Clinical Note: Bipolar disorder in Cerebrotendinous Xanthomatosis: a case report

Marta Migoya-Borja[1].
Fanny Cegla-Schvartzman[1]
Nora Palomar-Ciria[2*]
Miren Iza[1]
María Luisa Barrigón[1,3].
Enrique Baca-García[1,3-9].
[1] Department of Psychiatry, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain.
[2] Psychiatry Service, Complejo Asistencial de Soria, Soria, Spain.
[3] Department of Psychiatry, Universidad Autónoma, Madrid, Spain.
[4] Department of Psychiatry, Hospital Universitario Rey Juan Carlos, Móstoles, Spain.
[5] Department of Psychiatry, Hospital General de Villalba, Madrid, Spain.
[6] Department of Psychiatry, Hospital Universitario Infanta Elena, Valdemoro, Spain
[7] Insituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain.
[8] CIBERSAM (Centro de Investigación en Salud Mental), Carlos III Institute of Health, Madrid, Spain.
[9] Universidad Católica del Maule, Talca, Chile.
[10]Department of Psychiatry, Centre Hospitalier Universitaire de Nîmes, France

*Corresponding author: Hospital Virgen del Miron (Complejo Hospitalario de Soria). Carretera de Logroño, nº8, 42005. Soria (Spain). Telephone: +34 975 22 08 50. Fax: 0034 975 22 05 47. e-mail: npalomar@saludcastillayleon.es

ABSTRACT

Cerebrotendinous X anthomatosis (CTX) is a rare autosomal recessive disorder presenting with possible psychiatric manifestations that, once established, are difficult to control. We present the case of a 29-year-old woman diagnosed with CTX who developed bipolar disorder. Owing to difficulties in pharmacological management, the patient underwent electroconvulsive therapy (ECT), which lead to a favorable outcome. Little is known about the treatment of psychiatric symptoms of CTX, un uncommon disorder, though ECT may be an effective and safe approach.

Key words. *Cerebrotendinous Xanthomatosis; bipolar disorder; electroconvulsive therapy.*

RESUMEN

La xantomatosis cerebrotendinosa (XCT) es una rara enfermedad autosómica recesiva que puede cursar con manifestaciones psiquiátricas cuyo tratamiento puede resultar complejo. Presentamos el caso de una mujer de 29 años, diagnosticada de XCT, que desarrolló un trastorno bipolar que no respondió a tratamiento farmacológico, precisando terapia electroconvulsiva (TEC), cuyo resultado fue positivo. Al ser la XCT una enfermedad rara, existe poca evidencia sobre el abordaje farmacológico de la sintomatología psiquiátrica que puede aparecer en el curso de la enfermedad. En este sentido, planteamos que la TEC pueda ser una opción de tratamiento segura y eficaz.

Palabras clave. *Xantomatosis cerebrotendinosa; trastorno bipolar; terapia electroconvulsiva.*

INTRODUCTION

Cerebrotendinous Xanthomatosis (CTX) is an autosomal recessive disease caused by a mutation in the *CYP27A1* gene. Only a few hundred of CTX cases have been reported worldwide,and the disease has an estimated prevalence of 2/100 000[1,2]. The affected gene encodes the sterol-27-sterol-hydroxylase, resulting in an excess of cholesterol and its by-product, cholestenol, which accumulate in the tendons, blood, nerve cells, and other viscera, causing systemic disease with neurological impairment, early development of bilateral cataracts and chronic diarrhea[3]. Atypical and unspecific psychiatric manifestations can also occur and sometimes may appear years before other, more specific signs, potentially leading to misdiagnosis[4,5]. Early treatment with chenodeoxycholic acid (CDCA) could prevent the development of neurological and psychiatric symptoms, which are difficult to control once established[3,4].

CASE REPORT

On first contact, the patient, Ms. F., was 29 years of age, unmarried, and held a degree in business. She is second of five siblings in a family with no history of mental illness. During childhood she presented bilateral cataracts, which were surgically removed, chronic diarrhea, neurosensorial hearing loss, and Gilbert syndrome. She required psychological support due to learning impairment and difficulties socializing. At the age of 26 years (April 2015), she first experienced a mild depressive episode which resolved with no pharmacological treatment. This event was followed by an episode of hypomania in September, which responded favorably to low doses of valproic acid (700 mg per day) and olanzapine (10 mg per day). The patient was then diagnosed with Bipolar Disorder (BD), type II. Despite treatment, another depressive episode occurred at the end of December, at which time olanzapine was substituted with low doses of quetiapine (150 mg per day), causing an improvement in symptoms.

At age 28 years, the patient was tested for CTX after her older brother was diagnosed with the disease. She presented minimal neurological signs (tendon hyperreflexia and slight thickening of the Achilles tendon) and no major changes were evident on imaging tests. Treatment with 750 mg of CDCA per day was started.

At the age of 29 years, the patient presented to the emergency department (ED) with a manic episode characterized by

increased activity, psychomotor restlessness, logorrhea, distractibility, flight of ideas, inadequate behavior, unrestrained buying sprees, total insomnia, and inappropriate social interaction. No psychotic symptoms were observed. She had abandoned previous psychopharmacological treatment (valproic acid, 700 mg per day and quetiapine 150 mg per day) 8 months prior. In the ED, previous psychiatric treatment was reintroduced and she was discharged to the outpatient unit. Despite treatment, her manic symptoms worsened over the following days, including lack of inhibition and significant behavioral disruption; as she received scarce symptom management in the home, she was admitted to the inpatient unit a week later, where she stayed for 42 days. A magnetic resonance imaging (MRI) scan performed under sedation during admission showed symmetric signal changes in dentate nuclei, the left thalamus, and pulvinar nuclei. Furthermore, a slowing in background activity with mild diffuse cerebral involvement was observed on electroencephalogram (EEG). Treatment with high doses of asenapine (20 mg per day) in combination with valproic acid was initiated. After the symptoms had persisted for 10 days, the previous treatment was gradually replaced with olanzapine (20 mg per day) in addition to clonazepam (4 mg per day) and lithium (800 mg per day), though neither resulted in an improvement in symptoms. Her intense manic symptoms continued, especially hyperthymia and euphoria, hyperactivity and insomnia, and the patient also developed important side effects (drowsiness, sialorrhea, dysarthria, gait instability, and ataxia). Given that psychopharmacological treatment seemed to be ineffective, electroconvulsive therapy (ECT) was started on the day 22 of admission. After 3 sessions of ECT, a major improvement was observed, especially regarding insomnia and hyperactivity. Hyperthymia and logorrhea persisted until the sixth session. The side effects of treatment also improved progressively. At the time of discharge, the patient had undergone 9 sessions of ECT and she had reached a euthymic state. Diagnosis at discharge was CTX and BD with another medical condition . ECT was continued on an outpatient basis until she had received 15 sessions. Pharmacological treatment was maintained, consisting of lithium 800 mg per day, olanzapine 15 mg per day, and CDCA 750 mg per day in addition to simvastatin 20 mg per day. One year later, she was hospitalized again due to a depressive episode with suicidal risk that responded badly to pharmacological adjustments. ECT was restarted, and 6 sessions were administered during a 22-day admission, and the patient reached a euthymic state at discharge. Pharmacological treatment with lithium 800 mg per day, quetiapine 200 mg per day and lormetazepam 2 mg per day in addition to somatic treatment (simvastatin and CDCA) was also maintained. At the time of writing, Ms. F. continues to be in symptomatic remission, and displays good socio-occupational functioning.

CONCLUSION

Psychiatric symptoms among CTX patients may be atypical and not always reported, causing a scarcity in the published literature on managing the disease. Previously, BD and CTX have not previously been strongly linked[2]. The case reported here is striking due to the intense manic symptoms and challenging management due to pharmacological resistance. Somatic treatment with 750 mg of CDCA per day in combination with statins seems to prevent CTX progression[4]. Nonetheless, response to treatment in CTX patients is variable and mainly depends on the age at which treatment is initiated and the symptoms on diagnosis[3,6], though disease progression may continue despite treatment. It seems clear that somatic treatment alone is not enough to resolve acute psychiatric symptoms associated with CTX. Administration of antidepressants has been described previously, and seemed to be effective[5,7]. Antipsychotics have been used for behavioral and psychotic symptoms, though to uncertain results[5]. In our case, the manic symptoms of the patient were resistant to high doses of psychopharmacological treatment in addition to somatic treatment. It must be noted that the symptomatic worsening in this patient seemed to correlate with changes in MRI findings. This could be one of the reasons why pharmacological treatment was insufficient to bring about resolution of the acute episode; ECT was requiered, and the outcome in this patient suggests that it is a safe and effective treatment for both manic and depressive symptoms. To our knowledge, no evidence of using ECT or mood stabilizers for psychiatric symptoms in CTX have appeared in the literature. Our results indicate that ECT could be an option for this type of mental disorders with an underlying somatic illness.

BIBLIOGRAPHY

1. Carson BE, De Jesus O. Cerebrotendinous Xanthomatosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2021 Jan 14]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK564330/
2. Bonnot O, Herrera P, Kuster A. [Treatable neurometabolic diseases. Association with schizophrenia spectrum disorders]. Presse Med. 2015 Sep;44(9):889–97.
3. Preiss Y, Santos JL, Smalley SV, Maiz A. Xantomatosis cerebrotendinosa: aspectos fisiopatológicos, clínicos y genéticos. Revista médica de Chile. 2014 May;142(5):616–22.
4. Bonnot O, Fraidakis MJ, Lucanto R, Chauvin D, Kelley N, Plaza M, et al. Cerebrotendinous Xanthomatosis Presenting with Severe Externalized Disorder: Improvement After One Year of Treatment with Chenodeoxycholic Acid. CNS Spectrums. 2010 Apr;15(4):231–7.
5. Fraidakis MJ. Psychiatric manifestations in cerebrotendinous xanthomatosis. Transl Psychiatry. 2013 Sep;3(9):e302.
6. Yahalom G, Tsabari R, Molshatzki N, Ephraty L, Cohen H, Hassin-Baer S. Neurological Outcome in Cerebrotendinous Xanthomatosis Treated With Chenodeoxycholic Acid: Early Versus Late Diagnosis. Clinical neuropharmacology. 2013 May 1;36:78–83.
7. Lee Y, Lin P-Y, Chiu N-M, Chang W-N, Wen J-K. Cerebrotendinous Xanthomatosis with Psychiatric Disorders: Report of Three Siblings and Literature Review. 2002;25(5):7.