



# Whatever happened to multiple complex developmental disorder?

Çoklu karmaşık gelişimsel bozukluğa ne oldu?

Annio Posar<sup>1,2</sup>, Paola Visconti<sup>1</sup>

<sup>1</sup>IRCCS Institute of Neurological Sciences of Bologna, Child Neurology and Psychiatry Unit, Bologna, Italy

<sup>2</sup>Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

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## Abstract

Multiple complex developmental disorder is characterized by early-onset combined impairment in the regulation of affective states, in the social behavior, and in the thought processes. First described in the Eighties, so far multiple complex developmental disorder has so far not found recognition as an autonomous nosographic entity in international classifiers. In the past, the most common diagnosis for patients presenting with this clinical picture was that of 'pervasive developmental disorder not otherwise specified,' due to the early-onset impairment in various development areas, including the social functioning, with pervasive characteristics. Over recent years, based on literature data, the interest in multiple complex developmental disorder has seemed to decline. Yet, several clinical and neurobiological findings emerging from the literature seem to support the nosographic autonomy of multiple complex developmental disorder. The correct recognition of this clinical picture appears to be of considerable importance because children who are affected seem to be predisposed to develop a schizophrenia spectrum disorder during their lifetime. Multiple complex developmental disorder could be a very interesting entity, being a possible kind of "bridge" condition between autism spectrum disorder and childhood-onset schizophrenia. However, there is a lack of findings of the real recurrence, neurobiologic background, and course of this clinical picture.

**Keywords:** Autism spectrum disorder, childhood, multiple complex developmental disorder, psychosis, schizophrenia

## Öz

Çoklu karmaşık gelişimsel bozukluk, duygulanım halleri, sosyal davranış ve düşünme süreçlerinin düzenlenmesinde erken başlangıçlı bozuklukla belirgindir. İlk olarak 1980'li yıllarda tarif edilmiş olan çoklu karmaşık gelişimsel bozukluk, bugüne kadar uluslararası sınıflandırıcılar tarafından özerk bir nozografik antite olarak tanınmamıştır. Geçmişte, bu klinik tablo ile başvuran hastalar için en sık konulan tanı, sosyal işlevsellik gibi çeşitli gelişim alanlarında yaygın özellikler gösteren erken başlangıçlı bozukluğa bağlı olarak 'yaygın gelişimsel bozukluk, başka yerde tanımlanmamış' olmuştur. Son yıllar içinde, dizin verilerine göre, çoklu karmaşık gelişimsel bozukluğa ilgi azalmış görünmektedir. Ancak, dizinden ortaya çıkan bazı klinik ve nörobiyolojik bulgular, çoklu karmaşık gelişimsel bozukluğun nozografik özerkliğini destekliyor görünmektedir. Bu klinik tablonun doğru olarak tanınması dikkate değer derecede önem taşımaktadır, çünkü etkilenen çocuklar yaşam boyu şizofreni spektrum bozukluğu geliştirmeye yatkın görünmektedirler. Çoklu Karmaşık Gelişimsel Bozukluk, otizm spektrum bozukluğu ile çocukluk dönemi başlangıçlı şizofreni arasında muhtemel bir "köprü" durumu olarak çok ilginç bir antite olabilir. Ancak, bu klinik tablonun gerçek nüksü, nörobiyolojik zemini ve seyri ile ilgili bulgular yeterli değildir.

**Anahtar sözcükler:** Çocukluk, çoklu karmaşık gelişimsel bozukluk, otizm spektrum bozukluğu, psikoz; şizofreni

## Introduction

The early-onset clinical picture characterized by the combined impairment in the regulation of affective states (leading to intense anxious symptomatology), in the social behavior (withdrawal, aggressiveness), and in the thought

processes (magical thinking) is a long-known phenomenon. In the past, these patients were diagnosed as having 'borderline syndrome of childhood' or 'childhood schizotypal disorder' (1). In 1986, Cohen et al. (2) proposed the name 'multiplex developmental disorder' for these conditions, in 1993 modified by Towbin et al. (3) as 'multiple

Corresponding Author/Sorumlu Yazar: Annio Posar E-mail/E-posta: annio.posar@unibo.it

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**Table 1. Research criteria for Multiple Complex Developmental Disorder according to Buitelaar and van der Gaag (1998)**

1. Impaired regulation of affective state and anxieties:
  - a. Unusual or peculiar fears and phobias, or frequent idiosyncratic or bizarre anxiety reactions
  - b. Recurrent panic episodes or flooding with anxiety
  - c. Episodes of behavioral disorganization punctuated by markedly immature, primitive, or violent behaviors
2. Impaired social behavior:
  - a. Social disinterest, detachment, avoidance, or withdrawal
  - b. Markedly disturbed and/or ambivalent attachments
3. The presence of thought disorder:
  - a. Irrationality, magical thinking, sudden intrusions on normal thought process, bizarre ideas, neologism, or repetition of nonsense words
  - b. Perplexity and easy confusability
  - c. Overvalued ideas, including fantasies of omnipotence, paranoid preoccupations, over engagement with fantasy figures, referential ideation

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A total of five (or more) items from (1), (2) and (3), with at least one item from (1), one item from (2), and one item from (3)

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complex developmental disorder' (MCDD). Cohen et al. (2) suggested specific diagnostic criteria and considered this clinical picture as an intermediate between pervasive developmental disorders (PDDs) (4), indicatively corresponding to what today are called 'autism spectrum disorders' (ASDs) (5), and 'specific developmental disorders' (see learning and language/speech disorders) (4). Unlike autism, in MCDD, cognitive functioning is generally normal or only mildly retarded (2). Table 1 shows the research criteria for MCDD according to Buitelaar and van der Gaag (6). After 1986, the most common diagnosis for patients with MCDD was that of 'pervasive developmental disorder not otherwise specified' (PDDNOS), due to the early-onset impairment in various development areas, including social functioning, with pervasive characteristics (1). According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (7), PDDNOS was, in the context of PDDs, a residual category including, in particular, atypical autism, which did not meet the 'autistic disorder' (AD) (classic autism) criteria due to late-onset, atypical symptomatology, and/or subthreshold symptomatology. Follow-up studies suggested that MCDD could turn into a schizophrenia spectrum disorder (SSD): 22% of adolescents and 64% of young adults with a previous diagnosis of MCDD were affected by a SSD (8). Therefore, to detect early this type of evolution, patients with MCDD require careful clinical monitoring (9).

Prevalence of MCDD is not known: it is likely to be relatively low, but not negligible. For example, in a population of 101 children with 'high-functioning' pervasive developmental disorder (according to DSM-IV-TR criteria) (7), 8 cases (7.9%) also met the clinical criteria for MCDD (10). Among 491 children aged 6-12 years who were referred between July 2002 and September 2004 to an outpatient

department of child and adolescent psychiatry (Erasmus Medical Center Rotterdam, the Netherlands), 29 (5.9%) met research criteria for MCDD (1). So far, MCDD has not found recognition as an autonomous nosographic entity in international classifiers and has not been included even in the most recent DSM edition, namely the DSM-5 (5). It would, therefore, be important to check the limits between the MCDD and ASD as it is considered today according to the latest DSM version.

In this review, we aimed at evaluating the hypothesis that MCDD deserves to be considered as a distinct nosographic entity. We considered the most relevant papers, including reviews, among those published about MCDD till August 2019, available on PubMed (United States National Library of Medicine); we used the following keywords: multiple complex developmental disorder.

#### **MCDD: Clinical findings**

Van der Gaag et al. (11), using a factor analysis, found that the most characteristic factors in 105 children with MCDD pertained to psychotic thinking and anxiety, while in 32 children with autistic disorder pertained to lacking interaction and communication, as well as stereotyped and rigid behavior (note that all the considered subjects had an IQ>70). Therefore, the authors suggested the need for considering MCDD as a separate subcategory. From a clinical point of view, it is very important to keep in mind that one of the most noteworthy features in children with MCDD are the remarkable fluctuations in their functioning, as opposed to the stability in the functioning characteristic of children with AD (12). However, it should be taken into account that an impairment of formal thought, attributed to inadequacy of communication skills, has been reported both in patients with MCDD and AD (13).

If distinguishing MCDD and classic autism may appear relatively easy, differentiating between MCDD and a less defined clinical picture such as PDDNOS (see Introduction) seems to be more difficult due to an overlap between these two conditions. Earlier papers suggested that about half of children with MCDD also met the criteria for PDDNOS (3). However, the presence of significant clinical differences between MCDD and PDDNOS groups would support the concept of MCDD as being a distinct nosographic entity, with obvious implications at the level of etiology, prognosis, and treatment that should be studied irrespective of PDDNOS. Concerning the therapeutic level, if MCDD has to be considered as a PDDNOS subgroup, the treatment should focus primarily on improving social skills, whereas if MCDD has to be considered as a separate picture, the importance of thought disorder (with its implications for the development of SSD) and of anxiety symptoms would suggest a more medication-focused therapeutic approach (14).

De Bruin et al. (1) aimed to recognize behavioral differences between 25 children with MCDD and 86 children with PDDNOS. They found that children with MCDD showed social contact problems, but to a lesser extent than children with PDDNOS. On the other hand, children with MCDD presented with more anxiety, disruptive behavior (oppositional defiant disorder, conduct disorder), and psychotic thought problems (including paranoia, loose associations, and delusions) than children with PDDNOS. The authors concluded that MCDD could be distinguished from PDDNOS and should not inevitably be included among the PDDs. In this respect, it is no coincidence that only 11 out of these 25 children with MCDD also fulfilled the PDDNOS criteria, suggesting that MCDD might also be a disorder in itself (1).

Among the papers that dealt with the topic of the clinical differentiation between MCDD and PDDNOS, we must mention the article of Herba et al. (14), which compared 21 children with MCDD and 62 children with PDDNOS based on two important aspects of social cognition: face recognition and facial expression identification, respectively. Children with PDDNOS showed a strategy of face processing that was more attention-demanding, and they processed neutral faces more similarly to complex patterns, whereas children with MCDD presented with an advantage for face recognition in comparison with complex patterns. The disadvantages of face recognition in patients with PDDNOS appeared to be related more to their autistic features rather than to MCDD-specific characteristics. No significant differences between the MCDD and PDDNOS groups emerged for facial expression identification.

Van Rijn et al. (15) compared 24 children with PDDNOS, subtype MCDD, and 23 children with PDDNOS based on executive function skills. They found significant differences to the disadvantage of children with MCDD in various measures of executive functions. The results of this study suggest impairment of attention regulation and of inhibitory control in children with MCDD, which may explain the relevant thought problems that are often detected in these patients. According to the authors, the data emerged from this study underline the appropriateness of defining the MCDD subtype within the heterogeneous PDDNOS group, as a subgroup of children with marked impairment of the ability to regulate emotion, behavior and thought, which may result in psychotic disorders.

#### **MCDD: Neurobiological findings**

Lincoln et al. (16) found that children with MCDD differed from children with attention-deficit/hyperactivity disorder (ADHD) in internalizing and externalizing behaviors' prevalence, neuropsychological deficits connected to auditory processing, and (this is particularly remarkable in our opinion) event-related potential (ERP) brain physiology connected to auditory cognitive target attention tasks. The authors concluded that some part of the MCDD pervasive pathology might be related to biologic deficits, specifically the impairments of auditory processing.

Kemner et al. (12) used ERPs to evaluate if MCDD and autism should be distinguished. They measured ERPs in response to stimuli in a visual oddball task in five groups of children: 50 with AD, 16 with MCDD, 43 with ADHD, 30 with dyslexia, and 50 normal controls, respectively, to check if ERP peaks could help to distinguish children with AD and children with MCDD. The authors found that the P300 (a late positive peak) at four different leads and the frontal Nc (a late negative wave) were different among the five groups, and that the AD and MCDD groups showed differences between each other, as well as from the other three groups. The authors concluded that ERP findings suggested that AD and MCDD might differ in the underlying pathology and be considered as two distinct diagnostic entities.

Lahuis et al. (17), using electro-oculography, studied smooth pursuit eye movement (pursuit gain and saccadic parameters) in 18 children with MCDD, in 18 children with AD, in 36 controls matched for age and total IQ, in 14 adults with schizophrenia, and in 17 adult controls, respectively. As expected, the authors found a lower velocity gain as well as an increased frequency of saccades in patients with schizophrenia. Also, children with MCDD showed a velocity gain that was lower than in the control

children. On the contrary, the velocity gain was similar in subjects with AD and controls. However, there were no significant differences for velocity gain in a direct comparison between the MCDD and AD groups, even though the mean values suggest a reduced average gain in children with MCDD. There were no significant differences from the controls for saccadic parameters in either the MCDD or AD groups. The authors underlined that children with MCDD, like adults with schizophrenia, showed a decreased velocity gain, which could suggest the presence of a common neurobiologic background for schizophrenia and MCDD.

Another electrophysiologic study, performed by Oranje et al. (18), found no significant differences in sensory and sensorimotor gating (see filtering of stimuli) between 14 children with MCDD, 13 with AD, and 12 normal controls, matched for age and performance IQ. The authors came to this result assessing the prepulse inhibition of the acoustic startle reflex and gating of the auditory evoked potential (P50 suppression). As suggested by the authors themselves, because deficits of sensory gating are considered as possible endophenotypic markers of schizophrenia, the data that emerged from this study do not support a close link between MCDD and schizophrenia.

Jansen et al. (19) studied in a MCDD group the finding of a decreased cortisol response to stress reported in autistic-like cases. The authors evaluated the responses to a psychosocial stressor (speaking in public while video-recorded) in 10 children with MCDD and 12 healthy control children, respectively. Hypothalamic-pituitary-adrenal responses were assessed in salivary cortisol every about 20 minutes, and the heart rate was monitored continuously. Heart rate ( $p < 0.01$ ) and salivary cortisol ( $p < 0.05$ ) variations were significantly higher in controls than in children with MCDD. The authors hypothesized that the unresponsiveness to psychosocial stress of children with MCDD might be due to their difficulties in reacting appropriately to the social environment and might be a vulnerability factor to developing schizophrenia. Unfortunately, in this study, there was no control group of patients with autism who presented with more social impairments than children with MCDD. This last gap was filled a few years later by Jansen et al. (20), who compared the response to a psychosocial stressor (again speaking in public while video-recorded) between 10 children with AD, 10 children with MCDD, and 12 healthy control children. Children with AD had a relatively high cortisol response, and children with MCDD showed a decreased cortisol response. The authors concluded that the different cortisol response to psychosocial stress between children with AD and

MCDD suggests the presence of distinct biologic backgrounds of the abnormal social behaviors observed in these patients.

Assuming that MCDD is a phenotypically definite PDDNOS subtype, to study the MCDD neurobiologic specificity, Lahuis et al. (21) examined brain morphology using structural magnetic resonance imaging (MRI) measures in 22 high-functioning children with MCDD compared with 21 high-functioning children with AD and 21 matched typically developing controls. Compared with the controls, children with MCDD had an enlargement in the cerebellum, as well as a trend towards larger grey-matter volume, and they showed a smaller intracranial volume than subjects with AD. The pattern of brain volumetric changes reported by Lahuis et al. in subjects with MCDD is similar to that described in autism, but no head size enlargement was found in MCDD. Therefore, only some of the MCDD neurobiologic changes overlap with those found in autism, suggesting the presence of different developmental trajectories in these two groups. The lack of head size enlargement in MCDD suggests that MCDD onset may be later than that found in autism. This finding would be confirmed by clinical experience because parents of children with MCDD often report a later onset of symptoms.

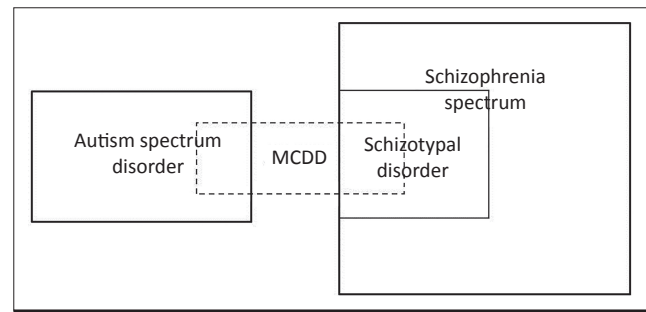
## Discussion

Several clinical and neurobiologic findings emerging from the literature seem to support the hypothesis that MCDD is a distinct nosographic entity. However, there is a lack of findings of the real recurrence, neurobiologic background, and course of MCDD. In the concept of MCDD, the emphasis was placed on impairment in affective state regulation, on thought problems, and on abnormal social behavior. Based on literature data, in the comparison between MCDD and ASD, impairment in affective state regulation and thought problems seem to prevail in MCDD, whereas abnormal social behavior seems to prevail in ASD. It remains an open issue if all MCDD cases should be included in the category of ASD. As an alternative hypothesis, a portion of the MCDD cases could be allocated on a continuum between ASD and specific developmental disorders (including, for example, developmental language disorders) (6).

Between the 1980s and 1990s, the concept of MCDD undoubtedly raised interest and discussions among the experts of neurodevelopment, even though most of the work on MCDD was performed in the Netherlands (22). Nevertheless, it is a fact that papers dealing with MCDD have become rare in recent years, as if the interest in this condition had faded before even realizing its actual

boundaries. Based on our personal experience, there are effectively several patients who closely resemble those affected by MCDD according to the criteria of Buitelaar and van der Gaag (6). These patients show some features on the neuro-behavioral phenotype (see in particular the impairment of affective state regulation and the thought disorders) that distinguish them from subjects affected by ASD, even though not infrequently MCDD has been diagnosed as PDDNOS (atypical autism). Specifically, are there any solid reasons to create (or maintain) the MCDD diagnostic category, distinct from ASD? This is a question for which the answer is still far from easy.

There are currently no adequate prognostic studies that will tell us whether these subjects do or do not have a different developmental trajectory than those with ASD and their outcome in adulthood is not well known. In this regard, it has been suggested that children with MCDD have an increased risk of developing SSDs throughout life (6, 8), and thus they require careful clinical monitoring. Conversely, the development of schizophrenia is rare in ASD, although not impossible. Further, unlike ASD, studies concerning possible medical comorbidities for patients with MCDD are substantially lacking. Regarding this topic, we found no systematic studies but only anecdotal reports: see for example the boy with MCDD who had a 22q11 deletion syndrome (otherwise known as velo-cardio-facial syndrome) reported by Scandurra et al. (23), or the boy with MCDD who presented with a left temporo-polar arachnoid cyst with a mass effect on the temporal lobe described by Vaivre-Douret et al. (24). In particular, it would be interesting to evaluate what emerges from the CGH-array of patients with MCDD, given the progress that this genetic technique has allowed over the last years in the etiologic diagnosis of developmental disorders in general and ASD in particular. In addition, in our opinion, MCDD could be a very interesting entity also for research purposes, being a possible kind of 'bridge' condition (22) between ASD and childhood-onset schizophrenia. These last two nosographic entities have been considered conceptually well distinct or even mutually exclusive for a long time: see for example the original report of Kanner (25) about early infantile autism that, despite the noteworthy similarities the author considered in many respects different from childhood schizophrenia, as well as the DSM-III diagnostic criteria for infantile autism that include also the "Absence of delusions, hallucinations, loosening of associations, and incoherence as in Schizophrenia" (4). However, in recent years it has been seen that they actually have overlapping points and can even coexist in the same patient. In this perspective, MCDD could be, at least in the developmental age, the link between ASD



**Figure 1.** This scheme summarizes the possible nosographic location of Multiple Complex Developmental Disorder (MCDD), using the terminology of the DSM-5 (American Psychiatric Association, 2013), where the MCDD is not present: see text for details. Please note that the dimensions of the rectangles are purely indicative

and childhood-onset schizophrenia. Using the terminology of DSM-5, where (as mentioned) MCDD is not present (5), the possible location of the MCDD diagnostic category could be represented as in Figure 1. On the one hand, there is a partial overlap of MCDD with ASD, with which it shares an impairment of social behavior (albeit less severe); on the other hand, there is a partial overlap with the schizophrenia spectrum, and in particular with an early-onset schizotypal personality disorder (see thought disorders).

Moreover, it should be taken into account that, with respect to the time when MCDD was initially described and discussed among specialists, the DSM classification has been greatly modified and in particular since 2013, with the advent of DSM-5, no longer includes the presence of several diagnostic subcategories within autism, but only the all-encompassing category of ASD with 3 levels of severity (5). It would, therefore, be important to check the limits between MCDD and ASD as the latter is today considered according to the latest DSM version. It is likely that a consistent number of patients with MCDD would be diagnosed as having ASD according to DSM-5 criteria, but this is only a hypothesis that requires to be verified. Currently, many questions about MCDD remain open, and we need further research about this topic (26).

## Conclusions

We hope for a reawakening of interest in MCDD, because, in our opinion, the real potential of this interesting nosographic entity has not yet been fully evaluated, both for assistance purposes and for research purposes. If this paper were to stimulate the debate on MCDD, this could be the sign that there might be a revival of interest in it. Otherwise, the concept of MCDD is likely destined to become lost to obscurity.

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