CASE REPORT

A Treatable Cognitive Regression in an Adolescent with Down Syndrome

Maria João Palha[1,2], Luísa Cotrim[2], Maria Teresa Guterres[2], David Casimiro de Andrade[3], Miguel Palha[2]

Port J Pediatr 2021;52:203-7
DOI: https://doi.org/10.25754/pjp.2021.20015

Abstract

Depression may manifest in different ways in people with Down syndrome. Cognitive regression and loss of adaptive skills could be the most noticeable signs. This report presents a 14-year-old female adolescent with Down syndrome and a proper premorbid function who developed progressive cognitive regression over four months. Additional symptoms consisted of irritability, psychomotor slowness, a deficit in social interaction, alienation, loss of interest, and permanent, incoherent, and implausible self-talk (with persecutory delirium). No signs of sadness were noted. The patient was diagnosed as having a major depressive disorder with mood-incongruent psychotic features. Organic causes were excluded. After starting treatment with fluoxetine 50 mg/day and aripiprazole 10 mg/day, an improvement was observed over a 12 week period. By presenting this case, we aim to highlight the specific challenges regarding the diagnosis and treatment of Down syndrome adolescents and young adults presenting with subacute cognitive regression.

Keywords: Adolescent; Aripiprazole/therapeutic use; Depressive Disorder/diagnosis; Depressive Disorder/therapy; Down Syndrome/psychology; Fluoxetine/therapeutic use; Neurobehavioral Manifestations; Regression, Psychology

Introduction

Only a few studies have focused on psychiatric morbidity in adolescents and young adults with Down syndrome. Depression is a common problem in these subjects and may present differently from the general population.[1-4] Subacute cognitive and language regression with adaptive behavior deterioration might be the most noticeable signs. Other features include psychomotor slowness, insomnia, and anorexia. Sadness or depressed mood are not always present. Association with psychotic features is unknown. Previous research has shown a prevalence of 0%-11%.[5] Treatment with psychotropic drugs has shown good efficacy.

Case Report

We report the clinical case of a 14-year-old female adolescent with Down syndrome. Since she was 8 years old, coherent, perceptible, and private self-talk was noted, on topics of interest to the age group. Over a period of three months, she progressively showed disinterest in social interactions, a deficit in social reciprocity, alienation of all the family events, and permanent irritability. Markedly cognitive and linguistic decline, adaptive behavior deterioration, psychomotor slowness, insomnia, and anorexia were also noted. Her parents also referred to a loss of interest in all activities and subjects. One month after the initial manifestations, self-talk became permanent (privately and publicly), implausible, and incoherent (with persecutory delusion). No signs of sadness were noted. Her past medical history was significant for strabismus and myopia since she was 2 years old (adequate vision with glasses) and obesity since she was 8 years old. No drugs were administered in the previous three years. She had a favorable neurodevelopment profile for Down syndrome: first words at 14 months, reading at 6 years, simple addition and subtraction at 8 years, multiplications and divisions with a calculator at 10 years, adequate capacity for abstraction and argumentation at 12 years, good gross and fine motor skills. The patient always attended regular school. In the past four months, she was set apart and started a professionalizing class for intellectual disability subjects.

1. Department of Pediatrics, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte, Lisboa, Portugal
2. Child Development Centre Diferenças, Lisboa, Portugal
3. Faculdade de Medicina Dentária, Universidade do Porto, Porto, Portugal
Corresponding Author
Maria João Palha
https://orcid.org/0000-0002-3354-4149
mariajoaopalha@gmail.com
Centro Comercial da Bela Vista, Loja 32, Avenida Santo Condestável, Via Central de Chelas, 1900-806 Lisboa, Portugal
Received: 05/05/2020 | Accepted: 07/01/2021 | Published online: 02/07/2021 | Published: 02/07/2021

No social nor economic issues were identified. There were no significant behavioral issues and family history was negative for psychiatric diseases.

On examination, we observed a non-cooperant and non-communicative female adolescent not answering any questions and showing marked irritability. Eye contact was absent. We also noted compulsive and unintelligible self-talk. Help to dress and undress was necessary.

A severe major depressive disorder was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria in a patient with intellectual disability and Down syndrome.[6] Psychotic features such as disorganized thinking and speech and persecutory delusions were also noted.

The patient underwent laboratory and cardiology evaluations that excluded organic causes. Thyroid-stimulating hormone, free thyroxine, electrolytes, liver tests, folates, cobalamin, 25-hydroxy vitamin D, homocysteine, anti-transglutaminase immunoglobulin (Ig) A, fast glycemia, and complete blood count were assessed and were all in the normal range.

Treatment was initiated with fluoxetine and aripiprazole with slow weekly titration increments up to 50 mg/day and 10 mg/day, respectively. The patient also started psychotherapy. Twelve weeks after starting treatment, the symptoms started to improve, particularly cognitive and linguistic decline, irritability, and interest loss. Eighteen months after the diagnosis, the self-talk returned to its previous characteristics. Pharmacological treatment is still maintained (up to two years now) because of the intellectual disability and severity of the presentation. No medication side effects were observed.

Discussion

Subacute cognitive and linguistic deterioration in adolescents and young adults with Down syndrome has been documented in many studies published over the last three decades. In most cases, other psychiatric indicators were present but they did not necessarily include a depressed mood. Cognitive improvement was observed in many patients after antidepressant and/or antipsychotic therapy.[4,7-9] This condition has been labeled differently, such as acute neuropsychiatric disorder, Down syndrome disintegrative disorder, acute regression, and major depressive disorder.[8-12] In older individuals, dementia should be carefully considered.

Based on DSM-5, a depressed mood is not necessarily present for the diagnosis of major depressive disorder.[6] At least one - depressed mood or loss of interest or pleasure - must be present according to A criteria. As such, our patient fulfilled all of the needed criteria for the diagnosis of major depressive disorder.[6] As stated above, we interpreted the new characteristics of self-talk as mood-incongruent psychotic manifestations.[6] However, we must note that self-talk is not strictly associated with psychiatric conditions in Down syndrome. It is instead a standard feature with a reported prevalence of 81%-90%.[13-16] It usually takes the form of monologue, it is perceptible, and it does not interfere with social interaction (such as previously observed self-talk). Some authors suggested that self-talk in individuals with Down syndrome serves the useful purpose of directing actions and thoughts, just like in younger healthy children.[14] It is essential to reinforce that it was not the soliloquies itself, but the change in its characteristics that were interpreted as psychotic features.

As we stated, no signs of depressed mood were reported. Cognitive and linguistic regression, a deficit in social interaction, deterioration of adaptive behavior, and loss of interest were the most noticeable manifestations. Clinical aspects of depression in subjects with Down syndrome seem to be like those of the general population, except that sadness or depressed mood are less frequently found. The main reported manifestations of major depressive disorder in Down syndrome patients are cognitive and linguistic regression (80%-100%), adaptive behavior deterioration (87%-90%), psychomotor slowness (37%), insomnia (10%-71%), obsessive-compulsive traits (57%), depressed mood (30%-57%), motor stereotypies (27%), deficit in social interaction (20%), self-talk (10%-14%), and anorexia (10%).[8-10] Other features included loss of interest in activities and subjects and anxiety.[1-4] Auto and hetero-aggressive behaviors were reported in one study.[9]

As far as we know, no previous studies focused on the association of psychotic features and depressive disorder in individuals with Down syndrome.

In our patient, we observed a progressive onset of symptoms over four months instead of an insidious and/or remitting course (as in many cases of depression in the general population). A clinical course of six months or less in 100% of Down syndrome patients was described (30% with abrupt onset).[9]

Besides limited cognitive impairment, Down syndrome itself seems to be a risk factor for depression, due to the overexpression of the G protein-coupled inwardly rectifying K^+ channel type 2 (GIRK2), encoded by the *Kcnj6* gene, located on chromosome 21.[17,18] Other potential risk factors include smaller total brain volume, smaller hippocampal volume, and reduction in serotonin tissue concentration.[5] Other authors also found an association with elevated levels of alpha-2 macroglobulin and lower

C-reactive protein in this specific population.[19]

Although positive family history is a known risk factor for depression in the general population, this has not been proven for individuals with Down syndrome.[5]

The change from the mainstream school and the separation from her classmates preceded the onset of symptoms. Many authors have associated symptoms with stressful life events.[4,9,10,12] The reported trigger factors include rejection from peers, loss of close relationships because of changes in residency (23%-25%), school or occupational changes (37%-51%), death or illness of close relatives (14%-20%), and major surgery (14%).[4,9,10,12]

Our patient was a 14-year-old female. Many authors pointed out a female predominance while others found no differences between genders.[9-11] The mean age of onset varied between 15.8-21.5 years (minimum 9 and maximum 34 years).[8,9-11,20]

Although the definitive diagnosis of depressive disorder is clinical, it is mandatory to ensure Down syndrome patients with rapid and unexplained cognitive deterioration do not have a concomitant organic condition such as hypothyroidism, obstructive sleep apnea (6%-86% of Down syndrome individuals), celiac disease, severe constipation, hearing loss, and leukemia. These pathologies should be systematically excluded, as they may mimic depressive symptoms or aggravate the course of disease and response to treatment.[5] Curiously, studies did not report a higher prevalence of hypothyroidism in Down syndrome subjects suffering from depression.[9,10] Accordingly, a systematic approach for these cases that includes a first-line workup was proposed: thyroid-stimulating hormone, free thyroxine, thyroid peroxidase, thyroglobulin antibodies, electrolytes, liver tests, folates, cobalamin, 25-hydroxy vitamin D, homocysteine, anti-transglutaminase IgA, total IgA, fast glycemia, hemogram, polysomnogram, hearing test, vision screen, and abdominal X-ray.[7]

We performed almost all of the first-line recommended exams and they were normal except for the polysomnogram, hearing test, and visual screening because there were no complaints regarding these fields and she already wore glasses.

In our patient, we observed clinical improvement with fluoxetine (titrated up to 50 mg/day) and aripiprazole (up to 10 mg/day). We opted to combine an antidepressant with low-dose antipsychotic medication following the American Psychiatric Association (APA) guidelines on major depressive disorder with psychotic manifestations, the European Medicines Agency (EMA) recommendations, and expert opinion.[4,21-24]

In the general population, the effectiveness of antidepressant medications seems to be comparable between classes and within classes of medications. Hence, the selection of the antidepressant should be based on the anticipated side effects, safety, cost, and interactions.[21] Psychotropic drugs showed effectiveness treating Down syndrome patients with a depressive disorder, although there are no standardized practices. Previous studies were unable to conclude the most suitable drugs and respective doses.[2,9,12] We chose fluoxetine because of the safety profile and approved use in the pediatric population by EMA.[24] On the other hand, fluoxetine inhibits the GIRK2 (a potential mechanism for treating depression) that is increased in the brain of patients with Down syndrome.[17] That is why fluoxetine might be the most suitable first-line antidepressant in these patients. Sertraline and citalopram are alternative drugs to fluoxetine.[22]

Aripiprazole was the chosen antipsychotic for the same reasons.[24] Aripiprazole has a lower potential for weight gain or metabolic changes than other antipsychotics, causes less frequently extrapyramidal symptoms, sedation, QT interval prolongation, and hyperprolactinemia.[25] Risperidone may substitute aripiprazole but has a less favorable safety profile.[21]

No side effects of the chosen treatments have been described in our patient. These could include akathisia, tardive dyskinesia, neuroleptic malignant syndrome, and weight gain.[21]

Psychotherapy was started as recommended by the APA guidelines for the treatment of major depressive disorders, although no study could be found assessing psychotherapy efficacy in individuals with Down syndrome and depressive disorder.[21]

During the acute phase, clinical improvement is commonly notorious in four weeks, but this may be extended up to 12 weeks.[21] We observed a slow clinical improvement with treatment, probably due to the slow titration scheme (to avoid possible side effects).

We decided to maintain our patient on psychotropic drugs more than the nine months after remission suggested by the APA guidelines.[21] Maintenance treatment should be considered according to the risk of recurrence that is higher in cases of the early age of onset, severe presentation, and intellectual disability.[21]

WHAT THIS CASE REPORT ADDS

- Clinicians should consider the diagnosis of major depressive disorder in individuals with Down syndrome presenting with subacute cognitive decline and the deterioration of adaptive function, even in the absence of sadness or a depressed mood.
- Self-talk should be interpreted with caution, but it might be a sign of psychosis.
- Stressful life events may precede the onset of major depressive disorder in patients with Down syndrome.
- Given its neuroanatomic and biochemistry particularities, Down syndrome is a risk factor for major depressive disorder beyond the intellectual disability.
- Fluoxetine is the most suitable antidepressant in individuals with Down syndrome suffering from depression, and aripiprazole may be added if psychotic features are present.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Provenance and peer review

Not commissioned; externally peer reviewed

Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

References

1. Myers BA, Pueschel SM. Psychiatric disorders in persons with Down syndrome. J Nerv Ment Dis 1991;179:609-13. doi: 10.1097/00005053-199110000-00004.
2. McGuire D, Chicoine B. Depressive disorders in adults with Down syndrome. Habilitative Ment Healthc Newsl 1996;15:1-7.
3. Cooper SA, Collacott RA. Clinical features and diagnostic criteria of depression in Down's syndrome. Br J Psychiatry 1994;165:399-403. doi: 10.1192/bjp.165.3.399.
4. Capone G, Goyal P, Ares W, Lannigan E. Neurobehavioral disorders in children, adolescents, and young adults with Down syndrome. Am J Med Genet C Semin Med Genet 2006;142C:158-72. doi: 10.1002/ajmg.c.30097.
5. Walker JC, Dosen A, Buitelaar JK, Janzing JG. Depression in Down syndrome: A review of the literature. Res Dev Disabil 2011;32:1432-40. doi: 10.1016/j.ridd.2011.02.010.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington: APA; 2013.
7. Jacobs J, Schwartz A, McDougle CJ, Skotko BG. Rapid clinical deterioration in an individual with Down syndrome. Am J Med Genet A 2016;170:1899-902. doi: 10.1002/ajmg.a.37674.
8. Akahoshi K, Matsuda H, Funahashi M, Hanaoka T, Suzuki Y. Acute neuropsychiatric disorders in adolescents and young adults with Down syndrome: Japanese case reports. Neuropsychiatr Dis Treat 2012;8:339-45. doi: 10.2147/NDT.S32767.
9. Mircher C, Cieuta-Walti C, Marey I, Rebillat AS, Cretu L, Milenko E, et al. Acute regression in young people with Down syndrome. Brain Sci 2017;7:57. doi: 10.3390/brainsci7060057.
10. Santoro SL, Cannon S, Capone G, Franklin C, Hart SJ, Hobensack V, et al. Unexplained regression in Down syndrome: 35 cases from an international Down syndrome database. Genet Med 2020;22:767-76. doi: 10.1038/s41436-019-0706-8.
11. Worley G, Crissman BG, Cadogan E, Milleson C, Adkins DW, Kishnani PS. Down syndrome disintegrative disorder: New-onset autistic regression, dementia, and insomnia in older children and adolescents with down syndrome. J Child Neurol 2015;30:1147-52. doi: 10.1177/0883073814554654.
12. Stein DS, Munir KM, Karweck AJ, Davidson EJ, Stein MT. Developmental regression, depression, and psychosocial stress in an adolescent with Down syndrome. J Dev Behav Pediatr 2013;34:216-8. doi: 10.1097/DBP.0b013e31828b2b42.
13. Gorzoni ML, Pinto CF, Ferreira A. Down syndrome in adults: Success and challenge. Geriatr Gerontol Aging 2019;13:111-7. doi: 10.5327/Z2447-211520191900022.
14. McGuire D, Chicoine B, Greenbaum E. "Self-talk" in adults with down syndrome. Disabil Solut 1997;2:1-4.
15. Patti P, Tsiouris J. Emotional and behavioral disturbances in adults with down syndrome. In: Davidson PW, Prasher VP, Janicki MP, editors. Mental health, intellectual disabilities, and the aging process. New Jersey: Wiley-Blackwell; 2008. p.81-93.
16. Glenn SM, Cunningham CC. Parents' reports of young people with Down syndrome talking out loud to themselves. Ment Retard 2000;38:498-505. doi: 10.1352/0047-6765(2000)038<0498:PROYPW>2.0.CO;2.
17. Cooper A, Grigoryan G, Guy-David L, Tsoory MM, Chen A, Reuveny E. Trisomy of the G protein-coupled K+ channel gene, Kcnj6, affects reward mechanisms, cognitive functions, and synaptic plasticity in mice. Proc Natl Acad Sci USA 2012;109:2642-7. doi: 10.1073/pnas.1109099109.
18. Mayfield J, Blednov YA, Harris RA. Behavioral and genetic evidence for GIRK channels in the CNS: Role in physiology, pathophysiology, and drug addiction. Int Rev Neurobiol 2015;123:279-313. doi: 10.1016/bs.irn.2015.05.016.
19. Tsiouris JA, Mehta PD, Patti PJ, Madrid RE, Raguthu S, Barshatzky MR, et al. Alpha2 macroglobulin elevation without an acute phase response in depressed adults with Down's syndrome: Implications. J Intellect Disabil Res 2000;44:644-53. doi: 10.1046/j.1365-2788.2000.00287.x.
20. Prasher V. Disintegrative syndrome in young adults. Ir J Psychol Med 2002 Sep;19:101. doi: 10.1017/S0790966700007205.
21. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Washington: APA; 2010
22. Vicari S, Pontillo M, Armando M. Neurodevelopmental and psychiatric issues in Down's syndrome: Assessment and intervention. Psychiatr Genet 2013;23:95-107. doi: 10.1097/YPG.0b013e32835fe426.
23. Palumbo ML, McDougle CJ. Pharmacotherapy of Down syndrome. Expert Opin Pharmacother 2018;19:1875-1889.

doi: 10.1080/14656566.2018.1529167.
24. European Medicines Agency. [accessed 30 April 2020]. Available at: https://www.ema.europa.eu/en
25. Pae CU. A review of the safety and tolerability of aripiprazole. Expert Opin Drug Saf 2009;8:373-86. doi: 10.1517/14740330902835493.

Uma Regressão Cognitiva Tratável numa Adolescente com Síndrome de Down

Resumo:
A depressão nos indivíduos com trissomia 21 apresenta manifestações distintas das do resto da população. As manifestações mais notórias podem ser regressão cognitiva ou deterioração do comportamento adaptativo. Reportamos o caso de uma adolescente de 14 anos, portadora de trissomia 21, com boa função pré-mórbida, que desenvolveu deterioração cognitiva progressiva, durante quatro meses. Concomitantemente, apresentava irritabilidade, lentificação psicomotora, défice na interação social, desinteresse por todas as atividades e solilóquios incoerente e impercetível. Não foram observados sinais de tristeza. Foi diagnosticada perturbação depressiva *major* com manifestações psicóticas não congruentes com o humor. Excluiu-se causa orgânica. Após o início de terapêutica com fluoxetina 50 mg/dia e aripiprazol 10 mg/dia, observou-se, ao longo de 12 semanas, melhoria das manifestações. Pretendemos, com este caso, destacar as dificuldades no diagnóstico e na orientação terapêutica de adolescentes e jovens adultos com trissomia 21 que se apresentam com deterioração cognitiva subaguda.

Palavras-Chave: Adolescente; Aripiprazol/uso terapêutico; Fluoxetina/uso terapêutico; Manifestações Neurocomportamentais; Regressão Psicológica; Síndrome de Down/Psicologia; Transtorno Depressivo/diagnóstico; Transtorno Depressivo/tratamento