Schizophrenia Research 261 (2023) 107–109

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the editor

Catatonia in Down's syndrome: An under-recognized syndrome during regression

Down syndrome (DS), caused by trisomy of chromosome 21 (Lejeune et al., 1959), is the most frequent chromosomal abnormality leading to intellectual disability (ID). DS is associated with various medical conditions (Bull, 2020). They are also at higher risk for neurologic and neurodevelopmental disorders like seizures, autism, and disintegrative disorder (Bull, 2020).

Clinical regression is frequently observed in DS patients and has been associated with various medical conditions such as Alzheimer's disease, severe epilepsy, and autism (Walpert et al., 2021). Recent researches have also highlighted the frequent occurrence of regression phenomenon in DS patients without a distinct cause, although its symptoms can sometimes overlap with features of dementia or autism (Walpert et al., 2021). This phenomenon is characterised by a decline in daily living skills, autonomy, and cognitive abilities (Walpert et al., 2021). Describing this condition in individuals with DS faces several challenges. There is a lack of consensus on the terminology used to describe regression in DS (Walpert et al., 2021). Although several studies have reported symptoms associated with regression in DS, the evidence quality is low according to Cochrane (Walpert et al., 2021). To the best of our knowledge, there is no specific scale for measuring regression in DS, and it is not included in any international classification of diseases. Recent reviews have attempted to compile the main signs of regression in DS reported in the literature, including sleep disorders, language decline, and disinterest/withdrawal (Rosso et al., 2020; Walpert et al., 2021). These main signs are listed in Table S1. The underlying pathophysiological mechanism of regression is still unknown (Hauptman et al., 2023), and there are no recommendations for its treatment.

Recent literature has emphasized the underrecognition of catatonia in DS patients experiencing regression (Ghaziuddin et al., 2015; Lyons et al., 2020). As for regression in DS, Catatonia symptoms also include a loss of daily living skills, language decline and social withdrawal (see Table S1). It is a severe neuropsychiatric syndrome with a high risk of mortality and a poor prognosis if left untreated (Hauptman et al., 2023). Its prevalence in children and young adults can be substantial, particularly in neurodevelopmental conditions (Hauptman et al., 2023). Catatonia due to medical condition or catatonia not otherwise specified is included in the DSM-5. Catatonia can be assessed using validated scales (Benarous et al., 2016).

Given the current state of knowledge surrounding regression and catatonia in DS, it remains challenging to determine whether they are synonymous or distinct conditions and whether one can cause the other (Hauptman et al., 2023; Walpert et al., 2021). Despite the lack of clear differentiation between the two disorders (see Table S1 for a comparison of respective signs), it is crucial not to overlook a diagnosis of catatonia. Failure to recognize catatonia can lead to missed opportunities for treatment and result in a poor prognosis.

The objective of our study was to investigate the prevalence of catatonia among adolescents and young adults with DS who experienced regression. For this purpose, we conducted a systematic search for catatonia signs by retrospectively evaluating the medical records of DS patients treated for regression at the Jerome Lejeune Institute (JLI), the largest clinical department dedicated to DS in France ($N = 6611$) (Mircher et al., 2017). Specifically, our study aimed to: (1) assess the prevalence of catatonia in DS patients suffering from regression; (2) compare this prevalence with the prevalence of catatonia in matched controls; and (3) evaluate whether DS patients suffering from catatonia show specific characteristics in terms of medical history and treatment. We hypothesized that a large proportion of patients with DS described as suffering from regression were actually suffering from catatonia.

The methods are detailed in Supplementary material. We retrieved all medical observations for DS patients diagnosed with regression from the JLI database. The diagnosis of regression was established by clinicians during the patients' treatment at the JLI. It primarily relied on the clinicians' observations of a decline in autonomy and daily functioning, as well as reduced speech or psychomotor activity. A total of thirty regression cases were found, and their descriptions has been previously published (Mircher et al., 2017). BJ conducted a thorough review of the medical observations related to their regression episodes, specifically searching for symptoms listed in the Pediatric Catatonia Rating Scale (PCRS). The diagnosis of catatonia was made based on the presence of at least two catatonic motor signs, or at least one catatonic motor sign combined with at least one non-motor catatonic symptom suggesting a severe impairment of behavioral and emotional functioning. The final Regression group included 30 DS patients suffering from regression. The Control group included 30 DS patients without regression, whose information was retrieved from the same JLI database. DS patients from the Control group were randomly selected and matched for age and sex with patients from the Regression group. Because the study is a retrospective cohort study that did not involve any medical interventions beyond usual medical treatment, it was, according to French law, waived from getting an approval by an external ethical committee. Yet, the French regulation for the protection of personal data and privacy (CNIL – *Commission Nationale de L'Informatique et des Libertés*) approved the handling of study data which preserved the full anonymity of the participants. The study was carried out in accordance with the Declaration of Helsinki (World Medical Association, 2013). Prior to participation, all individuals provided informed consent.

The results are detailed in Supplementary material. The main result of the study is the high prevalence of retrospective diagnosis of catatonia (80 %) among DS patients who were diagnosed with regression at the time of their initial medical care. None of these patients had a previous diagnosis of catatonia. In contrast, none of the DS patients classified as non-regressed during their care were found to have catatonia ($p <$ 0.001). Table S2 summarizes the prevalence of medical conditions

https://doi.org/10.1016/j.schres.2023.09.011
Received 17 November 2022; Received in revised form 28 July 2023; Accepted 4 September 2023

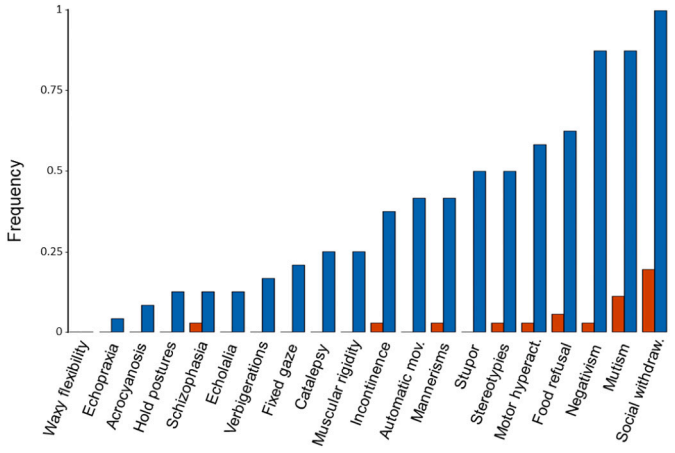

Fig. 1. Frequency of catatonia symptoms among DS patients with and without catatonia. Orange bars: frequency of the catatonia symptoms, screened using the Pediatric Catatonia Rating Scale, among DS patients without catatonia (N = 36). Blue bars: frequency of the catatonia symptoms, screened using the Pediatric Catatonia Rating Scale, among DS patients with catatonia (N = 24). (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

among patients with DS and catatonia ($N = 24$) and without catatonia ($N = 36$). The presence of at least one autoimmune disease or at least one specific autoantibody in the blood samples was more frequent in catatonic DS patients compared to non-catatonic DS patients.

Several reasons might explain the absence of catatonia diagnosis in this particular sample. Firstly, making a catatonia diagnosis in the context of multiple impairments (Hauptman et al., 2023), as often seen in DS patients, appears challenging. Indeed, patients with DS are particularly susceptible to various medical conditions and they frequently show diverse symptoms resulting from different disorders (Bull, 2020). Secondly, diagnosing catatonia becomes more difficult when the disorder progresses gradually in neurodevelopmental disorders (Hauptman et al., 2023). In addition, catatonia symptoms are nonspecific, and catatonia can co- occur with a major depressive episode or schizophrenia. All these challenges contribute to a complex clinical situation.

Regarding the expression of catatonia symptoms in DS patients, our results suggest that social withdrawal and mutism were the most frequent symptoms (see Fig. 1). Interestingly, a recent review of regression cases in patients with DS found that deterioration in language and social withdrawal were among the most frequent symptoms associated with the full range of regression's symptomatology (Walpert et al., 2021). Regarding the effectiveness of treatment, the majority of patients with catatonia (70.8 %) were prescribed multiple medications. Less than half of them were prescribed benzodiazepines, which previous studies have shown to be the most effective treatment for catatonia (Zaman et al., 2019).

Despite several limitations (see Supplementary material), our findings indicate that catatonia might be underrecognised in DS patients with regression. Nonetheless, it is crucial not to overlook this diagnosis because (i) it directs clinical decision-making towards the identification of potentially serious comorbidities commonly associated with catatonia and that require timely treatment (Hauptman et al., 2023), and (ii) there are effective treatments available for catatonia, some of which are accessible and have a low acquisition cost, such as benzodiazepines (Zaman et al., 2019). Therefore, we believe that when faced with a so-called “regression” episode in DS patients, catatonia should be considered as a possible disorder (Ghaziuddin et al., 2015) and should be systematically assessed for. Prospective and meticulous evaluation of regression and catatonia symptoms in DS patients could be the focus of future studies to explore the similarities and differences between the two disorders. It is possible that most regression episode in DS patients are, in fact, a manifestation of catatonia.

CRediT authorship contribution statement

Barbara Jakubowicz: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Axel Baptista:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Aimé Ravel:** Resources, Writing – review & editing, Funding acquisition. **Cécile Cieuta:** Resources, Writing – review & editing, Funding acquisition. **Clotilde Mircher:** Investigation, Resources, Data curation, Writing – review & editing, Funding acquisition. **David Cohen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Angèle Consoli:** Writing – review & editing, Supervision, Project administration. **Marie Raffin:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare no conflict of interest related to this article.

Acknowledgments

We thank the patients and family members who contributed to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.09.011.

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Barbara Jakubowicz[a,b,*], Axel Baptista[a,c], Aimé Ravel[d], Cécile Cieuta[d], Clotilde Mircher[d], David Cohen[a], Angèle Consoli[a], Marie Raffin[a]

[a] *Department of Child and Adolescent Psychiatry, Hôpital Pitié-Salpêtrière, AP-HP, 47-83 Boulevard de l'Hôpital, 75013 Paris, France*

[b] Fondation Santé des Etudiants de France (FSEF), Paris, France
[c] Centre de recherche en épidémiologie et en santé des populations, Inserm U1018, Université Paris-Saclay, Université Versailles Saint-Quentin, Paris, France
[d] Institut Jérôme Lejeune, 75015 Paris, France

[*] Corresponding author at: Department of Child and Adolescent Psychiatry, Hôpital Pitié-Salpêtrière, AP-HP, 47-83 Boulevard de l'Hôpital, 75013 Paris, France.
E-mail address: jakubowicz.barbara@gmail.com (B. Jakubowicz).