

# **Non-Autistic Pervasive Developmental Disorders: Rett's syndrome, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified**

## **Transtornos invasivos do desenvolvimento não-autísticos: síndrome de Rett, transtorno desintegrativo da infância e transtornos invasivos do desenvolvimento sem outra especificação**

---

**Marcos T Mercadante,<sup>1</sup> Rutger J Van der Gaag,<sup>2</sup>  
Jose S Schwartzman<sup>1</sup>**

### **Abstract**

*The category "Pervasive Developmental Disorders" includes autistic disorder, Asperger's syndrome, Rett's syndrome, childhood disintegrative disorder, and a residual category, named pervasive developmental disorder not otherwise specified. In this review, Rett's syndrome and childhood disintegrative disorder, which are well-defined categories, will be discussed, as well as the not well defined categories that have been included in the Pervasive Developmental Disorder Not Otherwise Specified group. Different proposals of categorization have been created, some of which based on descriptive phenomenological approach, and others based upon other theoretical perspectives, such as neuropsychology. Current proposals are presented and discussed, followed by critical appraisals on the clinical advantages and disadvantages of these concepts.*

*Keywords: Child psychiatry; Children development disorders, pervasive; Rett syndrome, Childhood disintegrative disorder; Diagnosis, clinical*

---

### **Resumo**

*A categoria "transtorno invasivos do desenvolvimento" inclui o autismo, a síndrome de Asperger, a síndrome de Rett, o transtorno desintegrativo da infância e uma categoria residual denominada transtornos invasivos do desenvolvimento sem outra especificação. Nesta revisão, a síndrome de Rett e o transtorno desintegrativo da infância, que são categorias bem definidas, serão discutidas, assim como as categorias não tão bem definidas que foram incluídas no grupo transtornos invasivos do desenvolvimento sem outra especificação. Diferentes propostas de categorização têm sido feitas, algumas baseadas em abordagem fenomenológica descritiva, outras baseadas em outras perspectivas teóricas, tais como a neuropsicologia. As propostas atuais são apresentadas e discutidas, seguidas por avaliações críticas sobre as vantagens e desvantagens desses conceitos.*

*Descritores: Psiquiatria infantil; Transtornos invasivos do desenvolvimento infantil; Síndrome de Rett; Transtorno desintegrativo da infância; Diagnóstico clínico*

---

<sup>1</sup> Pervasive Developmental Program, Universidade Presbiteriana Mackenzie, São Paulo (SP), Brazil

<sup>2</sup> Academic Centre for Child and Adolescent Psychiatry, University Medical Centre St. Radboud Nijmegen, Nijmegen, The Netherlands

### **Correspondence**

Marcos T. Mercadante  
R. da Consolação, 896 - 6º andar, sala 62  
CEP 01302-907 São Paulo, SP, Brazil

Financing: MackPesquisa (Dr. Mercadante and Dr. Schwartzman)  
Conflict of interests: None

## Introduction

### Definition of pervasive developmental disorder

The current concept of pervasive developmental disorder (PDD) has been coined since the late 60's, and mainly derived from M. Rutter, I. Kolvin and D. Cohen works'. A publication title change from *Journal of Autism and Childhood Schizophrenia* to *Journal of Autism and Development Disorders* at the end of the 70's, as well as the publication of the DSM-III might be considered milestones of this concept.

After sporadic case reports, such as the wild boy of Aveyron, the term childhood psychosis was introduced at the beginning of the 20<sup>th</sup> century, when Heller described a clinical presentation that is currently known as disintegrative disorder. Despite this, the category, as a whole, just obtained relevance in the 50' with Leo Kanner describing the Autism. Until the ICD-9, autism and disintegrative psychosis were classified as childhood psychoses. The recent nosography based on descriptive phenomenology began to be applied at the DSM-III and ICD-10.

The phenotype proposed for PDD includes manifestations in three domains (social, communication and behavior). The reciprocal sociability is qualitatively impaired, as well the communicative skills. The pattern of behavior and interests are restricted, tending to be repetitive and stereotyped.

Currently, researches are trying to look beyond the simple observable behavior, searching for endophenotypes, i.e. internal phenotypes built by biochemical, neurophysiological, neuroanatomical or neuropsychological measures.<sup>1</sup> In the field of PDD research, some endophenotypes have been studied, such as the patterns of Theory of Mind, central coherence performance, executive function, visual scanning strategies, etc. These endophenotypes can be more easily related to neurocircuitries and their functions. Moreover, they have allowed better candidate genes studies.

It is true that the progress in the field has been mostly supported by the development of neuroscience, however, the proposal of new models of comprehension such as the concept of autism spectrum disorders (ASD) has been extremely important too. To further understand the ASD, it would be important to have better definitions of all PDD categories. Today, the prototypes of PDD, autism disorder (AD) and Asperger Syndrome, are well known and two non-autism categories, Rett syndrome and disintegrative disorder, are well characterized either. The residual category is named PDD-NOS (pervasive development disorder-not otherwise specified), and does not have specific criteria. The classification for children who do not fit for any other PDD should be placed in this condition.<sup>2</sup> In this paper we discuss the two non-autism categories and present the several nosographic categories that have been proposed to subdivide the PDD-NOS.

### Nosographic categories

#### 1. Rett Syndrome

This disorder was identified in 1966 by Andréas Rett<sup>3</sup> but only after the work by Hagberg et al. (1983)<sup>4</sup> did it become better known. In this same work the eponym Rett Syndrome (RS) was proposed. The original description of Rett emphasized neuromotor deterioration, female predominance, particular signs and symptoms,

and the presence of hyperammonemia, and it named the condition "Brain Atrophy Associated to Hyperammonemia".

Today, it is known that hyperammonemia is neither a necessary nor a usual finding. The estimated prevalence of RS varies between 1:10.000 and 1:15.000 girls.<sup>4</sup> The clinical diagnosis is based either on criteria proposed by the Rett Syndrome Diagnostic Criteria Work Group<sup>5</sup> or on those defined by the DSM-IV-R.

#### 1) Clinical picture

RS can be divided in four stages. The first stage, named *precocious stagnation*, begins between ages six to 18 months and is characterized by development stagnation, deceleration of the brain perimeter increment, and tendency to social isolation. This stage lasts a few months. The second stage, called *rapidly destructive*, begins between ages one to three years and lasts for weeks or months. In this phase, a clear psychomotor regression is observed, as well as crying spells, irritability, loss of acquired speech, autistic behavior, and stereotypic hand movements with loss of their purposeful use. Breathing irregularities (apnea during wakefulness and hyperventilation episodes among others) and epilepsy can be present. The subsequent stage, called *pseudo-stationary*, occurs between ages two to ten and is characterized by a certain improvement in some of the signs and symptoms, particularly concerning social contact. From the motor point of view, ataxia and apraxia, spasticity, scoliosis, and tooth grinding are present. Episodes of breath loss, aerophagia, and air and saliva forced expulsion occur very frequently. The forth stage, the one of the *late motor deterioration*, begins at around the age of ten years and is characterized by a slow progression of motor impairments and occurrence of scoliosis and severe cognitive deviance. Choreo-athetosis, dystonia, and peripheral neuromotor disturbances may arise. Girls who are able to walk independently will present increasing difficulties and will usually need a wheel chair.<sup>6</sup>

Although the diagnostic criteria accepted today suggest that children with RS present a normal development during the first months of life, current evidences suggest that there are subtle signs of some abnormality already at a very early age, including a discrete motor retardation, presence of muscular hypotonia, and other motor alterations.

Severe speech impairments are the rule. In fact, most of these children do not speak at all, although some of them do acquire some speech but lose this ability in the regression phase. Few of the girls are able to speak thus this form of RS has been called *RS with preserved speech*.<sup>7</sup>

The occurrence of epilepsy is frequent and it can present itself under various types of seizures, which can be quite resistant to medication. The electroencephalogram presents normal recordings in the initial phases of the disease but becomes slower as the condition progresses. Sharp waves may appear in the centroparietal regions. Later at stage III spike-wave discharges may occur and they are more easily observed in sleep recording. At stage IV there may be an improvement in the electroencephalogram with a reduction of epileptiform elements.

Survival in RS can be limited, with death occurring in general as a result of infectious causes, respiratory complications, maybe related to severe scoliosis, or during sleep (sudden death).

## 2) Genetics

Most RS cases are isolated e sporadic cases with rare occurrence in the family. In the past the disorder was considered as X chromosome dominant disease, lethal to males, being exclusively observed in females. More recently few male cases have been reported, though with atypical and partial signs of the syndrome.<sup>7</sup>

In 1998,<sup>8</sup> a case of a two-year and nine month-old boy who had a typical RS phenotype and a XXY karyotype was described. This association of RS with the Klinefelter Syndrome has an occurrence probability of one to 10/15 million births. This boy, as eventually confirmed,<sup>9</sup> presented one of the possible mutations found in the RS gene.

In 1999,<sup>10</sup> mutations of the *MECP2* gene were described in patients with RS. More recent studies indicate that around 75% to 80% of the patients with the classical form of RS bear mutations in this gene.<sup>7</sup> The gene codifies the *MECP2* protein that works as a global transcription repressor. This protein acts in different sites and the different mutations already identified could be responsible for the various phenotypical patterns that have been observed.

We know today that males can be affected by this condition in some circumstances: boys who have co-morbidity with the Klinefelter Syndrome,<sup>9</sup> boys who present a severe encephalopathy, and in brothers of affected girls that are born with severe neurological impairments, usually having precocious death.<sup>7</sup>

## 3) Pathology

Although the gene was identified, the mechanisms underlying the RS still unknown. Significant reductions in the frontal lobe, in the caudate nucleus, and in the mesencephalus have been described and there are some evidences that there could be a post-natal deficiency in the synaptic development.<sup>11</sup>

## 4) Animal model

There is already an animal model for the RS, a transgenic mouse with a truncated mutation in the *MECP2* gene.<sup>12</sup> These animals present no abnormality up to the sixth week when they will tremble when held by the tail. After eight months some fur alterations appear as well as convulsive manifestations. An increase of histone acetylation was observed in these mice, a fact that compromises the architecture of the chromatin in certain brain regions, mainly in the cortex and in the cerebellum.

## 2. Disintegrative disorder

Childhood disintegrative disorder (CDD) has a longer history than autism. Heller first described it way back in 1908. Heller (1908) reported on six cases of young children who after a seemingly normal development over the first 3-4 years of life presented a very severe loss of social and communicative skills. Heller called the condition "dementia infantilis". This definition is unsatisfactory: first because the condition is not comparable with dementia, in the sense that the characteristics of loss of memory and executive skills are not prominent. And second because no organic cause of trace of damage can be found.<sup>13</sup>

In the DSM-III (1981) Heller's syndrome was first introduced in a psychiatric classification system. It was included under the umbrella category Pervasive Developmental Disorder because the loss of social and communicative skills was most prominent.<sup>14</sup> Yet CDD is not characterized in its course either by further

deterioration or by any progress. In other words after the dramatic regression at the start a status quo is reached, but a tremendous impact on the development can be observed during the long life.

CDD is an extremely rare condition. Fombonne reviewed 32 epidemiological surveys of autism and PDD.<sup>15</sup> CDD was mentioned only in four studies. The pooled prevalence estimate across these studies was 1.7 per 100.000 (95% Confidence Interval: 0.6-3.8 per 100,000). The differential diagnoses include metabolic disorders (e.g. mucopolysaccharoidosis San Filippo), neurological conditions (e.g. slow virus encephalitis<sup>16</sup> or epilepsy) though in the latter cases language is far more affected than in the case reports on CDD. It should also be differentiated from autism in which a near normal development in the first one or two years is seen in up to 30% of all cases.<sup>17</sup>

Its etiology is yet unknown. Therefore, CDD could be a category that is bound to disappear when diagnostic tools will make it possible to determine the genetic, metabolic or infectious causes involved in these yet now unexplained cases. One case report points at a possible genetic link with autism in a case where autism and CDD occurred in two half brothers.<sup>18</sup>

There is no treatment for CDD. As neurological complications especially epilepsy are common and these children function at the level of severe to profound mental retardation a multidisciplinary approach is necessary. Parents will need psycho-education focused on this condition. Often times when parents of children with CDD join associations of parents of children with autism they get extremely disappointed because the progress seen in other children with autism spectrum disorders will not occur in their child.

Little is known of the outcome. The largest follow-up study was conducted by Mouridsen<sup>19</sup> on 39 cases matched with autistic controls over a period of more than 22 years. It was seen that individuals with CDD had a lower overall functioning, were more aloof and had a great incidence of co-morbid epilepsy. This supports the notion that the outcome in CDD is poorer than in autism spectrum disorders in general.

## 3. PDD-NOS

### 1) Definition of PDD-NOS

PDD-NOS is an exclusionary diagnostic category, and does not have specified rules for its application. Someone may be classified as having PDD-NOS if met criteria in the social domain plus one of the two other domains (communication or behavior). Besides, it is possible to consider the condition if the person has fewer than six symptoms in total (the minimum required for autism diagnoses), or age of onset later than 36 months.

If the agreement among clinicians is high for autism diagnoses, the same is not true for PDD-NOS.<sup>20</sup> Although the epidemiological studies have suggested that PDD-NOS is twice as more common as AD, this category continues to be understudied. Today, different categories have been proposed, some based on descriptive phenomenological approach, some based on other theoretical perspectives, such as neuropsychology.

### 2) Proposed sub-categories

#### a) The proposed clinic descriptive categories

#### i) Multiple and complex developmental disorder

Along with classical autism, related clinical pictures of developmental disorders have been described under various names starting in the 40's of the last century.<sup>21</sup> Even before the seminal Camberwell study it was clear that not all children and adolescents were aloof in their social contacts. Clinical descriptions were given of individuals who were mainly passive and avoidant in their social engagement. These individuals have been described under nosological labels such as Asperger's syndrome or schizoid disturbances of childhood referring to rigid loners. On the other hand, cases were described of children presenting social difficulties emerging from one-sided overinvolvement. These developmental conditions received labels as borderline cases in childhood,<sup>22-23</sup> symbiotic psychosis<sup>24</sup> and schizotypal children.<sup>25</sup> These conditions (characterized by impaired social sensitivity reminiscent of autism spectrum disorder, in conjunction with severe problems in the regulation of affects especially anxiety and anger and cognitive deficits in regulating imagination and thoughts) emerged as an independent group in the cluster analysis<sup>26</sup> on a large series of well-documented cases examined at the developmental unit of Yale Child Study Center by Gesell and Provenca over more than twenty years. Finding this distinct group brought Cohen et al. to propose Multiplex Developmental Disorders as a distinct category within DSM-IV alongside Autistic Disorder and Asperger's syndrome.<sup>27</sup> The proposal was not successful in the sense that Multiplex (later Multiple Complex Developmental Disorder - McDD) did not reach the threshold for inclusion in DSM-IV. Yet over the past twenty years many studies have provided support for the face and external validity<sup>28-31</sup> of this category that is well recognized in clinical practice.<sup>32</sup> The cognitive distortions named in the definition may, at closer look, reflect communicative deficits more than psychotic features in young children.<sup>33</sup>

The clinical characteristics of McDD include:

- Impaired social sensitivity
  - They are one-sided and clinging in their contacts both with adults and children;
  - They are exclusive in their relationships and will have it only their way;
  - These individuals have difficulties in social empathy tuning into others needs.
- Impaired regulation of affects
  - Anger shifts rapidly into rage;
  - Anxiety turns easily into panic.
- Cognitive distortions: thinking disorder
  - These individuals are easily confused;
  - They get carried away by their vivid grandiose fantasies;
  - They may confuse fantasy and reality;
  - They tend to have idiosyncratic logics.

Many of these children get misdiagnosed as children with conduct problems or ADHD combined with anxiety. As a matter of fact nearly half of the children with McDD display hyperactive behaviour and at times both severe externalizing and internalizing features.<sup>29</sup>

Along with severe ADHD, disruptive disorders and anxiety disorders combined as described here above, the differential diagnoses include the very rare condition of childhood schizophrenia. When looking for children with childhood

schizophrenia the NIMH team found that the majority of the children who were referred were not psychotic but displayed developmental problems that they described as Multi-Dimensionally Impaired (MDI).<sup>34</sup> MDI and McDD are practically identical when one looks closely into the criteria.<sup>35</sup> Another area of confusion is the category of bipolar disorder in childhood that has come into favour recently.<sup>36</sup> Confusing here is that the manic episodes in these children are described as short and characterized in terms of irritability and being carried away by fantasies, whereas it remains unclear whether these children will develop bipolar disorder in adolescence and adulthood.

- Treatment issues

Making the confusing clinical picture fit into a developmental condition proves helpful in many cases where school and parents are blaming each other for the misbehaviour of these children. The treatment approach should be multidisciplinary. Psycho-education for the child, parents and all involved is of great importance. Individuals with McDD respond favourably to the structured educative programs used with individuals with autism spectrum disorders. Well structured school environment and respite care are important. If these educational approaches fail to sufficiently reduce the anxiety and aggressive bouts, medication may be considered along with cognitive behavioural therapy. There are no clinical trials but in practice, as in ASD, low dosage of atypical neuroleptics eventually in combination with an SSRI may prove beneficial.

- Outcome

McDD is highly persistent. More than 60% present with a stable clinical picture in adolescence<sup>21</sup> though the mood swings are less prominent and the social deficits are more on the foreground. In adulthood a shift toward psychosis and schizophrenia spectrum disorders may occur in up to 17% of the cases making early detection and adequate treatment important in order to prevent these episodes by careful monitoring of progress.<sup>29</sup>

ii) Pathological avoidance demand disorder

Newsom after 25 years working in the Early Years Diagnostic Centre from University of Nottingham proposed a new nosographic category named pathological demand avoidance (PDA). The group is comprised by the children who were referred to as not typical AD. These children had imaginative abilities; sometimes they were unusually sociable, some of them showed odds though and communicative skills less compromised than in Asperger's syndrome. After having studied 150 cases, the author found that the most prominent characteristic was an obsessional avoidance of the daily demands. Since these kids had some degree of sociability, a major skill in social manipulation made the parents care strikingly difficult.<sup>37</sup>

These children are usually passive during the first year of life. Around the fourth year almost all of them show the demand avoidance as well the manipulative skills. These characteristics usually persist to the adulthood, although the socially manipulative behaviors tend to be milder than previously. The majority does not have sense of pride, shame, responsibility, or identity, and frequently show aggression to others. Almost all have speech delay, and continue to show abnormalities during the life, being the speech

content superficial or bizarre. Lability of mood is frequent as well as the impulsive behavior.

Obsessive behavior is related to the avoidance as well as to role-play, which gives the impression of certain sociability. These kids have general symbolic play and the majority is very attached to role-play, frequently losing the sense of reality. Interestingly, these characteristics continue until adulthood.

Today there are no neuroimage, genetic and neurobiological hypothesis for PDA. Children with this disorder do not respond well to the interventions proposed for AD. Educational and handling guidelines can be accessed at <http://www.pdacontact.org.uk/frames/index.html>

iii) Multidimensionally impaired disorder (MDI)

This subgroup, differently from the other is supposed to be closer to the psychotic disorders. These children show difficulties in differentiating fantasy from reality, including perceptual disturbances; emotional lability, inability in social relationships, processing information's deficits, no formal thoughts disturbances. Although the descriptions of these children have included some clinical features observed in ASD, their social impairments are milder than in AD, and the behavior is not as rigid and stereotyped as is presented by children in the ASD. As a whole, it was rational to propose that MDI might be a variant of very early onset of schizophrenia rather than of PDD.<sup>34</sup>

iv) Childhood schizoid disorder

Before the introduction of Asperger's syndrome to the English clinical literature by Lorna Wing, several studies describing these feature were conducted under the study name about schizoid children. They were described as solitaires, fantasists, showing special interests, and specific developmental delays, especially of language-related skills. It was not observed cognitive impairment and the comorbid used to be high.<sup>38</sup>

These cases were progressively assumed as having Asperger syndrome, maybe a subgroup with some common outcomes such as higher incidence of antisocial conduct and less social disadvantage.<sup>39</sup>

On the other hand, recent data in adults suggest that is possible to differentiate Schizoid Personality Disorder from Asperger Syndrome.<sup>40</sup> Today, the hallmark of schizoid personality disorder is the social interaction disinterest, and the operationalized criteria ask for the presence of four out of seven listed symptoms. Although studies in adults with schizoid personality disorder have suggested a childhood age of onset, there is a lack of studies focus on children, probably due to the disease classificatory manuals that "discourage" the personality diagnosis in kids.<sup>41</sup>

v) Attachment disorders

This category lies on the crossing point of two different approaches, a clinical-descriptive and a theoretical one. From psychodynamically oriented works of Spitz and Bowlby a group of children have been identified as having inappropriate responses to caregivers. A variety of phenotypes can be observed, and by definition these behaviors are related to a history of gross neglect, lack of contingent responses, and little or no attention, interaction, and affection. Currently, operationalized criteria show that two subtypes are proposed, inhibited and disinhibited.<sup>42</sup> The inhibited child does not initiate

or respond to social interactions, while the disinhibited child does in a diffuse and indiscriminate way, showing an excessive familiarity with strangers.

This category is out of the PDD chapter in the ICD-10, based on the lack of a pervasive dysfunction and a close relationship with environmental deprivations. However, the boundaries of these conditions are not clearly stated, and it can be assumed that long life damage in limbic systems might be the result of maternal deprivation<sup>43</sup> and might have a long-lasting and pervasive detrimental effect to social and communicative abilities.

b) Classifications based on other approaches

i) Nonverbal Learning Disabilities

This terminology was proposed to describe a group of patients with dysfunctions in nonverbal abilities, combined with poor visual contact, impaired gesture communication, facial expression, and prosody.<sup>44</sup> In fact, this is a proposal mainly based on neuropsychological profile, in which it should be observed a discrepancy between verbal IQ and performance IQ.

The deficits in social interaction do not seem to depend on problems associated to language, which usually seems to function normally. Ritualistic behaviors are common, as well as difficulties with mathematics, visual-motor damages, reduced nonverbal IQ, neurological motor signs in the left hemi-body, and neglect of space on the left side.<sup>45</sup>

The first reports considered this as a language developmental disorder. However, from the description of the damages involved it becomes evident that the picture is in many aspects very similar to that of the PDD, especially to Asperger's syndrome. The difference could merely be the emphasis put on the general communicative problems, or on the social interaction disturbances. According to Rourke<sup>45</sup> the disorder he studied could be characterized by the abilities present in it on the one hand, and by the damages observed on the other.

Regarding the preserved abilities, Rourke emphasizes the following neuropsychological ones:

- **Primary abilities:** motor activity (simple repetitive motor skills seem intact); auditory perception (there seems to be a deficit in this ability at the beginning, but with evolution it develops very well); memorized material (repetitive tasks, mainly those dependent on auditory assessment are very well-developed. Repetitive motor activities, including certain language aspects, and other activities such as writing can be present to an above average degree);

- **Secondary abilities:** attention (the use of attention in activities involving simple and repetitive verbal material (especially when supplied by the auditory modality) seems well developed);

- **Tertiary abilities:** memory (verbal material is easily memorized therefore this ability develops well);

- **Verbal skills:** speech and language (linguistic abilities seem to be retarded in the early stages, but they develop fast, to the extent that phonemic memory, word segmentation, repetition, and memory skills lead to a fairly large vocabulary and the possibility of making quite meaningful verbal associations. All these characteristics tend to become more evident as time goes by); academic skills (difficulties can be present in the early learning stages due to the visual-motor deficits; but the practice leads to an adequate reading and writing performance).

The neuropsychological impairments presented by these patients are:

- **Primary deficits: tactile perception** (bilateral perception deficits, with some prevalence in the left side, are usually evident but tend to decrease with time); visual perception (impaired discrimination and recognition of details and space awareness are usually present; they tend to become more evident as the years go by); complex motor activity (deficient motor coordination is commonly observed, generally prevailing in the left side. Handwriting excepted, this disability tends to worsen with age); new material (difficulties with modifications in the stimuli configuration are the rule).

- **Secondary deficits: attention** (attention to tactile and visual stimuli is deficient; sustained attention is more efficient as far as simple and repetitive stimuli are concerned and less efficient in terms of nonverbal, new, and complex stimuli); exploratory behavior (there is very little inclination to physically explore the environment; sedentary behavior and limited functional physical modes aggravate as years go by).

- **Tertiary deficits: memory** (poor for tactile and visual events; memory for nonverbal material is not good); concept building, problem solving, strategy development, hypotheses testing (important deficits are usually present in these domains); verbal deficits (discrete deficits can be observed in the oro-motor praxia, prosody, and other aspects of language).

Due to the impairments listed above, it is common to find failures in the academic learning skills and in the social as well as adaptive functions. It has been speculated that the picture of Nonverbal Disabilities could derive from an impaired right brain hemisphere as a consequence of a possible destruction/dysfunction of the white substance involved in the intermodal integration processes.<sup>46</sup>

It is important to state that this hypothesis is based on theoretical formulations that have not yet been proved. The diagnosis is based on the identification of signs and symptoms defined as characteristic. In an attempt to facilitate the diagnosis, Goldstein created a specific questionnaire, the *Children's Nonverbal Learning Disabilities Scale*.<sup>47</sup> On the other hand, as a semantic-pragmatic syndrome, it is arguable whether nonverbal learning disabilities should be regarded as an independent condition, or if they merely represent a manner to highlight one of the features present in the pictures of PDD.

#### ii) Semantic-pragmatic syndrome

The term semantic-pragmatic syndrome (SPS) was first introduced by Rapin and Allen and refers to one of the six conditions that the authors categorized and named a *medical classification* of developmental language disorders: verbal auditory agnosia; semantic-pragmatic deficit disorder; verbal dyspraxia; phonological-syntactic disorder; and lexical-syntactic deficit. These categories were established by identifying the more evident alterations in expressive language, social interaction, and verbal comprehension.<sup>48</sup>

Children with this disorder present wide-scale language impairments and generally also an initial language delay, and deficits in receptive language features followed by adequate speech learning. This learning includes the use of more complex sentences with semantic and pragmatic difficulties that becomes more evident as their verbal efficiency increases.

This diagnosis should be applied when the child does not meet the criteria for a diagnosis of autism.<sup>49</sup>

Bishop and Rosenbloom changed the term to Semantic-pragmatic Disorder (SPD) and suggested that this clinical picture was merely an accidental association of behaviors that shaded into the ASD on one hand and of normality on the other.<sup>50</sup> Even though they admitted that most children with this diagnosis would not be identified as autistic, they realized that some of them showed significant abnormalities regarding social interaction. At that time they have already noted that Asperger's syndrome patients showed a language pattern very similar to the one described in individuals with SPS, and thus they concluded that although the language and social impairments could coexist in certain cases they could be dissociated.

In a paper of 1989, Bishop discussed the limits between autism, Asperger's syndrome, and SPD and suggested that autism and the developmental language disorders were not necessarily mutually exclusive.<sup>49</sup> He suggested further a two-dimensional continuum: one dimension representing verbal communicative abilities and the second one, the other social relationships and interests. According to him, children with relatively normal communicative abilities but abnormal social relationships would have Asperger's syndrome, whereas children with virtually normal social abilities but with communicative abnormalities would have SPD.

Discrete criticism of this position was brought forth by Happé<sup>51</sup> who argued that it could be misleading to presume the inexistence of a relationship between social and communicative competence, as there are reasons to suppose that the two abilities might rely on the same cognitive mechanisms.

Some authors do not admit to set semantic and pragmatic difficulties apart from the clinical picture of autism, and they suggested that a better term to refer to these alterations would be "semantic and pragmatic difficulties" instead of SPS.<sup>52</sup> However, this should be used merely within a descriptive approach and not as a diagnostic label, since the correct diagnosis for the disordered children should be high-functioning autism.

Studies utilizing neuropsychological tests which included social cognition tests in high-functioning autistic children and children with SPS<sup>53</sup> showed clear similarities between the two groups.<sup>54</sup> In both, the authors could verify a result pattern indicative of dysfunction of the right brain hemisphere and dysfunction in social abilities. These studies also support the view that SPS would be a disorder of the autistic spectrum and would indicate that the problems relating to communicative ability could result in or be associated to an underlying cognitive failure that would not primarily be of the linguistic order.

The similarities that have been described between the communication failures observed in SPS and in patients with acquired lesions in the right hemisphere are the following ones:

- 1) Within both groups patients have difficulties for integrating information, which can compromise their verbal expression.

- 2) Both groups have intact language form, using complex and grammatically correct forms, but communication is impaired by content and use.

3) Both groups have imperfect comprehension, prosody, and use of non-verbal communication.

4) Both groups make fewer errors performing concrete and literal tasks.

5) Both groups had difficulties with assimilating and using contextual cues.

6) Both groups tend to produce literal interpretation, finding it difficult to comprehend metaphorical and figurative language as well as humor.

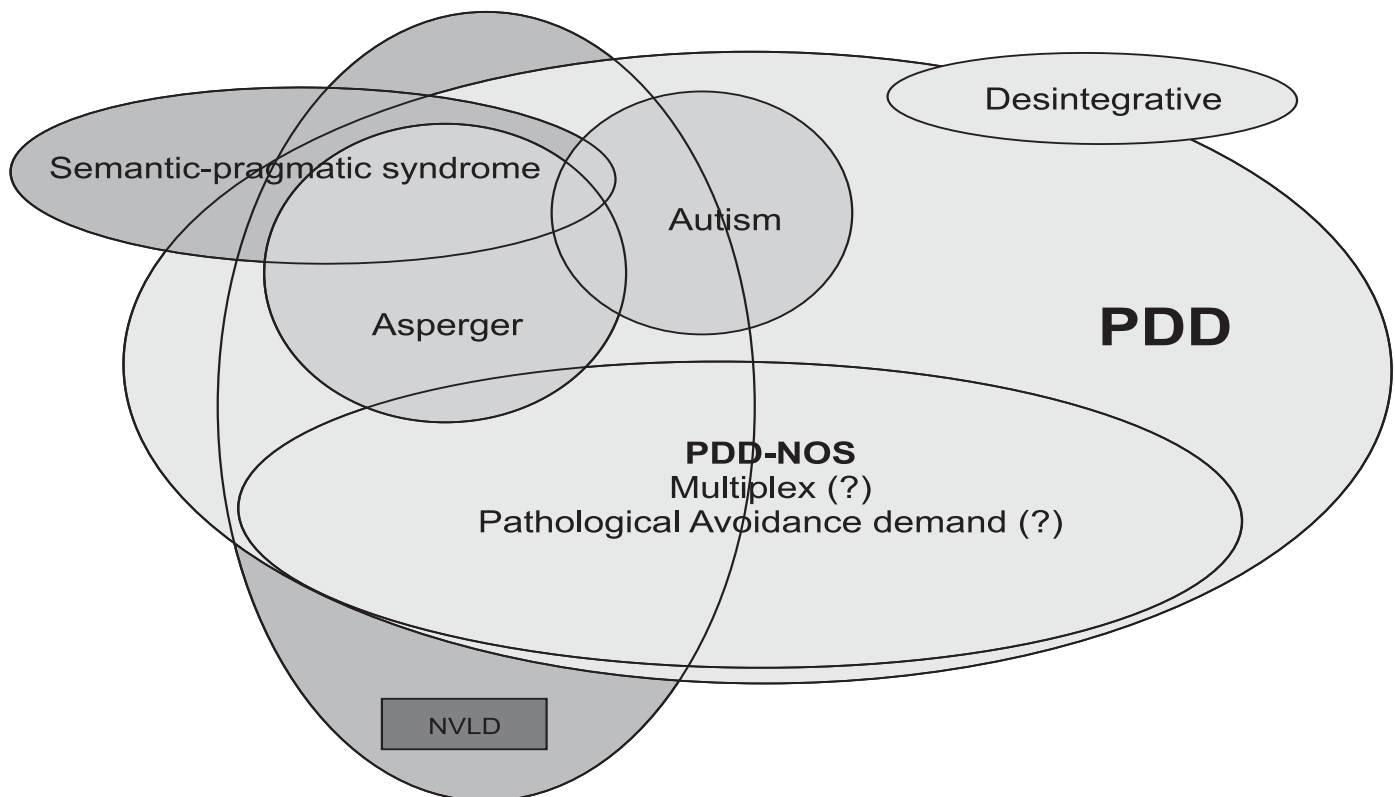
These studies also indicate that both groups do not easily admit their communication problems.<sup>53</sup> Although most works published tend to favor the view that SPS should be regarded as being part of the autistic spectrum, Rapin and Allen consider that even though SPS affects mostly autistic individuals, less frequently it can also take hold of persons with hydrocephaly, Williams' syndrome, and other forms of encephalopathy.<sup>54</sup> These authors stress the inadequacy of using the diagnosis of SPS in some cases with the single purpose of avoiding that of autism, which is less easily accepted.

Currently, the more widely held opinion among professionals working in the field of developmental disorders is to consider that SPS integrates the autistic disorder group instead of being a developmental language disorder. The use of the term "semantic and pragmatic difficulties" in a descriptive way can be an interesting means to indicate the type of communicative

difficulties found. However, it should not be used, as a diagnostic label for it may be misleading: it can raise doubts to the family and lead to therapeutic misconduct.

#### Differential diagnosis

Differential diagnosis in PDD group has some particularities. PDD are comprised by conceptual groups, such as Asperger syndrome defined according criteria that can change over time, or even under authorship.<sup>55</sup> In this sense, to make a differential among the PDD categories is not an easy task. It should be noted that along with the symptoms on Wing's trials, children with autism and related PDD show high levels of anxiety, hyperactivity and mood swings. In some cases these symptoms may meet the criteria for a comorbid ADHD, anxiety disorder or bipolar disorder. In clinical practice it is important to focus on functional analysis of the co-morbid behaviors, before starting to treat the comorbid conditions as such. On the other hand there is an overlap: children with ADHD may perform less well on Theory of Mind tests<sup>56</sup> and social anxiety may be difficult to discern from a lack of reciprocity as seen in PDD. Sometimes, the definitive diagnose has to be postponed until older ages. This should not mean that the clinician postpones interventions too. Instead of a definite diagnosis parents and teachers will have to come to terms with a diagnosis that is postulated as a working-hypothesis.



*PDD-NOS Pervasive Developmental Disorder neither other specified*  
*NVLD: Non-verbal learning disability*

**Figure 1 - Diagram of the pervasive developmental disorder categories**

The differential diagnosis between schizoid children and PDD seems to be not based on evidence, since the children who were classified as schizoid are currently identified as having Asperger syndrome.

The differential diagnosis between PDD and Schizophrenia can be done according the age of onset, early in PDD, the sex ratio (more males in PDD), family history, presence of delirious and hallucinations in schizophrenia

It is possible to identify two categories among children described as borderline personality disorder (BPD)/borderline spectrum proper, and the schizotypal personality disorder (SPD)/schizotypal spectrum. Both show transient psychotic episodes, magical thinking, intensity in fantasizing, and loss of reality sense. The BPD seems not to have familiar history, disturbance of affect, speech, social avoidance as SPD usually does. On the other hand, they show an intense and dramatic affect, and neediness of social interaction.<sup>57</sup>

### Conclusion

The non-autism PDD is comprised by two nosographically well-defined categories, including operationalized criteria (disintegrative disorder and Rett's syndrome) and one larger residual category (PDD-NOS). The current researches are trying to identify groups within PDD-NOS category. There are some clinical-based categories proposes (MCDD; multidimensionally impaired disorder; PDA; and schizoid children), and some categories that are related to assumptions of a primary etiological deficit, which would lead to behavioral phenotype (non-verbal learning disabilities, SPS, attachment disorders). It is important to note that not everyone who met criteria for non-verbal learning disabilities, SPS or attachment disorder will meet criteria for PDD (Figure 1). Notwithstanding, these comprehensive approaches have been useful in the therapeutic planning.

To further explore the impairments observed in PDD, the neuroscience researchers are studying basic functions in the three domains. Trying to travel from the observed phenotype to the measurable endophenotype, complex behaviors, such as social interactions, have been decoded in its possible origins. The study of joint attention might be an example of these initiatives. This skill refers to the capacity of coordinating attention to an object with a social partner. Several behaviors can be observed from the capacity in jointing attention, e.g.; responding joint attention, initiating joint attention, etc. These behaviors complex regulations are done by several different brain areas, which can be individually dysfunctional resulting in a broader spectrum of manifestations.

Moreover, it has been possible to identify some of the molecular mechanisms involved in the regulation of those brain regions, such as the oxytocin and vasopressin roles in the social recognition memory. With the new technologies that are arriving, it will be possible to identify the dysfunctional molecules in the different brain areas of the affected individuals. With the capability of doing this, a new nosography will be developed. From this point of view, it is reasonable to consider that in the future, new subgroups probably will also emerge from the current AD and Asperger's syndrome groups, as the new subgroups that are emerging from the current PDD-NOS.

### References

- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160(4):636-45.
- Walker DR, Thompson A, Zwaigenbaum L, Goldberg J, Bryson SE, Mahoney WJ, Strawbridge CP, Szatmari P. Specifying PDD-NOS: a comparison of PDD-NOS, Asperger syndrome and Autism. *J Am Acad Child Adolesc Psychiatry*. 2004;43(2):172-80.
- Rett A. [On a unusual brain atrophy syndrome in hyperammonemia in childhood.] *Wein Med Wochenschr*. 1966;116(37):723-6.
- Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol*. 1983;14(4):471-9.
- [No authors listed]. Diagnostic criteria for Rett syndrome. The Rett Syndrome Diagnostic Criteria Work Group. *Ann Neurol*. 1988;23(4):425-8.
- Hagberg B, Witt-Engerström J. Rett syndrome: a suggested staging system for describing impairment profile with increasing age towards adolescence. *Am J Med Genet*. 1986;1:47-59.
- Schwartzman JS. Rett syndrome. *Rev Bras Psiquiatr*. 2003;25(2):110-3.
- Schwartzman JS, Souza AM, Faiwchow G, Hercowitz LH. Fenótipo Rett em paciente com cariótipo XXY. *Arq Neuropsiquiatr*. 1998;56(4):824-8.
- Schwartzman JS, Bernardino A, Nishimura A, Gomes RR, Zatz M. Rett syndrome in a boy with a 47,XXY karyotype confirmed by a rare mutation in the MECP2 gene. *Neuropediatrics*. 2001;32(3):162-4.
- Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet*. 1999;23(2):185-8.
- Belichenko PV, Hagberg B, Dahlström A. Morphological study of neocortical areas in Rett syndrome. *Acta Neuropathol (Berl)*. 1997;93(1):50-61.
- Shahbazian MD, Young JL, Yuva-Paylor LA, Spencer CM, Antalffy BA, Noebels JL, Armstrong D, Paylor R, Zoghbi H. Mice with truncated MeCP2 recapitulate many Rett Syndrome features and display hyperacetylation of histone H3. *Neuron*. 2002;35(2):243-54.
- Mouridsen SE. Childhood disintegrative disorder. *Brain Dev*. 2003;25(4):225-8.
- Malhotra S, Gupta N. Childhood disintegrative disorder. Re-examination of the current concept. *Eur Child Adolesc Psychiatry*. 2002;11(3):108-14.
- Fombonne E. Prevalence of childhood disintegrative disorder. *Autism*. 2002;6(2):149-57.
- Dyken PR. Neuroprogressive disease of post-infectious origin: a review of a resurging subacute sclerosing panencephalitis (SSPE). *Ment Retard Dev Disabil Res Rev*. 2001;7(3):217-25.
- Davidovitch M, Glick L, Holtzman G, Tirosh E, Safir MP. Developmental regression in autism: maternal perception. *J Autism Dev Disord*. 2000;30(2):113-9.
- Zwaigenbaum L, Szatmari P, Mahoney W, Bryson S, Bartolucci G, MacLean J. High functioning autism and Childhood Disintegrative Disorder in half brothers. *J Autism Dev Disord*. 2000;30(2):121-6.
- Mouridsen SE, Rich B, Isager T. The natural history of somatic morbidity in disintegrative psychosis and infantile autism: a validation study. *Brain Dev*. 1998;21(7):447-52.



20. Volkmar FR, Klin A, Siegel B, Szatmari P, Lord C, Campbell M, Freeman BJ, Cicchetti DV, Rutter M, Kline W. Field trial for autistic disorder in DSM-IV. *Am J Psychiatry*. 1994;151(9):1361-7.
21. Van der Gaag RJ. Multiplex developmental disorder: an exploration of borderlines on the autistic spectrum [Thesis]. *Utrecht: Universiteit of Utrecht*; 1993.
22. Rosenfeld SK, Sprince MP. An attempt to formulate the meaning of the concept 'Borderline'. *Psychoanal Study Child*. 1963;18:603-35.
23. Pine F. On the Concept 'Borderline' in Children. *Psychoanal Study Child*. 1974;29:341-68.
24. Mahler MS, Furer M. Development of symbiosis, symbiotic psychosis, and the nature of separation anxiety. Remarks on Weiland's paper. *Int J Psychoanal*. 1966;47(4):559-60.
25. Nagy J, Szatmari P. A chart review of schizotypal personality disorders in Children. *J Autism Dev Dis*. 1986;16(3):351-67.
26. Dahl EK, Cohen DJ, Provence S. Clinical and multivariate approaches to the nosology of pervasive developmental disorders. *J Am Acad Child Psychiatry*. 1986;25(2):170-80.
27. Cohen DJ, Volkmar FR, Paul R. Issues in the classification of pervasive developmental disorders: history and current status of nosology. *J Am Acad Child Psychiatry*. 1986;25(2):158-61.
28. Towbin KE, Dykens EM, Pearson GS, Cohen DJ. Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. *J Am Acad Child Adolesc Psychiatry*. 1993;32(4):775-82.
29. Van der Gaag RJ, Buitelaar J, Van den Ban E, Bezemer M, Nijjo L, Van Engeland H. A controlled multivariate chart review of multiple complex developmental disorder. *J Am Acad Child Adolesc Psychiatry*. 1995;34(8):1096-106.
30. Ad-Dab'bagh Y, Greenfield B. Multiple complex developmental disorder: the 'multiple and complex' evolution of the 'childhood borderline syndrome' construct. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):954-64.
31. Jansen LM, Gispens-de Wied CC, van der Gaag RJ, van Engeland H. Differentiation between autism and multiple complex developmental disorder in response to psychosocial stress. *Neuropsychopharmacology*. 2003;28(3):582-90.
32. Green J, Jacobs B. In-patient child psychiatry: modern practice, research and the future. London: Routledge; 1998.
33. van der Gaag RJ, Caplan R, van Engeland H, Loman F, Buitelaar JK. A controlled study of formal thought disorder in children with autism and multiple complex developmental disorders. *J Child Adolesc Psychopharmacol*. 2005;15(3):465-76.
34. Kumra S, Jacobsen LK, Lenane M, Zahn TP, Wiggs E, Alagband-Rad J, Castellanos FX, Frazier JA, McKenna K, Gordon CT, Smith A, Hamburger S, Rapoport JL. Multidimensionally impaired disorder": is it a variant of very early-onset schizophrenia? *J Am Acad Child Adolesc Psychiatry*. 1998;37(1):91-9.
35. Paul R, Cohen D, Klin A, Volkmar F. Multiplex developmental disorders. The role of communication in the construction of a self. *Child Adolesc Psychiatr Clin N Am*. 1999;8(1):189-202, viii.
36. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 2005;44(9):846-71.
37. Newson E, Le Marechal K, David C. Pathological demand avoidance syndrome: a necessary distinction within the pervasive developmental disorders. *Arch Dis Child*. 2003;88(7):595-600.
38. Wolff S. 'Schizoid' personality in childhood and adult life. III: The childhood picture. *Br J Psychiatry*. 1991;159:620-9, 634-5.
39. Wolff S, Cull A. 'Schizoid' personality and antisocial conduct: a retrospective case not study. *Psychol Med*. 1986;16(3):677-87.
40. Tantam D. Lifelong eccentricity and social isolation II: Asperger's syndrome or schizoid personality disorder? *Brit J Psychiatry*. 1988;153:777-82.
41. Scheeringa MS. The differential diagnosis of impaired reciprocal social interaction in children: a review of disorders. *Child Psychiatry Hum Dev*. 2001;32(1):71-89.
42. Boris NW, Zeanah CH, Larrieu JA, Scheeringa MS, Heller SS. Attachment disorders in infancy and early childhood: a preliminary investigation of diagnostic criteria. *Am J Psychiatry*. 1998;155(2):295-7.
43. Joseph R. Environmental influences on neural plasticity, the limbic system, emotional development and attachment: a review. *Child Psychiatry Hum Dev*. 1999;29(3):189-208.
44. Rourke BP, Finlayson MA. Neuropsychological significance of variations in patterns of academic performance: verbal and visual-spatial abilities. *J Abnorm Child Psychol*. 1978;6(1):121-33.
45. Rourke BP. Nonverbal Learning Disabilities: the syndrome and the model. New York: Guilford Press; 1989.
46. Rourke BP. Introduction: the NLD Syndrome and the White Matter Model. In: Syndrome of Nonverbal Learning Disabilities. Neurodevelopmental Manifestations. New York: Guilford Press; 1995.
47. Rapin I, Allen DA. Developmental language disorders: nosological considerations. In: Kirk U. Neuropsychology of language, reading and spelling. New York: Academic Press; 1983.
48. Bishop DV. Autism, Asperger's syndrome and semantic-pragmatic disorder: where are the boundaries? *Br J Dis Commun*. 1989;24(2):107-21.
49. Bishop DV, Rosenbloom L. Childhood language disorders: classification and overview. In: Yule W, Rutter M, eds. Language development and disorders. London: MacKeith Press; 1987.
50. Happe FG. Autism: an introduction to psychological theory. London: UCL Press; 1994.
51. Aarons M, Gittens T. Semantic-pragmatic disorder (or a little bit autistic?). *College of Speech and Language Therapists Bulletin*. 1993;June:18.
52. Shields J, Varley R, Broks P, Simpson A. Social cognition in developmental language disorders and high level autism. *Dev Med Child Neurol*. 1996;38(6):487-95.
53. Brook SL, Bowler DM. Autism by other name? Semantic and pragmatic impairments in children. *J Autism Dev Disord*. 1992;22:61-81.
54. Rapin I, Allen DA. The semantic-pragmatic deficit disorder: classification issues. *Int J Lang Commun Disord*. 1998;33(1):82-7, discussion: 95-108.
55. Volkmar FR, Klin A, Pauls D. Nosological and genetic aspects of Asperger syndrome. *J Autism Dev Disord*. 1998;28(5):457-63.
56. Buitelaar JK, van der Wees M, Swaab-Barneveld H, van der Gaag RJ. Theory of mind and emotion-recognition functioning in autistic spectrum disorders and in psychiatric control and normal children. *Dev Psychopathol*. 1999;11(1):39-58.
57. Petti TA, Vela RM. Borderline disorders of childhood: an overview. *J Am Acad Child Adolesc Psychiatry*. 1990;29(3):327-37.