An Etiologic Classification of Autism Spectrum Disorders

Lidia V. Gabis MD[1] and John Pomeroy MD[2]

[1]Weinberg Developmental Center, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, and Ono Academic College, Kiryat Ono, Israel
[2]Cody Center for Autism, Stony Brook, NY, USA

ABSTRACT: **Background:** Autism spectrum disorders (ASD) represent a common phenotype related to multiple etiologies, such as genetic, brain injury (e.g., prematurity), environmental (e.g., viral, toxic), multiple or unknown causes.
Objectives: To devise a clinical classification of children diagnosed with ASD according to etiologic workup.
Methods: Children diagnosed with ASD (n=436) from two databases were divided into groups of symptomatic, cryptogenic or idiopathic, and variables within each database and diagnostic category were compared.
Results: By analyzing the two separate databases, 5.4% of the children were classified as symptomatic, 27% as cryptogenic and 67.75% as idiopathic. Among other findings, the entire symptomatic group demonstrated language delays, but almost none showed evidence for regression. Our results indicate similarities between the idiopathic and cryptogenic subgroups in most of the examined variables, and mutual differences from the symptomatic subgroup. The similarities between the first two subgroups support prior evidence that most perinatal factors and minor physical anomalies do not contribute to the development of core symptoms of autism.
Conclusions: Differences in gender and clinical and diagnostic features were found when etiology was used to create subtypes of ASD. This classification could have heuristic importance in the search for an autism gene(s).

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The diagnosis of autism spectrum disorders requires evidence of impaired verbal and non-verbal communication, deficits in social interest and interaction, and narrow or repetitive interests and behaviors. Although these characteristics define the features of these disorders across the diagnostic spectrum, much diversity exists among diagnosed individuals. This variability is portrayed in the severity and range of symptoms, and the presence of additional characteristics such as cognitive impairment, neuropsychiatric symptoms (emotional and behavioral), and physical or biomedical features.

The estimated rate of subnormal cognitive function is about 50%. It is measured as two standard deviations below the mean, which reflects a score of < 70 on most standardized IQ measures. However, areas of higher function and savant skills are prevalent even among the more cognitively impaired [1]. As for additional common comorbidities, as many as 40% of children with autism in clinical settings are diagnosed with epilepsy [2], neuropsychiatric disorders such as depression, anxiety, obsessions and phobias [3], attention deficit/hyperactivity disorder [4], and Tourette syndrome [5]. In addition, dysmorphic features are present in many individuals diagnosed with ASD, sometimes indicating known genetic syndromes [6,7].

Thus, the clinical presentation of ASD appears to have marked heterogeneity, which has undoubtedly obscured efforts to identify simple or unified causes of this condition. As a result, current etiological research is focused on numerous and varied pathogenetic pathways that lead to the manifestation of the ASD phenotype. For example, autistic features are a common phenotypic characteristic of several genetically determined neurodevelopmental disorders, such as Rett syndrome, fragile X syndrome, Angelman syndrome, and tuberous sclerosis [8]. It has been noted that individuals diagnosed with one of these syndromes, who additionally meet diagnostic criteria for ASD, usually display more severely impaired cognitive and adaptive skills than those who do not present associated ASD [9-11]. In addition, several physiological insults have been associated with significantly higher incidence of autistic features. These include low birth weight [12], congenital malformations [13], fetal distress [14], hypoxic ischemic encephalopathy [15], congenital cytomegalovirus infection [16], phenylketonuria [17], and prematurity [18]. Evidence suggests that at times, autistic symptomatology can result from less specific brain insult, similar to the varied processes causing intellectual impairment. As such, autistic features can present either as a primary feature with unknown etiology, or as secondary to a specific syndrome or brain disorder.

For both heuristic and clinical purposes in the field of ASD classification it is important to identify specific syndromes, such as Rett and fragile X, to ensure that they do not serve as a confound in research analysis and are appropriately addressed

ASD = autism spectrum disorder

in subsequent counseling and prognostication in the clinic. A number of recent studies have addressed such classification issues. Miles et al. (2005) divided a group of 260 ASD individuals into two subgroups: "essential autism" and "complex autism," of which the latter was defined by evidence of insult or abnormality of early morphogenesis, manifested by either significant dysmorphology or microcephaly. The former, which comprised 80% of the ASD group, had higher IQ and better outcome [19].

A new approach emphasizes the incorporation of behavioral and physiological characteristics, generated by neuroimaging technologies, in order to facilitate the identification and differentiation of biologically and genetically distinct subgroups in autism [20]. Yet, the findings from these neuroimaging studies have not been incorporated into genetic studies of autism, which are predominantly based on a diagnosis of the disorder. Diagnostic criteria for the American Psychiatric Association-produced DSM-V were recently finalized, and all present *pervasive developmental disorder* subtypes (other than Rett syndrome) will be encompassed under one diagnostic category – Autism Spectrum Disorders. In addition, severity levels have been introduced in the classification and further clarifying characteristics, such as level of cognitive impairment, are required to be incorporated into diagnostic qualifying statements or codes. Such subtyping within a broad diagnostic concept expands the timeliness and relevance of the current study.

The objective of this study was to produce a causative classification of ASD that resembles the system used in in the past in epilepsy [21]. This etiologically based classification identifies autism as idiopathic, cryptogenic or symptomatic in order to create a system that can aid in the formulation of a shared diagnostic process. Subsequently, the objective was to employ this classification system for two separate databases to assess further validity. Symptomatic autism is classified when a clear underlying syndrome is revealed, Cryptogenic is defined when an underlying cause is suspected, though no specific causative link has been proved, such as perinatal minor difficulties, dysmorphism without identified syndrome, and premature delivery without specific neuroimaging findings. This clinical distribution might have epidemiological significance [22,23].

SUBJECTS AND METHODS

The study consisted of children diagnosed with ASD (n=436) from an Israeli and an American database. The U.S. data were retrieved for the years 2000–2003 and the Israeli data for 2003–2005. All subjects were diagnosed with ASD according to the DSM-IV diagnostic criteria, as well as additional assessment tools such as ADOS and ADI-R when necessary. Israeli subject information was gathered from the database of the Weinberg Child Development Center at Sheba Medical Center, while American subject information was collected from the database of the Cody Center for Autism and Developmental Disabilities at Stony Brook University Medical Center. All data were de-identified to ensure confidentiality.

PROCEDURE

In this retrospective study, data regarding diagnoses, perinatal history, general and neurological examination (head size, dysmorphic features, skin, etc.), clinical tests (chromosomal analysis, fragile X testing, electroencephalogram, and magnetic resonance imaging), developmental and family history, and comorbid symptoms were collected from the electronic medical files. Neurological/medical conditions were determined when electronic medical files indicated diagnoses of abnormal EEG, epilepsy, seizures, metabolic or genetic conditions, allergies and/or other chronic medical conditions (otolaryngologic, endocrinologic, etc.).

Subsequently, comparable with epilepsy classification, ASD subjects in each database were divided into three subgroups:

- **Symptomatic:** ASD for which there was an underlying recognized organic or neurological cause (after excluding Rett syndrome)
- **Cryptogenic:** ASD for which an underlying cause is suspected, but the etiology remains undetected (such as abnormal perinatal course, infection involving the brain, dysmorphic features, or other severe associated clinical findings)
- **Idiopathic:** ASD for which no evidence of other neurological or biomedical disorder was revealed, except disorders that are considered comorbid phenomena, such as ADHD or Tourette's syndrome

RESULTS

A group of 436 subjects served as a control. Children recruited from Israeli (n=351) and American (n=85) databases were divided into the three subgroups, and variables within each database and diagnostic category were compared. Eight subjects were diagnosed with Rett syndrome in the Israeli database and were therefore excluded from the symptomatic subgroup. Classification and developmental history are presented in Table 1.

The distribution of subjects into symptomatic, cryptogenic and idiopathic subgroups was similar in both databases (10%, 27%, 63% vs. 4%, 27%, 69% for the American and Israeli databases respectively). In both databases the percentage of males in the cryptogenic and idiopathic subgroups was significantly higher than in the symptomatic subgroup. Delays in development (e.g., language, motor skills, global cognition) were less prevalent, and rates of regression were higher in the cryptogenic and idiopathic subgroups than in the symptomatic subgroup. ASD diagnoses and other medical and psychiatric comorbidities in the three classified subgroups are presented

EEG = electroencephalogram
ADHD = attention deficit/hyperactivity disorder

Table 1. Classification and developmental history collected from American and Israeli databases

		Medical & developmental history						
		N	Males	High risk pregnancy	Language delay	Motor delay	Global delay	Regression
American database	Symptomatic	9	44%	67%	89%	67%	66.60%	0
	Cryptogenic	23	74%	43%	66%	56.50%	39.10%	34%
	Idiopathic	53	81%	26%	66%	34%	34.60%	21%
Israeli database	Symptomatic	14	57.10%	27.20%	100%	66.60%	85.70%	7.10%
	Cryptogenic	92	86.90%	46.40%	› 90%	50.60%	39.10%	20%
	Idiopathic	237	79.30%	15.90%	› 90%	20.10%	26.50%	20%

Table 2. Summary of ASD and other medical and psychiatric comorbidities

			ASD diagnoses				Neuroimaging abnormal findings	Genetic or metabolic disorder	Other diagnoses		
		N	Autism	PDD-NOS	Asperger	Neuro/ Medical	(n performed)	(n performed)	Psych (x ADHD)	ADHD	Sibling with ASD
American database	Symptomatic	9	11%	89%	0	67%	1 (6)	3 (9)	22%	44%	0
	Cryptogenic	23	39%	35%	26%	43%	2 (13)	0 (11)	13%	52%	9%
	Idiopathic	53	43%	30%	27%	11%	3 (21)	0 (16)	13%	36%	7%
Israeli database	Symptomatic	14	42.80%	57.10%	0	85.70%	5 (8)	2 (9)	28.50%	7.10%	0
	Cryptogenic	92	47.80%	51%	1.10%	43.10%	1 (19)	0 (26)	7.60%	9.70%	9.30%
	Idiopathic	237	43.40%	52.70%	3.80%	30.40%	0 (24)	0 (50)	8.80%	11.80%	8%

Psych = psychiatric diagnoses, PDD-NOS = pervasive developmental disorder not otherwise specified

in Table 2. The extent of workup did not differ much between experts and was based on clinical judgment, while positive findings were prevalent in the symptomatic group. In both databases, the symptomatic subgroup included fewer subjects diagnosed with autistic disorder, more diagnosed with pervasive developmental disorder not otherwise specified PDD-NOS, and no subjects diagnosed with Asperger's disorder, compared to the other two subgroups. According to DSM-5 classification this might be attributed to a higher severity of autistic symptoms in the idiopathic and cryptogenic groups, while the symptomatic group was less severe in terms of autistic criteria; however, the intellectual disability was prevalent. In addition, this subgroup showed higher rates of neuro/medical conditions and psychiatric comorbidities and none had siblings diagnosed on the spectrum. Overall, ADHD and other psychiatric comorbidities were more prevalent in the American than the Israeli database (41% vs. 11% for ADHD, and 24% vs. 9% for the others, respectively).

DISCUSSION

This study employed an etiologically based causative classification of ASD, which resembles the system used by neurologists for epilepsy, identifying groups with known (symptomatic), suspected (cryptogenic), or lacking evidence (idiopathic) of probable etiologies. Our results indicate that the idiopathic and cryptogenic subgroups are similar in most of the examined variables, while both are unlike the symptomatic subgroup. The similarities between the first two subgroups, including significant male predominance, support prior evidence that most perinatal factors and minor physical anomalies do not contribute to the development of core symptoms of autism. However, these factors might determine cognitive functioning. In the symptomatic group, the gender distribution depends on the underlying etiology.

The overlap of ASD symptomatology in underlying organic or neurologically caused syndromes is a subject of debate in the existing literature. One opinion argues that the presentation of ASD characteristics in different genetic syndromes arises from a common biological or neural pathway which lays downstream to the abnormal molecular function. Others propose that intellectual disability in genetic syndromes serves as an additional risk factor for ASD characteristics since it diminishes the possibility for cognitive compensation of these independently inherited traits [22]. Our results show that the symptomatic subgroup, in both databases, does indeed demonstrate a higher rate of global delay but does not include a higher prevalence of subjects diagnosed with autism (compared to the other two sub-

PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified

groups). These results may give additional support to the former view, which implies that separate neural circuits could, but not necessarily, result in a common ASD diagnosis. Furthermore, the existence of an idiopathic group is determined by an "autism gene" that has a strong predisposition towards males and shares phenotypic traits with many other genes coding for ASD combined with global delays/intellectual disability.

Results indicate that there may well be a valid difference between the symptomatic subgroup and the other two groups. Therefore, future research should focus on the symptomatic subgroup in various ways that may further our understanding of the factors that lead to autistic symptomatology. For example, the symptomatic group can be evaluated in terms of genetic and environmental factors that determine the occurrence of autism symptoms, in distinction from other children with the same syndrome. Similarly, the knowledge of a specific genetic or chromosomal abnormality may allow for the identification of contiguous gene abnormalities that lead to autistic characteristics. Furthermore, in large group studies seeking to identify "autism genes" it is vital that the symptomatic autism subgroup be excluded from analyses.

LIMITATIONS

The main limitation of this study is the retrospective nature of data collection. Moreover, data were gathered from subjects' medical records, which include varied clinical evaluation workup, depending on the index of suspicion of the neurologist, the degree of disability, and the concern of the parents or the primary care physician.

CONCLUSIONS

The similarities between the Israeli and the American databases strengthened the validity of a relatively simple classification of three etiologically based subtypes. It is plausible that some of the children classified as cryptogenic or idiopathic might in fact have been symptomatic. However, the validity of the reported subgroup differences is strengthened by the similarities of the two databases. Studies searching for etiological causes and pathophysiology of autism should include a careful general and neurological examination of individuals diagnosed with autism spectrum disorders and other medical and psychiatric comorbidities. In this study, differences in gender, clinical and diagnostic features were found when etiology was used to create subtypes of ASD. This classification could have heuristic value in the search for autism-related gene abnormalities.

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Corresponding author

Dr. L. Gabis

Weinberg Developmental Center, Sheba Medical Center, Tel Hashomer 52621, Israel

Phone: (972-3) 530-2236

Fax: (972-3) 530-3184, **email:** lidiagabis@gmail.com

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