DIAGNOSTIC BOUNDARIES of AUTISM DISORDER vs PERVASIVE DEVELOPMENTAL DISORDER NOS: COMPARATIVE OBSERVATIONAL STUDY and LITERATURE REVIEW

Short running title

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ABSTRACT

Diagnosis of pervasive developmental disorders (PDDs), and above all diagnosis of the different PDD subtypes, is an ongoing challenge in psychopathology. Application of categorical criteria is complex and problematic in the clinical field where the boundaries dividing some of the PDD entities are blurred, creating particular problems for the clinician. A dimensional clinical approach, considering autistic symptom severity, level of functioning, developmental characteristics and symptoms other than the ones typically observed in autism, may be a more suitable approach in the clinical field and could provide the clinician treating these disorders with empirical guidance. To identify the clinical features that might differentiate the PDD subtypes, we conducted a comparative study in a clinical sample of children affected by autism disorder (AD) or pervasive developmental disorders not otherwise specified (PDD-NOS) and a mini critical review of the available literature addressing clinical and psychopathological differences between the two subtypes. The results of both our study and our literature review seem to show little support for the current PDD subtypes. In such a framework, the most significant element in clinical practice appears to be a deep knowledge of the characteristics of the individual in question. By adopting a broad and multi-faceted perspective, it becomes possible to define the most effective rehabilitation treatment. This applies particularly to the pharmacological treatment, since, to date, no specific therapies for PDDs are known and the choice of pharmacotherapy can be decided only on the basis of the patient's general profile and specific features.

KEYWORDS

Autism - Classification - Pervasive developmental disorder - Pervasive developmental disorder not otherwise specified - Pharmacological treatment - Subtype

INTRODUCTION

The term pervasive developmental disorders (PDDs) refers to a cluster of psychiatric disorders characterized by impairment in social interaction and communication, restricted interests and stereotyped behaviors. In the DSM-IV IV-TR classification [1], five disorders are included under the heading PDDs: autism disorder (AD), Asperger disorder (AspD), pervasive developmental disorders not otherwise specified (PDD-NOS), Rett syndrome (RTT), and childhood disintegrative disorder (CDD). The last two disorders are less frequent; furthermore, RTT is usually more prevalent in females and associated with well-defined genetic abnormalities, while CDD is characterized by a clear regression following a period of normal development. There is still uncertainty over the nosographic framing of these two disorders, which are sometimes included among the so-called autism spectrum disorders (ASDs) and sometimes not [2; 3]. In fact, this latter diagnostic category is typically used to describe only the pure autistic disorders, namely AD, AspD and PDD-NOS [4]. These three entities are often investigated together because they are considered to belong to the same clinical spectrum [5].

According to the DSM-IV-TR criteria [1], AD is diagnosed when children present a series of symptoms within three core domains. They must present at least two of the following four symptoms in socialization: marked impairment in use of multiple non-verbal behaviors; failure to develop peer relationships; lack of spontaneous seeking to share enjoyment, interests, or achievements; and lack of social or emotional reciprocity. They are required to show at least one of the following qualitative communication impairments: delay or total lack of spoken language; impairment in the ability to initiate or sustain conversation; stereotyped or repetitive language; or lack of make-believe or imitative play. Finally, they should present at least one of the following restrictive, repetitive or stereotypic behaviors, interests, or activities: an encompassing preoccupation with one or more stereotyped and restricted patterns of interest; an apparent inflexible adherence to specific, non-functional routines or rituals; stereotyped and repetitive motor mannerisms; or persistent preoccupation with parts of an object.

The above impairments in reciprocal social interaction and a restricted, stereotyped, repetitive repertoire of interests and activities are also typical of AspD. The difference lies in the fact that children with AspD do not show language delay and cognitive impairment. According to the existing classification systems, if criteria for both AD and AspD are met, the diagnosis of AD should be preferred.

PDD-NOS, on the other hand, is a less clearly defined diagnostic category, being described in terms of a severe and pervasive impairment in reciprocal social interaction associated with impairment in either verbal or non-verbal communication skills or with the presence of stereotyped behaviors, interests, and activities [6]. PDD-NOS must be diagnosed when the diagnostic criteria for other PDDs are not met.

Classification systems are important tools in both research and clinical practice, not least because they allow standardization of measurements and outcomes across these two settings. Moreover, diagnostic classifications are used to establish eligibility for services, studies, and reimbursement [7]. However,

the application of strict categorical criteria is far more complex and problematic in the clinical field of psychopathology than it is in other clinical fields. Physicians, for example, face difficulties due to the blurred diagnostic boundaries between some of the PDD entities; PDD-NOS, in particular, lacks clear criteria and thus tends to be diagnosed, on the basis of its similar but less severe symptoms, as a "subthreshold" form of autism [5]. PDD-NOS is also the most frequent PDD category encountered in the clinical field and it encompasses a heterogeneous group of patients [5]. Categorical diagnosis of PDDs is particularly complicated early in the disease course, when symptom profiles are even more subtle and aspecific [8].

Considerable efforts have been made to develop specific psychometric methods and instruments that might facilitate the clinical diagnosis of PDDs. The Autism Diagnostic Interview-Revised (ADI-R) [9] and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) [10] are, to date, the only validated diagnostic instruments in this field [11]. These instruments have shown high specificity and sensitivity in the research field. In the clinical setting, however, they still give inconsistent results [12]. Moreover, whereas evidence exists supporting the validity of both ADOS-G and ADI-R in the differential diagnosis of autism versus other developmental disorders (such as mental retardation and language disorders) [2], the concordance between clinical diagnosis and standardized diagnostic measures has been found to be lower when seeking to differentiate between autism (AD) and PDD-NOS or AspD [13].

A dimensional clinical approach that takes into account autistic symptom severity, level of functioning, developmental characteristics, and symptoms other than the ones typically observed in autism could be more suitable for application in the real clinical setting, where efforts to define the most effective treatment program are based on the definition of individual profiles of strengths and weaknesses in terms of social, cognitive and communicative abilities [4; 14]. Such an approach may also cater better for the dynamic developmental trajectory of PDD symptoms. In addition, considering that no specific psychopharmacological treatments are available for PDDs, an accurate definition of the overall clinical picture could provide the clinician treating these disorders with empirical guidance. Finally, in addition to a categorical diagnosis, a detailed description of the symptom dimensions may provide prognostic information.

To address the above issues and identify clinical features that might prove able to differentiate AD from PDD-NOS, we conducted an observational cross-sectional study in a clinical sample of AD and PDD-NOS children. Specifically, we looked for differences and similarities between these two diagnostic entities in sociodemographic, developmental and instrumental measures. The results were subsequently further discussed and included in a brief critical review of the available literature dealing with the clinical and psychopathological differences between AD and PDD-NOS.

MATERIALS AND METHODS

Study

Sample recruitment

The sample was recruited from children who were consecutively referred to three centers in northern Italy (the Department of Child and Adolescent Neurology and Psychiatry at the Casimiro Mondino National Institute of Neurology Foundation, IRCCS, in Pavia; the "Dosso Verde" Center for Pervasive Developmental Disorders in Pavia; and the Child Neuropsychiatry Unit of the Del Ponte Hospital - Macchi Foundation in Varese) between September 2005 and September 2008, and diagnosed with AD or PDD-NOS, according to the DSM-IV-TR criteria.

Study design

Cross-sectional observational study.

Sample assessment

The assessment procedure was performed at the three centers by two specialists in child psychiatry and neurology (neuropsychiatrists) trained in the administration of the ADOS-G. To ensure inter-rater reliability, videotaped play observation ratings for two observational scales – the Childhood Autism Rating Scale (CARS) [15] and the Behavioral Summarized Evaluation (BSE) [16] – were compared during meetings held before the project began.

Clinical and sociodemographic characteristics

All the parents of the included children underwent a semi-structured interview to collect information about the children's family and developmental history. The following information was collected: demographic variables i.e., gender and age at assessment; family history, i.e. ethnicity, mother's and father's age, mother's and father's educational level (primary school, secondary school, college/university), family history of neuropsychiatric disorders; developmental and clinical history, i.e., normal or complicated pregnancy, normal or abnormal delivery, birth weight, presence of eating and sleeping problems, age at acquisition of walking, presence of sphincter control, presence of any regression of development, and acquisition of pointing.

Once the parents' written consent had been obtained, a clinical assessment was performed. This involved videotaped play observations in semi-structured setting, the use of observational scales and standardized developmental scales, compiled by clinicians, and the administration of standardized interviews and questionnaires aimed at parents. Both PDD-specific and non-PDD-specific evaluation scales were used. The former, i.e. ADOS-G, ADI-R, Gilliam Autism Rating Scale (GARS), CARS and BSE, which are all standardized tools, were used to support the diagnostic process and to define the clinical severity. Instruments not specific to PDDs, i.e. the Griffiths' Mental Development Scale (GMDS), Vineland Adaptive Behavior Scale (VABS), Clinical Global Impression Scale (CGI), Child Behavior Checklist (CBCL) and EuroQoL, were used to record the children's levels of development and adaptive behavior, global functioning, emotional-behavioral profile, and quality of life. The questionnaires for caregivers (CBCL, EuroQoL) were administered to both parents in order to be able to compare the perceptions of both mothers and fathers.

Psychometric assessment of patients diagnosed with AD or PDD-NOS

The PDD-specific instruments used in this study are detailed below:

- *Autism Diagnostic Interview-Revised (ADI-R)* [9]: the ADI-R is a semi-structured, standardized interview with the caregivers of children (chronological age over 24 months, mental age over 18 months) who have a possible diagnosis of autism. It allows open-ended responses and consists of 93 items, clustered, in line with DSM-IV-TR and ICD-10, into three domains reflecting the areas typically impaired in PDDs: social interaction (ADI-R A), communication and language (ADI-R B), and restricted/repetitive behavior (ADI-R C). The instrument also includes a further five items aimed at detecting developmental impairment before the age of three years. The ADI-R provides a diagnostic algorithm (ADI-R dg) and a current behavior one. The domains have the following specific cutoffs (which, in the communication domain, are different for verbal and non-verbal subjects): 10 for ADI-R Adg, 7 for non-verbal ADI-R Bdg and 8 for verbal ADI-R Bdg, 3 for ADI-R Cdg. A patient exceeding the cutoffs in all three domains is diagnosed with AD. The ADI-R does not allow differential diagnosis between the different PDDs.

- *Autism Diagnostic Observation Schedule-Generic (ADOS-G)* [10]: the ADOS-G is a semi-structured, standardized play assessment instrument that focuses on social interaction, communication, play, imaginative use of materials and stereotyped behaviors in individuals with AD or other PDDs. Structured activities and materials and less structured interactions are used to create planned and social occasions or standardized contexts, referred to as "presses", that are likely to elicit social, communicative and symbolic-imaginative behaviors relevant to the understanding of PDDs. Unlike other diagnostic instruments, the ADOS-G is able to differentiate between AD, other PDDs and non-PDDs. Diagnosis depends on whether or not the subject exceeds cutoffs in the language and communication subscale (ADOS-L), social interaction subscale (ADOS-R) and total scale (ADOS-T). The ADOS-L and ADOS-R scores are summed to obtain the ADOS-T score. Play and stereotyped behavior scores are not included in the diagnostic algorithm. The instrument has four modules, designed to assess children with different developmental and language abilities as well as high-functioning adolescents and adults, and the domain cutoffs are different in each of these modules.

- *Gilliam Autism Rating Scale (GARS)* [17]: this behavior checklist is based on the DSM-IV-TR criteria, and designed to be used by parents, teachers and healthcare professionals. The aim of the instrument is to help identify and estimate the severity of autism in individuals aged 3 to 22 years. It consists of 56 items, each rated on a four-point scale (from 0=never observed to 3=frequently observed), clustered into four domains: stereotyped behaviors, communication, social interaction, and developmental disorders. The sum of the four domain scores provides an "autism quotient" (AQ), which expresses the likelihood of a diagnosis of autism. An AQ less than 90 suggests a low probability, a value between 90 and 120 a medium probability, and an AQ greater than 120 a high probability of autism. To evaluate the likelihood of autism in non-verbal subjects, the communication domain score is left out. The tool can be useful in the diagnostic phase, in the planning of rehabilitation programs, and in treatment outcome assessment.

- *Childhood Autism Rating Scale (CARS)* [15]: the CARS is a 15-item Likert-type (1=normal to 4=severely abnormal) observational scale, suitable for assessing children with a chronological age of over 2 years. Scores range from 15 to 60. The tool can be used to identify autism (cutoff > 30) and to evaluate the severity of autistic disorders (a score of 30 to 36 suggests a diagnosis of mild to moderate autism, and a score above 36 moderate to severe autism).

- *Behavioral Summarized Evaluation (BSE)* [16]: the BSE is a 20-item Likert-type scale (items are rated from 0=never observed to 4=always observed), designed to facilitate the recording of behavioral parameters in children with autistic disorders and to detect and quantify changes in autistic behaviors over time.

Developmental level was assessed using the *Griffith's Mental Development Scales (GMDS)* [18]: the GMDS is a quantitative measure of cognitive abilities, divided into six subscales: locomotor (A), personal-social (B), language (C), eye and hand co-ordination (D), performance (E), and practical reasoning (F). Raw scores are computed for each individual subscale and can be converted into different types of standard score, including age equivalents/mental age or general quotient (GQ). The mean value of GQ is 100 ± 15; a GQ less than 70 identifies developmental delay.

- *Vineland Adaptive Behavior Scales (VABS)* [19]: this instrument was used to define adaptive behavior. It is a semi-structured interview administered to caregivers to measure patients' personal and social skills. It covers different domains of everyday living: communication, daily living skills, socialization and motor skills.

The patients were also assessed using the following non-PDD-specific instruments:

- *Clinical Global Impression Severity Scale (CGI-S)* [20]: this is a 7-point scale used by the clinician to rate the severity of the patient's mental illness at the time of assessment, on the basis of his or her own past experience of patients with the same diagnosis. On this basis, patients are rated as 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

- *Child Behavior Checklist (CBCL)* [21]: the CBCL is a parent-compiled questionnaire used to identify emotional-behavioral problems in children. Depending on the age of the child being assessed, we use the CBCL 1.5-5 years or the CBCL 4-18 years version. Each scale item describes a specific behavior, which has to be rated on a three-point Likert scale (0=not true, 1=somewhat or sometimes true, 2=always true). Both the 1.5-5 years and 4-18 years versions have global scales (total problems, internalizing problems, externalizing problems) and syndrome scales; the 1.5-5 years version also includes scales consistent with the DSM categories, the so-called DSM-oriented scales. Depending on the scales used, T-score cutoffs of 65 or over (total, internalizing, externalizing) and 70 (syndrome and DSM-oriented scales) are used to indicate clinical range. In this study, we analyzed only the total, internalizing, and externalizing scales.

- *EuroQoL* [22]: this scale measures health status on a visual analog scale, where the extremes are 'best imaginable health state' (100) and 'worst imaginable health state' (0).

Mini review

A comprehensive literature search was conducted to identify studies evaluating differences between AD and PDD-NOS. The following search terms were used: autism spectrum disorders, pervasive developmental disorders, autism, pervasive developmental disorders not otherwise specified, diagnostic boundaries, classification, subtypes, gender, ethnicity, intelligence quotient (IQ), behavioral problems, and psychopharmacological treatment. Studies were included if they were in English, had been published in the last five years, focused on children and adolescents (under 18 years of age), used the DSM- IV-TR or ICD-10 criteria, and directly compared AD and PDD-NOS.

Statistical analysis

Data were analyzed after application of Levene's test to check for equality of variances. Independent t-tests were used to compare continuous variables, while categorical variables were analyzed with the chi-square test adjusted with Fisher's exact test in the event of small counts in the contingency cells.

RESULTS

Study

Sample

We recruited 117 children aged 17-175 months (mean 52; SD 29.4). The sample was predominantly male (83%) and Caucasian (93%). Forty-six subjects (39%) met the DSM-IV-TR criteria for AD and 71 (61%) for PDD-NOS.

Sociodemographic, developmental and clinical characteristics were compared between the two groups. The results are shown in Table 1.

Differences in sociodemographic variables

The sociodemographic variables evaluated included the child's age at assessment, gender, ethnicity, the age and educational level of both parents and the family history of neuropsychiatric disorders. The only significant difference to emerge between the groups was age at assessment (AD 62.78 months vs PDD-NOS 45.20 months; p=0.006). However, this difference could be driven by the presence of three outliers in the AD group.

Differences in developmental variables

Of the developmental variables considered (delivery, weight at birth, walking age, eating and sleeping problems, presence of sphincter control) a significant difference emerged only with regard to sleeping patterns, which were more frequently irregular in the AD group (AD 67% vs PDD-NOS 38%; p=0.004).

Clinical differences

With regard to the clinical characteristics considered, age at onset of symptoms and presence of regression did not differ between the two groups. Conversely, the presence of pointing was significantly less frequent in the AD group (AD 30% vs PDD-NOS 52%; p=0.021).

Psychometric differences

Comparison of the results of the psychometric assessments between the two groups revealed many significant differences, all of which seemed to show that AD is the more severe disorder. Significant differences were found on all the clinician-rated observational instruments: ADI-R social interaction (p<0.001) and communication and language (p=0.01) scales; ADOS-G social interaction (p<0.001) and total score (p=0.001); CARS total score (p<0.001); BSE total score (<0.001); CGI (p=0.049). The GARS, which is the only tool to focus on core symptoms as rated by parents, showed significant differences only on the communication scale (p=0.02), but not on the other scales (GARS total p=0.923; developmental disturbances p=0.955; stereotyped behaviors p=0.074). Among the other scales, the GMDS showed developmental delay in both groups, with significantly lower scores recorded in the AD subjects (p=0.025). Reinforcing the suggestion that AD is the more severe disorder, the EuroQoL also showed lower scores in the AD group according to the ratings given both by fathers (p=0.007) and by mothers (p=0.002). The general emotional-behavioral profile, evaluated using the CBCL, did not differ between the groups on any scale (total p=0.787; internalizing p=0.966; externalizing p=0.227) (see table II).

Mini review

Our literature search uncovered 14 studies dealing with clinical and psychopathological differences between AD and PDD-NOS: 10 that had already been included in a previous review by Witwer & Lecavalier [14] and four more recent ones.

The review by Witwer & Lecavalier [14] examined published studies directly comparing a series of variables between three PDD subgroups: AD, PDD-NOS and AspD. The variables compared were: diagnostic instruments and criteria, other measures of core symptoms, gender, IQ functioning, executive functioning, motor functioning, comorbidity, family history, prognosis and follow-up.

We here report data on the comparison between AD and PDD-NOS subjects, first considering the data emerging from the study by Witwer & Lecavalier and then the findings of subsequent studies.

Psychometric instruments

Two of the studies reviewed by Witwer & Lecavalier [14] examined differences between AD and PDD-NOS on diagnostic instruments, in particular the ADI-R and the ADOS-G [23; 24]. Both of these studies found higher scores in the AD group on both the instruments. Buitelaar *et al.* [25] instead set out to establish which ICD-10 criteria discriminated AD (n=205 subjects) from PDD-NOS (n=80 subjects), and showed a lower number/lesser severity of symptoms in the PDD-NOS group.

Language skills

Witwer & Lecavalier [14] identified only one study that compared language skills in the two groups of interest [26]: subjects with PDD-NOS were found to score lower than AD subjects on the Pragmatic Composite and Restricted Interest subscales of the Children's Communication Checklist (CCC).

Prevalence

The prevalence of the different PDD subgroups was analyzed by Chakrabarti and Fombonne [27] and Sponheim and Skejeldal [28], who found the following prevalence rates per 10,000: AD 16.8 – PDD-NOS 36.1 and AD 3.8 – PDD-NOS 0.009, respectively. The difference between the results of the two studies was interpreted as a consequence of the limited sampling procedure used in the latter study.

Gender

The same two studies also considered gender in AD versus PDD-NOS. Chakrabarti and Fombonne [27] found no differences in the proportion of males in different PDD groups. Sponheim and Skejeldal [28] compared AD with combined PDD-NOS and AspD, subdividing the two groups by IQ level. The male-to-female ratio was found to be higher in the high-functioning AD group (AD 9:0 vs 5:2 in PDD-NOS/AspD), but not in the low-functioning one (AD 1:1 vs PDD-NOS/AspD 1:1).

IQ functioning

Differences in IQ functioning were examined only by Chakrabarti and Fombonne [27], who found that 50% of AD subjects had mild to moderate intellectual delay (ID) and 19% severe to profound ID. By contrast, only 8% of PDD-NOS subjects showed mild ID (and the remainder were in the normal range of intellectual functioning).

Neuropsychological abilities

With regard to neuropsychological abilities, Verté *et al.* [26] found that PDD-NOS subjects scored lower than high-functioning AD subjects on a visual working memory task (number of errors) but recorded a significantly faster time on the Tower of London test.

Comorbidity

Witwer & Lecavalier identified several studies that dealt with comorbidity [29; 30; 31]. In 2004, Gadow *et al.* [29] administered the Early Child Inventory-3 (ECI-3) to a sample of preschool-age children (3-5 years old) and compared the performances of the AD, PDD-NOS and AspD subgroups: the PDD-NOS subjects showed fewer compulsions and vocal and motor tics than those with AD. In 2005 [30], the same research group looked for differences between PDD subtypes in a sample of older children (6-12 years), this time using the Child Symptoms Inventory-4 (CSI-4). Symptoms of oppositional defiant disorders, major depressive disorders and dysthymia were more frequent in the PDD-NOS than in the AD group. Using the same instruments (ECI-3 and CSI-4) and dividing their sample into two subgroups according to age (3-5 and 6-12 years), Weisbrot *et al.* [31] found no differences in the younger group; conversely, the older PDD-NOS subjects scored significantly higher than the older AD subjects in obsessions, symptoms of generalized anxiety disorder and delusions, but significantly lower in grossly disorganized behavior. Verté *et al.* [26] instead applied the Disruptive Behavior Scale and the Diagnostic Interview Schedule for Children, but found no differences between the different ASD subtypes.

Family history

With regard to family history, the sample studied by Chakrabarti and Fombonne [27] included five sibling pairs showing PDD symptoms: in three pairs both children were diagnosed with PDD-NOS, in another pair one had AD and the other PDD-NOS, while in the last pair one had AspD and the other AD.

Prognostic outcome

Witwer & Lecavalier's review [14] also included data regarding studies on prognosis and outcome differences between PDD subtypes [32]. At follow-up evaluation, verbal IQ was found to be increased in both AD and PDD-NOS, whereas performance IQ was decreased in AD but increased in PDD-NOS.

In addition to the studies included in Witwer & Lecavalier's review [14], we identified four other studies reporting data from direct comparisons of AD and PDD-NOS.

Developmental/intellectual changes

Takeda *et al.* [33], in a short communication, compared developmental/intellectual changes between AD and PDD-NOS in preschool children assessed both at age 2 and at age $\geq$ 5 years. The CARS was used to evaluate the children for PDD symptoms and gave higher scores in the AD patients than in the PDD-NOS children both at baseline and at outcome assessment. With regard to developmental quotient (DQ) or IQ, the authors found that the PDD-NOS children had higher DQ/IQ values than the AD ones, both at initial and at outcome evaluation; moreover, the difference in the change in DQ/IQ over time between the two groups was significant.

Quality of life

Mugno *et al.* [34] used the WHOQOL-BREF, a self-administered instrument developed by the World Health Organization, to study quality of life in subjects belonging to different PDD subgroups. Comparison of the scores in the different subgroups revealed no statistically significant differences.

Regression

Analyzing the occurrence of regression in a PDD sample, Meilleur & Fombonne [35] found higher levels of regression (30%) in AD compared with PDD-NOS (14%) subjects. AD subjects were also found to have presented developmental abnormalities at a younger age (19.9 vs 25.1 months; p=0.028) and to have been referred for assessment at a significantly younger age (4 vs 7.4 years; p=<0.001) than those with PDD-NOS. Comparison of regression in the two groups showed that the AD subjects were marginally more likely than the PDD-NOS ones to show regression of any skill (30% vs 13.6%; p=0.050) and significantly more likely to show regression in an area other than language skills (25.3% vs 5%; p=0.010).

Emotional-behavioral profiles

Finally, Snow & Lecavalier [36] compared the performances of children with AD, PDD-NOS and other developmental disorders on the ADOS-G and CBCL. The AD sample recorded significantly higher ADOS-G scores than PDD-NOS group. To evaluate the CBCL scores, in particular the syndrome scale and DSM-oriented scale scores, the authors analyzed the preschoolers (2.5-5 years) and the school-age children (6-12 years) separately. No significant differences were found in the preschool-age group, while in the older sample, the only differences to emerge were higher scores in the PDD-NOS versus the AD subjects on the anxious-depressed subscale.

Table 1. Comparison of sociodemographic and clinical characteristics in AD versus PDD-NOS

	AD			PDD-NOS			Between groups comparison		
Continuous variables	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*t-test*	*df*	*p*
Age (months)	46	62.78	39.59	71	45.20	17.28	2.843	56	**0.006**
Age at onset of symptoms (months)	46	22.30	7.90	71	22.41	8.84	-0.065	115	0.948
Mother's age (years)	46	36.83	5.73	71	35.54	5.15	1.267	115	0.208
Father's age (years)	46	40.33	6.07	70	38.51	4.94	1.762	114	0.081
Birth weight (g)	45	3161.56	585.28	62	3152.21	513.77	0.088	105	0.930
Age at acquisition of walking (months)	45	14.18	2.74	68	14.53	3.66	-0.550	111	0.584
Categorical variables	*n*	*total*	*%*	*n*	*Total*	*%*	*X2 test*	*df*	*p*
Gender									
Male	41	46	89.13	56	71	78.87	2.072	1	0.150
Female	5	46	10.87	15	71	21.13			
Ethnicity									
Caucasian	40	46	86.96	69	71	97.18	5.282	2	0.079
African	5	46	10.87	1	71	1.41			
Asian	1	46	2.17	1	71	1.41			
Mother's level of education									
Primary school	13	45	28.89	21	68	30.88	2.738	2	0.254
Secondary school	27	45	60.00	32	68	47.06			
College/University	5	45	11.11	15	68	22.06			
Father's level of education									
Primary school	15	45	33.33	18	68	26.47	0.764	2	0.682
Secondary school	21	45	46.67	37	68	54.41			

College/University	9	45	20.00	13	68	19.12			
Neuropsychiatric disorders - mother									
No	40	46	87	63	71	88.73	0.203	2	0.977
Yes	6	46	13	8	71	11.27			
Neuropsychiatric disorders -father									
No	38	45	84	68	71	95.77	5.261	2	0.262
Yes	7	45	16	3	71	4.23			
Delivery									
Normal	27	46	59	42	71	59.15	0.112	2	0.945
Abnormal	19	46	41	29	71	40.85			
Eating habits									
Regular	30	46	65	47	71	66.20	0.012	1	0.913
Irregular	16	46	35	24	71	33.80			
Sleeping patterns									
Regular	16	46	35	44	71	61.97	8.26	1	**0.004**
Irregular	30	46	65	27	71	38.03			
Sphincter control									
Yes	15	46	33	20	71	28.17	0.262	1	0.608
No	31	46	67	51	71	71.83			
Regression									
No	32	46	70	55	71	77.46	0.914	1	0.339
Yes	14	46	30	16	71	22.54			
Pointing									
No	32	46	70	34	71	47.89	5.335	1	**0.021**
Yes	14	46	30	37	71	52.11			

Table 2. Comparison of psychometric assessments in in AD versus PDD-NOS

	AD			PDD NOS			Between-groups comparison		
	n	Mean	SD	n	Mean	SD	t	df	p
ADI-R social interaction	45	24.33	4.91	62	17.11	5.35	7.137	105	**<0.001**
ADI-R communication and language	45	14.4	3.53	62	12.32	4.68	2.613	105	**0.01**
ADI-R restricted and repetitive behaviors	45	5.09	2.98	61	4.3	2.58	1.465	104	0.146
ADOS-G communication	46	7.07	1.44	66	6.82	3.48	0.455	93	0.65
ADOS-G social interaction	46	11.59	2.01	66	9.41	2.27	5.24	110	**<0.001**
ADOS-G total	46	18.52	2.79	66	16	4.53	3.354	109	**0.001**
CARS total	44	42.03	7.87	66	36.36	5.39	4.488	108	**<0.001**
BSE total	44	42.86	11.15	65	31.58	11.88	4.983	107	**<0.001**
GARS total	38	83.39	26.61	62	83	14.07	0.097	50	0.923
GARS developmental disturbances	34	6.65	2.94	63	6.68	2.98	-0.056	95	0.955
GARS social interaction	37	13.65	6.87	62	9.52	5.93	3.162	97	**0.02**
GARS communication	32	11.28	4.76	57	9.19	5.48	1.811	87	**0.074**
GARS sterotyped behaviors	38	15.63	9.08	63	9.38	6.047	3.769	57	**<0.001**
CBCL total	36	61.31	10.57	66	60.7	10.96	0.271	100	0.787
CBCL internalizing	36	61.17	8.591	65	61.08	10.64	0.043	99	0.966
CBCL externalizing	36	54.45	8.89	65	56.98	11.76	-1.215	99	0.227
CGI	46	5.54	1.01	70	4.6	3.109	1.99	114	0.049
Vineland total	41	261.02	107.87	43	244.47	104.72	0.714	82	0.477
Griffiths total	24	53.04	10.58	57	59.86	15.42	-2.293	62	**0.025**
EuroQoL father	41	62.22	18.35	61	71.44	15.18	-2.765	100	**0.007**
EuroQoL mother	41	57.71	18.39	65	68.42	16.49	-3.113	104	**0.002**

ADI-R, Autism Diagnostic Interview-Revised; ADOS-G, Autism Diagnostic Observation Schedule-Generic; CARS, Childhood Autism Rating Scale; BSE, Behavioural Summarized Evaluation; GARS, Gilliam Autism Rating Scale; CBCL, Child Behavior Checklist; CGI, Clinical Global Impression scale; EuroQoL, Health-related Quality Of Life questionnaire.

DISCUSSION

Among the various PDD categories included in DSM-IV-TR, AD, AspD and PDD-NOS are the ones that are likely to present overlapping symptoms. Although the classification system provides specific diagnostic criteria for each of these subtypes, these criteria seem much more difficult to apply in the clinical setting than in the research field. Indeed, the clinical presentations of these disorders are rarely well defined and a single subject will frequently present manifestations, characteristics and features ascribable to different subtypes. This situation has, over time, led the main PDD subtypes to be interpreted as different degrees of severity on a single clinical spectrum [5]. Such interpretations support the fifth revision of the DSM criteria, in which a single diagnosis of autism spectrum disorder replaces the various autism subtypes considered to date, which, under DSM-5, will no longer be considered distinct diagnostic categories.

The current situation, characterized by well-defined subtype criteria not easily applicable in the clinical setting, makes the differential diagnosis of these conditions extremely challenging. This is particularly true in the case of AD versus PDD-NOS, both of which show the main typical PDD manifestations (impairment in social interaction and communication and a restricted repertoire of interests and behaviors); moreover, the definition of PDD-NOS is rather vague and not readily applicable.

In an effort to overcome these diagnostic difficulties, observational scales have been introduced as a means of identifying and recording symptoms typical of PDDs [11]. However, while such scales have been shown to provide valid support in the differential diagnosis of PDDs versus other developmental disorders (i.e. language delay or general delay), they are less useful for differential diagnosis between the different PDD subtypes [12]; moreover, such differential diagnosis is an objective that some of them (e.g., ADI-R) do not even contemplate. One possible way of rising to the challenge of subtype differential diagnosis could be to combine a dimensional approach with categorical classification: this would mean taking into account not only the fulfilment of diagnostic criteria, but also the intensity and severity of the symptoms and their impact on the subject's development and family functioning, and identifying different features that might help to differentiate between the subgroups. The definition of endophenotypes, based on clinical observation, could provide not only a direction for the diagnostic process but also a starting point for developing treatment programs and a basis for prognostic hypotheses. All this, in fact, is already seen in clinical practice where, irrespective of classification subtyping, the focus is on tracing the patient's profile of competences and deficits, strengths and weaknesses, with a view to defining a better tailored rehabilitation program.

In order to identify specific subgroup features, we conducted a comparative study between AD and PDD-NOS children referred to three northern Italian centers and performed a mini review of the literature. Both our study and the literature reports seem to highlight a paucity of data supporting the currently established PPD subgroups. The few differences that did emerge between the subgroups support the idea that AD is a more severe disorder than PDD-NOS and has a greater impact on patients

and their families. This was shown particularly clearly when comparing the use, in the different subgroups, of the standardized instruments supporting the diagnostic process.

Sociodemographic and clinical variables

In our study, significant differences in sociodemographic and clinical variables were found only for age at evaluation (higher in AD), absence of pointing, presence of sleep disorders, and use of pharmacological treatment, all of which were more frequent in the AD group.

Psychometric variables

On comparison of the psychometric variables recorded in the two groups, the PDD-specific instruments were more often found to show differences. Higher scores were recorded in the AD than in the PDD-NOS group both on the clinician-rated instruments (ADOS-G, CARS, BSE, CGI) and on the instrument where parents were interviewed by the clinician (ADI-R). Instead, the results of the parent-compiled instruments appear less clear. In particular, no significant differences were found on any of the GARS scales except the one related to language. This result is in line with literature evidence that the GARS shows low psychometric properties when applied in clinical practice. The same trend emerged with regard to the non-PDD-specific instruments, with clinician-rated ones being found to show more serious impairment in AD than in PDD-NOS patients (namely, the GMDS, evaluating DQ and the CGI, evaluating mental disease severity). As regards the parent-compiled questionnaires, the CBCL did not show significant differences between AD and PDD-NOS subjects on any scale (total, internalizing or externalizing), while the EuroQoL scores were in line with the interpretation of AD as a more severe disorder than PDD-NOS.

Mini review

As mentioned, our brief review of the literature seemed to highlight a paucity of data supporting the current PDD subgroups. Findings indicative of differences between AD and PDD-NOS emerged for the following variables: DQ/IQ, comorbidity and emotional-behavioral profile. Furthermore, the studies tended to suggest that the observed differences across subtypes might be better explained by age at evaluation or IQ differences [14].

Impact on the diagnostic process

The findings of our study and literature review seem to offer little support for distninguishing between the PDD subtypes on the basis of demographics, IQ profiles, executive functioning, comorbidity, family history, and natural history. In such a framework, once a relational-communication impairment is recognized, the most significant element in clinical practice appears to be a deep knowledge of individual's characteristics. The starting point is to obtain a clear and detailed picture of the subject's developmental and clinical history and family functioning, and of the impact of his disease on his life and his family; it is also important to understand the reciprocal impact between the developmental

trajectory and disease features, obtaining a clear definition of general functioning in the presence of disease, and to identify potential comorbidities.

Impact on treatment program

A wide and multi-faceted perspective is the basis for defining the most effective rehabilitation treatment possible, which is, of course, the primary goal in patient care. This also applies to pharmacological treatments. To date, no specific therapy exists for PDDs. Pharmacotherapy can play a role, but the choice of treatment must be made taking into account the patient's general profile and also his specific features. For example, the presence of sleep disorders can prompt the introduction of a hormone treatment to regulate sleep; identification of epilepsy will indicate a need for antiepileptic drugs; the presence of psychiatric comorbidity, such as anxiety or obsessive symptoms, can constitute an indication for the use of an SSRI (e.g. fluoxetine), while the presence of behavioral disorders, specifically aggressive behavior, can make it necessary to introduce antipsychotic drugs (such as haloperidol, risperidone or aripiprazole). The identification of an appropriate and specific pharmacotherapy is fundamental for fostering caregiver compliance, while correct definition of the subject's profile at the time of initiating pharmacotherapy is the best basis for monitoring pharmacological treatment efficacy.

CONCLUSION

The differential diagnosis of PDD subtypes has been a major topic in the literature, ever since the establishment of the DSM-IV-TR criteria. Subjects with PDD-NOS appear to constitute a heterogeneous group who show fewer PDD symptoms than those with AD and AspD, but differ very little from AD and AspD subjects on other measures. This observation brings us back to the question of whether autistic subtypes are actually distinct subtypes (categorical) or just represent different degrees of severity on a clinical continuum. A dimensional clinical approach allows the different autism subtypes to be differentiated with regard to quantity, but not quality and it seems to be more suitable for the clinical field where it could be a source of guidance for clinicians involved in the treatment of these disorders. However, further research is needed in order reach a deeper understanding of the etiopathological pathways underlying PDDs. The idea of going beyond symptom severity and examining the nature of symptoms, as well as their evolution during development, in order to obtain more effective diagnostic processes and care programs could constitute a useful direction for future research. Moreover, widening the research field to autistic traits and to the so-called broad autism phenotype could also favor a deeper understanding of the interaction between PDD symptoms and developmental trajectories [37]. The diagnosis and classification of PDDs has progressed considerably in the last 60 years, but much remains to be done.

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