and Carey, 2003], and provides significant and long-lasting...
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Autistic spectrum disorders or pervasive developmental disorders (PDDs) are one of the nosologic categories of childhood developmental disability. PDDs are characterized by severe and pervasive impairment in reciprocal social interaction and communication skills, as well as repetitive and stereotyped behavior and interests, with onset before age 3. PDDs comprise, autistic disorder, Rett disorder, childhood disintegrative disorder, Asperger disorder and pervasive developmental disorder not otherwise specified (PDD-NOS) [American Psychiatric Association, 1995]. Autistic disorder or autism is the prototypical pervasive developmental disorder, and affects at least 5 in 10,000 individuals [Fombonne, 1999]. A number of etiologies have been described in association with autistic spectrum disorders [Gillberg and Coleman, 2000], and, as a consequence, autism has been claimed to be a behavioral syndrome, which is the final common pathway triggered by a number of different medical disorders. On the other hand, the evidence for a complex genetic predisposition to most cases of PDDs has prompted many investigations to identify susceptibility loci. The lack of robust pointers to the nature or location of susceptibility genes has led most researchers to perform genome-wide scans for linkage in affected relative pair samples [Weeks and Lathrup, 1995]. Recently, six potential genomic susceptibility regions for PDDs have been identified on 7q, 2q, 16p, 17q, 3q and 3p [IMGSAC, 1998; 2001; Philippe et al., 1999; Auranen et al., 2002]. Nevertheless, the size of the susceptibility regions and resource limitations have impeded identification of the putative susceptibility alleles. As a result of these different viewpoints, the clinician does not yet have a clear idea of how extensive medical investigations in the autistic children should be. Of note, between 65% and 85% of individuals with autism spectrum disorders also show mental retardation [Mauk, 1993; Chudley et al., 1998; Gillberg, 1998; Sponheim and Skjeldal, 1998]. Chromosomal rearrangements are known to be one of the most common causes of cognitive impairment, accounting for 4–34.1% of subjects with MR [Xu and Chen, 2003]. Our prospective study presents the results of extensive medical investigations of 85 patients with PDD.

SUBJECTS AND METHODS

The Institutional Review Board of the Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry approved this project, and informed consent was obtained from each participant. Eighty-five (85) patients with PDD and their first degree relatives participated in this study. These patients were selected from a sample of 236 subjects who had received a clinical diagnosis of PDD at the Stella Maris Institute between March 2002 and 2005. Eighty-one (81) out of the 236 patients were excluded from the study enrollment due to failure to attend diagnostic investigations requested by the evaluating physician or due to sociofamilial problems. Selection criteria for entering the study were: (1) a diagnosis of PDD (with exclusion of the Rett syndrome) confirmed after the administration of the ADI-R (autism diagnostic interview-revised) [Lord et al., 1994] and the ADOS-G (autism diagnostic observation schedule-generic) [Lord et al., 2002]. Both instruments assess the symptoms of PDD, including autism, as defined in DSM-IV [American Psychiatric Association, 1995]. In addition, a clinical diagnosis was made by the child psychiatrist evaluating the child, on the basis of presence or absence of DSM-IV symptoms of autism; (2) chronological age between 4 and 18 years; (3) IQ>30; (4) availability of both biologic parents.

Consequently, 43 of the patients were excluded from the study because the previous clinical diagnosis of PDD was not confirmed after performing ADI-R and ADOS-G; while the remaining 27 were excluded from the study due to an IQ <30.

Pregnancy, medical, and developmental histories together with a three to four generation pedigree were obtained on each patient. Physical and neurological examinations were performed. Particular attention was paid to growth parameters, to any dysmorphic trait or minor anomaly especially involving the face, limbs and skin; and to abnormal muscle tone or reflexes, to the presence of involuntary movements, or coordination abnormalities. Blood was collected on all subjects to perform high resolution banding (HRB), molecular fragile X studies, and subtelomeric FISH analysis [Battaglia and Bonaglia, this issue]. Due to funding restraint, CGH-microarray was performed only in the 14 subjects with apparent idiopathic PDD-NOS, in order to exclude a possible microduplication 15q11-13 [Cook et al., 1997; Schroer et al., 1998; Gurrieri et al., 1999]. Parental bloods were banked to determine if any detected anomalies were de novo or inherited. Electroencephalograms (EEGs), brain magnetic resonance imaging (MRI) (to exclude the presence of any brain abnormality), a thorough metabolic evaluation, and audiologic evaluation (including brain stem auditory-evoked potentials when needed) were carried out virtually on all patients.
RESULTS

During the 3 years of study enrollment 85 patients met the inclusion criteria and completed the evaluating physician’s requested laboratory investigations. Sixty-five (76.5%) patients had autism, 18 (21.2%) had PDD-NOS, and the remaining 2 (2.3%) had Asperger syndrome. As expected, there was a marked male preponderance (68/85) in this group as a whole. The ages of the enrolled subjects varied between 4 years 2 months and 12 years 5 months (mean 7.6 years). The initial age of parental concern regarding their child’s developmental progress ranged between 18 months and 3 years.

Most of these 85 patients had been referred to our Institute by the child psychiatrist working in the area health authority of the child’s residence; whereas the remaining had been referred by the family pediatrician. With respect to possible etiologic determination, a detailed history and physical examination in this group of patients with PDD was informative in 10.5% (9/85).

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Distinctive historical features included an acute Epstein–Barr virus encephalitis at age 18 months in one child. Distinctive physical features were evident in eight children, leading to a provisional clinical diagnosis of Sotos syndrome (1), Angelman syndrome (1), inv dup(15) syndrome (1), and to the recognition of a pattern of human malformation in five. Four of these five children were classified as having a “provisionally unique syndrome,” after HRB karyotype, DNA fragile-X, and subtelomeric FISH analysis had given normal results. HRB was diagnostic in one of the five subjects, showing a mosaicism with two cellular lines, one male aneuploid with trisomy 8, the other male euploid: 47,XY,+8(40%)/46,XY(60%). All the three provisional clinical diagnoses (Sotos, Angelman, inv dup(15) syndromes) were confirmed by the respective molecular cytogenetics analyses. Molecular fragile X studies were informative in one further child, aged 5 years and thought to be nonsyndromic, showing a CGG full mutation. Brain MRI was informative in two children (2.3%) with relative macrocrania but no neurological features, showing a focal band heterotopia at the level of the right lateral ventricle (1), and partial agenesis of the corpus callosum with right cerebellar hemisphere hypoplasia (1). Etiologic yield of waking and sleep video-EEG-polygraphy was very low, identifying only a Landau–Kleffner picture in one child (1.1%). A single child was identified as having a congenital bilateral sensori-neural deafness, on audiometry and brainstem auditory-evoked potentials (BAEPs) (Table I). CGH-microarray did not show any 15q11-q13 microduplication in the PDD-NOS subjects studied. Metabolic evaluation gave normal results in all subjects. Physical/neurological examination, and all laboratory investigations were normal in the other 71 patients. None ever had seizures.

DISCUSSION

Studies addressing etiologic yield in childhood developmental disabilities have mainly looked at individuals with developmental delay/mental retardation [Opitz et al., 1978; McLaren and Bryson, 1987; Bodensteiner and Schaefer, 1995; Majnemer and Shevell, 1995; Battaglia et al., 1999; Hunter, 2000; Battaglia and Carey, 2003; Shevell et al., 2003; Moog, 2005; van Karnebeek et al., 2005]. The overall variations in reported yields largely depends on the application of and advances in testing modalities, especially in molecular cytogenetics and neuroimaging. As of now, only very few studies have addressed the question of etiologic yield in patients with PDDs [Chudley et al., 1998; Skjeldal et al., 1998; Shevell et al., 2001; Steiner et al., 2003]. However, all of them have a major limitation, as the enrolled subjects were diagnosed as having classic infantile autism, PDD-NOS, or Asperger syndrome based only on history and clinical examination, and/or on unspecified “well-established instruments.”

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<table>
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<th>TABLE I. Diagnostic Yield of PDDs (n = 85)</th>
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diagnosed as having classic infantile autism, PDD-NOS, or Asperger syndrome based only on history and clinical examination, and/or on unspecified “well-established instruments.”

In addition, only part of the study sample underwent a complete laboratory evaluation. Therefore, to reexamine the etiologic yield of PDD, we undertook this larger prospective study on subjects selected according to very strict criteria and diagnosed as having PDD based on the present “gold standard” (ADI-R and ADOS-G), in addition to a clinical diagnosis made by the child psychiatrist, on the basis of the presence or absence of DSM-IV symptoms of autism. In our cohort of children with PDD a causal/pathogenetic diagnosis was reached in 16.5%. This is in agreement with the results of previous studies of PDD children, showing a range of 10%-30% with another associated or etiologically relevant condition [Rutter et al., 1994; Gillberg and Coleman, 2000]. On physical examination, eight children (9.4%) were felt to have a genetic syndrome. The pathognomonic clinical and neurophysiologic features led to a likely diagnosis of Sotos, Angelman and inv dup(15) syndromes in three of them, and molecular cytogenetic testing confirmed the clinical diagnosis in all. Sporadic children with Sotos syndrome have previously been described as having autism [Morrow et al., 1990; Zappella, 1990], whereas a strong association between isodicentric chromosome 15 and autistic features has been reported in several subjects [Rineer et al., 1998; Borgatti et al., 2001], and about 40% of AS patients have been shown to meet criteria for autism on ADOS-G and ADI-R [Peters et al., 2004]. One cytogenetic abnormality was discovered in 1/8 children, who was found to have trisomy 8 mosaicism. A “ provisionally unique syndrome” was the possible diagnosis in the remaining 4/8 patients, in whom, however, we are planning to pursue CGH-microarray. Of note, a CGG full mutation was found in one nonsyndromic child. Depending on the age of the patients, between 15% and 28% of individuals with fragile-X syndrome have significant social deficits fulfilling DSM-III-R or DSM-IV criteria for autism [Reiss and Freund, 1992; Baumgardner et al., 1995; Cohen, 1995; Turk and Graham, 1997; Hagerman, 2002]. The occurrence of a CGG full mutation in individuals thought to be nonsyndromic prior to puberty, is well known [Curry et al., 1997; Battaglia et al., 1999].

Based on these results, an evaluation paradigm for individuals with PDD with reference to etiologic determination can be suggested. A detailed history and physical examination by a geneticist with special interest in these disorders remains essential. The relevance of making a genetic diagnosis in children with PDD, mainly in relation to the familial and recurrence risk implications, is quite obvious, and mandates state-of-the-art cytogenetic and molecular cytogenetic investigations [Rutter et al., 1997; Gillberg and Coleman, 2000]. Serious consideration should also be given to routine EEG-polysgraphic recordings both during wakefulness and sleep [Beaumanoir, 1992; Tuchman and Rapin, 1997], since a condition such as the Landau–Kleffner syndrome that may mimick an autistic disorder, can be pharmacologically treated. Full audiometric evaluation to rule out a treatable hearing impairment that may masquerade as autistic disorder is also a necessary component of the assessment of the child with PDD. Brain MRI seems to be useful in showing brain abnormalities even in the absence of neurological features. However, seeing its low yield (2/85), it is hard to recommend it in a routine assessment of PDD children. The same should apply to the metabolic evaluation, which should only be carried out in the presence of specific indications. This is consistent with the recent recommendations of a consensus conference sponsored by the American College of Medical Genetics, and with the practice parameters published by the American Academy of Neurology and the Child Neurology Society on the evaluation of the child with developmental delay/mental retardation [Curry et al., 1997; Shevell et al., 2003].

Bearing in mind the complexity of the PDDs, and the consequent multiple needs both for the individual and his/her family, we stress the importance of evaluating children with PDDs in a multidisciplinary clinic that brings together professionals with various expertise sharing the goal of the best possible patient and family care.

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