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RESEARCH REPORT

Onset of psychiatric signs and impaired neurocognitive domains in inherited metabolic disorders: A case series

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Abstract

Inherited metabolic disorders (IMDs) can present with psychiatric signs that vary widely from one disease to another. This picture is further complicated by the fact that these features occur at very different illness time points, which may further delay appropriate diagnosis and treatment. In this case series of 62 children and adolescents suffering from IMDs, we clustered psychiatric signs (on the basis of the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders classification) as well as impaired cognitive domains (on the basis of the Research Domain Criteriamatrix) according to their mean age of onset (5.7 ± 4 years). We observed consistent patterns of occurrence across disorders. Externalizing symptoms, sleep problems, and cross-domain self-regulation deficits were found to precede the IMD diagnosis. Repetitive thoughts and behaviors as well as emotional dysregulation were found to occur around the disease onset. Finally, late-onset features included dissociative or eating disorders, together with impaired emotion knowledge. Clinicians should specifically look for the co-occurrence of age-specific atypical signs, such as treatment resistance or worsening with psychotropic medication in the earliest stages and symptom fluctuation, confusion, catatonia, or isolated visual hallucinations. We believe that the combined characterizations of psychiatric signs

François Medjkane, Marine Bohet, Dries Dobbelaere, and Renaud Jardri contributed equally to this study.

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and impaired neurocognitive domains may enable the earliest detection of IMDs and the appropriate care of these particular manifestations.

Key Points

- Psychiatric signs are common in inherited metabolic disorders (IMDs) and may occur in the same age-range as other clinical manifestations.
- Three clusters of psychiatric signs and two clusters of neurocognitive domains can be defined according to their mean age of onset.
- Warning signs to be used in liaison psychiatry should include age-specific cognitive impairments

KEYWORDS

cognition, development, DSM, psychiatry, rare disease, RDoC

1 | INTRODUCTION

Inherited metabolic disorders (IMDs) represent a vast and heterogeneous collection of genetic conditions that impact the normal functioning of systemic biochemical processes.¹ More than 800 rare genetic diseases fit this definition. When considered in isolation, each of these IMDs is quite rare, but together, they may affect at least 3.5% to 5.9% of the worldwide population.² Early detection of IMD appears to be critical as late diagnosis can lead to severe neurodevelopmental degeneration and death.³ In contrast, if recognized early, some IMDs may benefit from specific treatments that allow prevention or stabilization of the clinical condition; some conditions may even reach partial recovery.⁴⁻⁶ An example is phenylketonuria, which is systematically screened for at birth and treated with a specific diet to prevent neurodevelopmental consequences. It is now well known that metabolic defects can deeply impact physiological central nervous system functioning, but despite such awareness, the exact place for psychiatric assessment in diagnosis strategies remains unclear.

Because psychiatric manifestations of IMDs are wrongly considered late onset, there is a risk that first psychiatric manifestations will be overlooked. This does not mean that all of psychiatric signs reported in IMDs occur during childhood, but that most of them will and that they can even be the only symptoms for many years.⁶ Because they occur within the same age range, psychiatric manifestations of IMDs constitute an accurate phenocopy of major childhood mental disorder categories (eg, attentional deficit with or without hyperactivity, neurodevelopmental disorders including autism, mood disorders, psychosis, or anxiety), further delaying adequate care.

Interestingly, several attempts have been made to increase medical condition recognition in childhood

psychopathology. First, some authors have proposed atypical signs or red flags in the context of acute psychosis, such as catatonia or cognitive regression.^{7,8} Second, causality scores have been developed to better select young patients with a higher probability of medical conditions.^{9,10} Third, some experts have recently emphasized the need to move from conventional categorical diagnoses to more translational domains in the characterization of rare genetic disorders in psychiatry.¹¹ Such a translational approach aims to better capture the full spectrum of phenotypic severity in rare diseases and improve the understanding of their neurodevelopmental origin across disorders.

Of course, some medical aspects are crucial, and it appears to be clinically useful to group IMDs according to their onset and course: (a) clinical emergencies, characterized by an acute episode followed by recurring episodes of confusion (eg, urea cycle disorders and porphyria); (b) chronic treatable diseases (eg, Wilson disease and some lysosomal storage disorders); and (c) chronic less-treatable diseases (eg, homocystinuria and late-onset metachromatic leukodystrophy). However, a more dimensional approach may also help clinicians from different fields assess and manage psychiatric manifestations, even in the earliest stages of these disorders.

To investigate the potential discriminant values of both psychiatric signs and dimensions, we took advantage of the data from a series of children and adolescents with IMDs referred to the Lille University Reference Center for Inherited Metabolic Diseases (G2 MLille). To do so, we retrospectively explored medical records not only for psychiatric signs, which are known to vary widely across IMDs but also for neurocognitive trait distribution over time, both in accordance with recent nosological systems (ie, the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5¹²) and the

TABLE 1 Diagnostic list of the 1994-2010 case series from the Lille University Reference Center for Inherited Metabolic Diseases, with respective gene(s), OMIM entries, frequency, and counts for psychiatric signs

Etiological Categories	Gene (inheritance): OMIM	Prevalence in the sample, n (%)	Current freq. of psych. signs, n (%)	Previously reported freq. psych. signs (%)
Urea cycle disorders	OTC (<i>X-linked R</i>): 311 250	15 (24.2%)	8 (53.3%)	21 ¹⁵
Hyperammonaemia due to NAGS deficiency	NAGS (<i>AR</i>): 237 310	1	1 (100%)	NA
Wilson disease	ATP7B (<i>AR</i>): 277 900	2	1 (50%)	51 ¹⁶
Homocystinurias	CBS (<i>AR</i>): 236 200	5 (8.1%)	3 (60%)	64 ¹⁷
Acute intermittent porphyria	HMBS (<i>AD</i>): 176 000	2	0	30 ¹⁸
Niemann-Pick C disease	NPC1, NPC2 (<i>AR</i>): 257 220	2	1 (50%)	40 ¹⁹
Neonatal adrenoleukodystrophy	PEX (<i>AR</i>): 202 370, 266 510, 601 539	3 (4.8%)	1 (33.3%)	NA
Propionic aciduria	PCCA, PCCB (<i>AR</i>): 606 054	2	0	21 ²⁰
Fabry disease	GLA (<i>X-linked R</i>): 301 500	5 (8.1%)	0	4 ²¹
X-linked adrenoleukodystrophy	ABCD1 (<i>X-linked R</i>): 300 100	2	1 (50%)	50 ²²
Hexosaminidase A deficiency	HEXA (<i>AR</i>): 272 800	1	0	40 ²²
Alpha mannosidosis	MAN2B1 (<i>AR</i>): 248 500	1	0	25 ²³
Neuronal ceroid lipofuscinoses	CLN3, CLN8 (<i>AR</i>): 204 200, 600 143	4 (6.5%)	3 (75%)	74 ²⁴
Mucopolysaccharidosis type II	IDS (<i>X-linked R</i>): 309 900	3 (4.8%)	3 (100%)	NA
Mucopolysaccharidosis type III	SGSH, NAGLU (<i>AR</i>): 252900, 252 920	4 (6.5%)	4 (100%)	NA
Nonketotic hyperglycinemia	GLDC, AMT (<i>AR</i>): 605 899	2	2 (100%)	38 ²²
Smith-Lemli-Opitz syndrome	DHCR7 (<i>AR</i>): 270 400	4 (6.5%)	4 (100%)	NA
MELAS syndrome	Unknown (<i>MA</i>): 540 000	4 (6.5%)	3 (75%)	NA
Total		62	36 (58%)	

Note: The general frequency of psychiatric signs for each disease (when available) is provided in the right column (readers should notice that we did not consider isolated *mental retardation* as a psychiatric sign).

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MI: mitochondrial inheritance; NA, not available; NAGS: N-acetylglutamate synthase; X-linked R, X-linked recessive.

National Institute of Mental Health Research Domain Criteria (Research Domain Criteria [RDoC]¹³). Our aim was to determine whether we could use psychiatric signs

and cognitive domains to narrow the differential diagnosis for first-line health care providers who may consult on patients with psychiatric manifestations.

2 | METHODS

2.1 | Participants and data extraction

We retrospectively collected data from the medical records of all children and adolescents born between 1994 and 2010 and followed-up at the G2 MLille Center. These data were anonymously used in accordance with GDPR European legislation and after collecting written consent from the patients and their parents. Patients referred to the G2 MLille Center are notably assessed using a multidisciplinary work-up that includes neuro-pediatric and psychiatric assessments and a systematic psychological and neurocognitive exploration. We created a grid for data extraction that listed all the retained variables of interest (see Section 2.2). For each of these variables, we indicated their occurrence time in relation to the time of diagnosis. To ensure the validity of data extraction, two authors (M. I. and D. D.) first extracted the data from all medical records. In cases of disagreement, the other senior authors (R. J. and F. M.) were consulted.

2.2 | Variables of interest

The first extracted variable of interest was the presence/absence of psychiatric signs according to the DSM-5 classification during the course of the IMD (these criteria were revised within the study timeframe and were retrospectively applied to the medical report descriptions). Psychiatric signs could have been observed during acute or more stabilized stages of the disorders. We also collected descriptive data regarding medical history, clinical examinations, and complementary investigations, as well as the personal-family context. We notably gathered the following data: (a) the age at the onset of the first psychiatric and nonpsychiatric signs (to specify an acute or a progressive onset as well as the primary or secondary nature of the symptoms); (b) the presence of trigger factors; (c) the presence of previously described atypical clinical features⁶ (ie, catatonia, unimodal visual hallucinations, delirium, clinical fluctuations and cognitive regression); and finally (d) the therapeutic management and response (including the propensity to experience side effects or worsening under psychotropic medications after 4 weeks of continuous treatment) and follow-up information.

Based on systematic psychological and neurocognitive assessments, we further reported the presence/absence of a particular deficit among four constructs previously linked with developmental psychopathology¹⁴ based on the RDoC framework, that is, the delay of gratification

(the ability to delay hedonically attractive rewards), the regulation of frustration (the ability to modulate or adjust the intensity of the affective response to frustration), executive control (the ability to deploy attention and inhibit some responses, based on Wechsler IQ scale subtests), and finally, emotion knowledge (the ability to understand emotional expressions and social contexts).

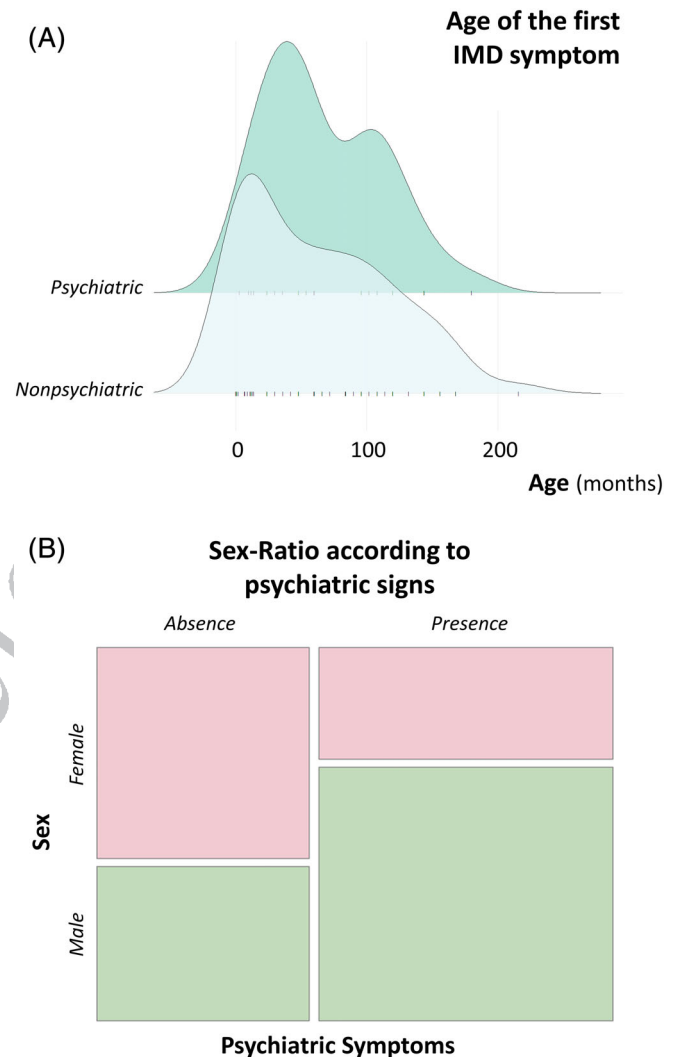


FIGURE 1 Sociodemographic of children and adolescents referred to the Lille University Reference Center for Inherited Metabolic Diseases (IMDs, $n = 62$). A, Comparative age distribution of the first psychiatric (dark green) and nonpsychiatric (light green) symptoms in IMD patients. The mean age of onset for psychiatric and nonpsychiatric signs in children with IMDs is similar. On average, nonpsychiatric symptoms are first diagnosed at 5.2 ± 4.6 years old, while the first psychiatric signs are reported at 5.6 ± 3.7 years old. B, Mosaic plot of sex distribution according to the presence/absence of psychiatric signs. Males with IMDs (green) exhibited psychiatric signs more often than females with IMDs did (pink, $P = .03$). This corresponds to a 2.3 male-to-female sex ratio for IMDs with psychiatric signs vs a 1.4 female-to-male sex ratio among those without such clinical features

2.3 | Statistical analyses

Statistical analyses were performed using R software for statistical computing v3.6.1, including the *jmv*, *ggplot*, and *ggridges* libraries. The sample was first described based on symptom frequency rates and the visualization of symptom distribution over time. Due to nonnormality, we used nonparametric tests for statistical comparisons. Continuous variables were compared using Welch's *t* tests or Wilcoxon rank tests (for independent and paired samples, respectively). Dichotomous variables were compared using chi-squared tests. Significance was assigned to a *P* value below .05.

3 | RESULTS

A total of 62 children and adolescents with rare IMDs were included in the series. The etiological distribution of this sample is summarized in Table 1. On average, the diagnosis of an IMD was made at 5.2 years old (SD = 4.6, ranging from birth to 18 years old). In total, 36 (58%) children and adolescents exhibited multiple psychiatric signs

during follow-up. In 11 (31.4%) of these children, psychiatric signs were present at onset, and in 15 (42.9%) patients, they even preceded the IMD diagnosis. Among the 29 patients described as having a progressive onset, 6 exhibited acute psychiatric manifestations. Regarding trigger factors, hypercatabolic episodes (ie, intense physical activity, infections) or nonobservance of the increased protein diet in patients at risk for hyperammonemia were identified. Some alerting signs that are regularly described as atypical in psychiatric disorders were also reported with a high prevalence; these included isolated visual hallucinations (17.1% vs 12.5% in the general pediatric population²⁵), delirium (28.5% vs 21% on average in children hospitalized in ICU independently of IMDs), symptom fluctuations (54.3%), and inefficacy or poor tolerance of psychotropic drugs (42.9%, 9/21 who received such medication).

We found no significant difference in the mean age at diagnosis between the IMD patients with or without psychiatric features in this sample ($n = 62$, mean age: 69.9 ± 60.3 and 52 ± 47.6 months in patients with or without psychiatric signs, respectively, $t_{60} = -1.31$, $P = .196$). Furthermore, in a more detailed examination of the

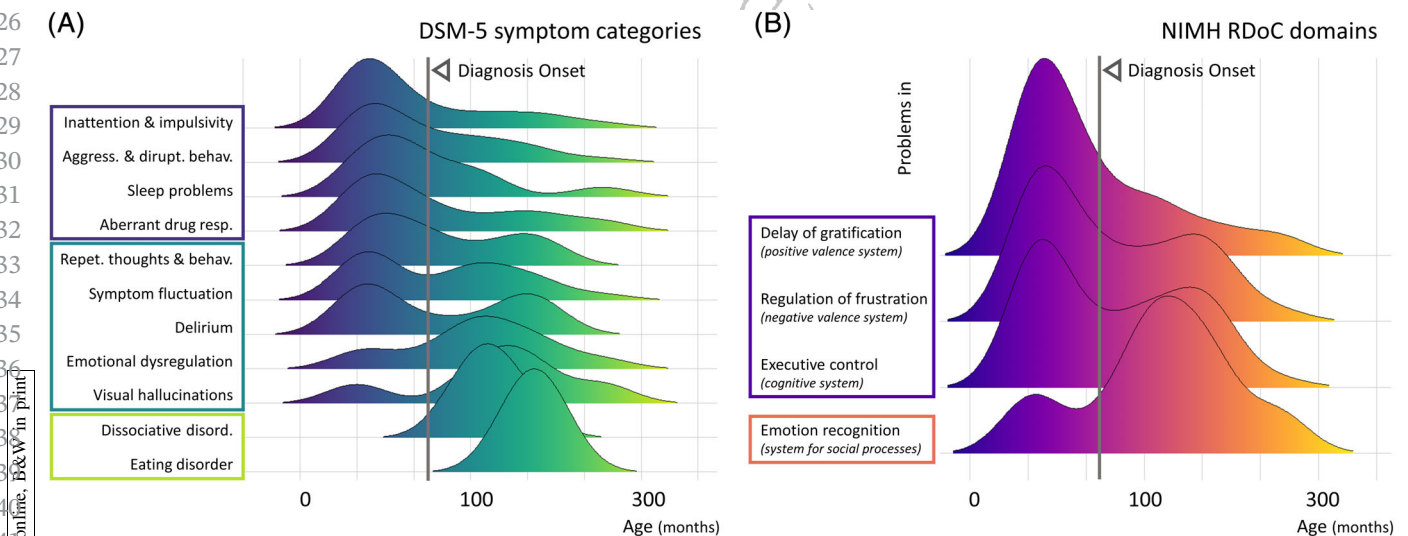


FIGURE 2 Ridgeline plots of the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) symptoms and Research Domain Criteria (RDoC) in children and adolescents from the Lille University Reference Center for inherited metabolic diseases (IMDs, $n = 62$). A, Symptom distributions according to DSM-5 categories are aligned to the same time scale. Among these symptoms, three clusters can be identified in regard to the mean age at IMD diagnosis (62.4 months, represented as a vertical gray line). First, framed in violet: inattention and impulsive behaviors, aggressive and disruptive behaviors, sleep problems, and aberrant drug response precede, on average, the IMD diagnosis. In contrast, dissociation and eating problems occur, on average, after the IMD diagnosis (framed in light green). A third category of symptoms framed in dark turquoise exhibits a bimodal distribution, may precede or follow diagnosis (ie, repetitive thoughts and behaviors, visual hallucinations, symptom fluctuation, delirium and emotional dysregulation). B, Domain distributions according to the RDoC matrix aligned to the same time scale. Four behavioral and cognitive constructs that have been previously proposed in the context of early childhood were used. Two clusters could be identified. First, framed in violet, self-regulation deficits across multiple domains (frustration, executive control, and delay of gratification) occur early in the course of the disease, while problems in emotional recognition and understanding often occurred later (framed in orange), after the mean age of IMD diagnosis (vertical gray line)

1 subsample of IMD patients with psychiatric features, we
2 found no significant difference between the age of occur-
3 rence of the first psychiatric symptom (5.6
4 ± 3.7 years old) and the age of occurrence of any other
5 clinical manifestation (5.8 ± 5 years old; $n = 36$,
6 $W = 224$, $P = .644$). The sample distribution by the age of
7 occurrence of psychiatric and nonpsychiatric signs is
8 reported in Figure 1A. Interestingly, a differential sex dis-
9 tribution was observed; there were significantly more
10 males in the sample with psychiatric signs (male-to-
11 female sex ratio = 2.3) than in the subsample without
12 such clinical features (female-to-male sex ratio = 1.4;
13 $n = 62$, chi-squared = 4.57, $P = .03$, see Figure 1B).

14 Regarding the nature of psychiatric features, the IMD
15 patients mainly presented externalized symptoms (80.5%),
16 followed by sleep disorders (28.6%), autistic traits (25.7%),
17 and depressive symptoms (20%). A fine-grained exploration
18 of the distribution of these DSM-5 symptoms as a function
19 of time allowed us to identify three different patterns of
20 occurrence during the natural course of the disease (see
21 Figure 2A). A first subset of psychiatric signs occurred on
22 average before or at the time of the IMD diagnosis (purple
23 cluster in Figure 2A, left). This was the case for inattention
24 and impulsivity (4.32 years old), aggressive and disruptive
25 behaviors (5 years old), sleep problems (5 years old), and
26 aberrant drug response (5.7 years old). In contrast, another
27 subset of psychiatric signs occurred late in the course of
28 the disease; these included dissociative symptoms
29 (9.7 years old) and eating disorders (13 years old) and are
30 represented in the green cluster in Figure 2A, left. Finally,
31 a third cluster of psychiatric signs exhibited two peaks of
32 occurrence around the mean age of IMD diagnosis (blue
33 cluster in Figure 2A, left). This was the case for repetitive
34 thoughts and behaviors, delirium, emotional dysregulation,
35 visual hallucinations, and symptom fluctuations.

36 Regarding neurocognitive domains, the IMD patients
37 mainly exhibited problems with executive control function-
38 ing, which occurred in 35.5% ($n = 22$) of patients. In
39 addition, 29% exhibited problems delaying gratification
40 ($n = 18$), 25.8% had problems regulating frustration
41 ($n = 16$), and 14.5% had difficulty recognizing emotion
42 ($n = 9$). We applied the same visualization and analysis
43 scheme for these RDoC constructs (Figure 2B) and identi-
44 fied two patterns of cognitive traits based on their distribu-
45 tion around the mean age at diagnosis. First, deficits in the
46 ability to pay attention and inhibit responses to stimuli
47 (executive control, 6.1 years old) and to delay rewards
48 (delay of gratification, 4.5 years old), or regulate frustration
49 (5.9 years old) occurred early in the course of the IMD (pur-
50 ple cluster in Figure 2B, left), mainly before or at the time
51 of the diagnosis. In contrast, emotional knowledge was
52 found to be impaired later in the course of the disease
53 (9.4 years old, orange cluster in Figure 2B, left).

4 | DISCUSSION

54
55
56 It has been regularly described that metabolic disorders
57 that disrupt neurodevelopment may result in psychiatric
58 syndromes, but this case series is the first to specifically
59 address the profile and timing of psychiatric manifesta-
60 tions of IMDs according to recent nosological classifica-
61 tions and the major impacted neurocognitive domains.^{11,14}
62 Although these findings need to be interpreted with cau-
63 tion due to the presence of X-linked disorders in the sam-
64 ple (see Table 1), we first evidenced that boys with IMDs
65 experience psychiatric signs more frequently than girls
66 with IMDs do. For one-third of the whole sample, these
67 psychiatric manifestations were primary, in accordance
68 with previous reports showing that such clinical signs may
69 remain isolated for years, notably in Niemann-Pick C
70 disease,²⁶ adrenoleukodystrophy,²⁷ Wilson disease,²⁸ or
71 cerebrotendinous xanthomatosis.²⁹ This is critical because
72 four of these diseases do have specific therapeutic options
73 (ie, miglustat in Niemann-Pick C disease, haematopoietic
74 stem cell therapy in X-ALD, chelating agents in Wilson
75 disease, and chenodeoxycholic acid replacement therapy
76 for cerebrotendinous xanthomatosis).⁷ Because clinical
77 symptoms stay the most directly observable features of a
78 disease, the early co-occurrence of psychiatric and non-
79 psychiatric signs in the same age-range (~5-6 years old)
80 supports the idea of a common origin (ie, linked with
81 IMDs) for both of these markers.

82 Another strength of this case series is its ability to
83 extract symptoms and domain clusters based on their
84 time of occurrence. Using ridgeline plots, we represented
85 psychiatric signs and cognitive trait distributions as a
86 function of time and in reference to the age at diagnosis.
87 A total of 83% of children with psychiatric signs also pres-
88 ented with neurocognitive impairments. Because the
89 RDoC approach allows the results to be organized on the
90 basis of putative mechanisms, we believe that this partial
91 co-occurrence with psychiatric features illustrates the
92 complementarity of the two approaches. For instance,
93 beyond a strict acute/chronic distinction, we were able
94 to provide the first evidence regarding one extreme of the
95 spectrum: externalizing symptoms (ie, problems with the
96 self-control of emotions and behavior), sleep problems
97 and cross-domain self-regulation deficits, which often
98 preceded the IMD diagnosis. Though poorly specific
99 taken in isolation, the co-occurrence of these signs
100 should warn the clinician, notably when they are associ-
101 ated with resistance or worsening in response to psycho-
102 tropic medication. On the other extreme of the spectrum,
103 late-onset features encompass psychotic dissociative or
104 eating disorders together with emotional recognition and
105 understanding, which occur on average several years
106 after the IMD diagnosis. Around the time of diagnosis,

1 the most frequent psychiatric features are repetitive
2 thoughts and behaviors and emotional dysregulation.
3 Again, this analysis showed that clinicians should specifically
4 look for the co-occurrence of period-specific atypical
5 signs, such as symptom fluctuation, delirium or isolated
6 visual hallucinations, for which the prevalence was found
7 to be higher than in clinical and nonclinical populations.

8 We need to acknowledge some limitations of the
9 work. First, the data set is heterogeneous since we col-
10 lapsed markedly different IMD manifestations and typi-
11 cal ages of presentation, making the generation of disease
12 subtype-specific recommendations impossible. Second,
13 the absence of a difference in the mean age of onset
14 between the first psychiatric signs and other clinical
15 manifestations should be interpreted with caution. How-
16 ever, the similarity of their respective distributions (see
17 Figure 1A) supports the idea that psychiatric signs occur
18 on average within the same age range as other features.
19 Second, despite their clinical relevance and all the efforts
20 made to exhaustively collect the necessary data from the
21 medical records of the retained 62 children with IMDs
22 and properly assign DSM-5 symptoms and RDoC traits,
23 the outcome measures were defined a posteriori to
24 patient enrollment, exposing this case series to potential
25 reporting biases.

26 We cannot exclude the possibility that such bias may
27 account for the absence of notified catatonia in this sam-
28 ple, despite previous descriptions of this alerting sign in
29 the literature.⁸ This may also be a result of the non-
30 systematic use, until recently,³⁰ of adapted rating scales
31 for catatonia in children, such as the PCRS.³¹ Of note,
32 other first-line warning signs reported in the litera-
33 ture^{4,6,18} were correctly identified and extracted from the
34 sample. As previously stated, we were able to move
35 beyond what was previously known and identify early
36 and late patterns of occurrence for these atypical signs.

37 Overall, we confirmed that psychiatric manifestations
38 are frequent and highly polymorphic in IMD and occur
39 within a range of occurrence similar to that indicated in
40 isolated previous reports (Table 1). By providing evidence
41 of clusters of symptoms and cognitive domains with spe-
42 cific onset profiles (ie, before, at same age as and after the
43 IMD diagnosis), we hope that such findings, if replicated,
44 could pave the way for the development of more global
45 and interdisciplinary management algorithms for chil-
46 dren suffering from IMDs. First-line clinicians should
47 consider using neurocognitive domain clusters as useful
48 tools to complement psychiatric red flags in children with
49 (or at risk of) IMD due to the high co-occurrence of these
50 signs during specific disease stages. A better detection of
51 associated cognitive traits as a complement to the cate-
52 gorical diagnostic procedure appears to be crucial from a
53 global health perspective not only for early detection and

appropriate care but also for screening various levels of 54
risk and for informing family planning and support. 55

56 ETHICS APPROVAL AND CONSENT TO 57 PARTICIPATE 58

This study received a CNIL-DEC2015-152 authorization. 59
Written consent was obtained from each patient and 60
their parents. 61

62 CONSENT FOR PUBLICATION 63

Not applicable. 64

65 CONFLICT OF INTEREST 66

The authors declare no potential conflict of interest. 67

68 AUTHOR CONTRIBUTIONS 69

Marielle Ister and Dries Dobbelaere collected the data. 70
François Medjkane and Renaud Jardri performed the first 71
analyses. All the authors were involved in discussing the 72
findings and writing the manuscript. They all approved 73
its final version. 74

75 DATA AVAILABILITY STATEMENT 76

The anonymized data set is available from the 77
corresponding author upon reasonable request. 78

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