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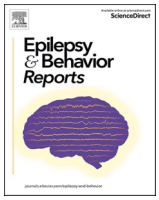

A functional seizure case in Wilson's disease

Lucas D'Andrea *, Raphael Mosqueira, Alcenor C. Miranda Filho, Renato L. Marchetti

Department of Neuropsychiatry, Institute of Psychiatry, Hospital das Clínicas, Faculty of Medicine, University of São Paulo, São Paulo, Brazil

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ABSTRACT

Wilson's disease (WD) is a rare disorder characterized by abnormal copper metabolism, leading to its accumulation in various tissues, particularly the brain and the liver. Psychiatric and neurological symptoms are common manifestations of WD. We present a case of a 22-year-old woman diagnosed with WD who exhibited neurological symptoms and experienced functional seizures (FS) that were misdiagnosed as epilepsy secondary to WD for almost two years. The patient's history of childhood trauma and interpersonal difficulties underscored the complex interplay between organic and psychogenic factors contributing to FS development. This case highlights the diagnostic challenges associated with the neuropsychiatric manifestations of Wilson's disease, as well as the complexities in differentiating functional seizures from epilepsy. It emphasizes the importance of comprehensive assessment and multidisciplinary care in optimizing patient outcomes.

1. Introduction

Wilson's disease (WD) is a rare disorder of copper metabolism characterized by accumulation of copper in various tissues, especially the brain and liver. It is caused by a genetic defect affecting the ATP7B gene (an autosomal recessive inheritance), which encodes transmembrane copper-transporting ATPase2, an important protein related to the excretion of copper in bile and helps bind copper to apoceruloplasmin, forming ceruloplasmin, a protein responsible for transporting more than 90 % of serum copper [1]. In WD, this function is compromised, leading to the accumulation of copper in tissues and generating symptoms depending on its location.

Many symptoms related to cerebral copper accumulation have been described, e.g.movement disorders, speech disturbances, drooling, gait and balance disturbances, seizures, cognitive impairment and a range of psychiatric symptoms [1]. Since it was first described, in 1912 Wilson's dissertation, 8 of 12 cases had psychiatric symptoms [2], but the disease was recognized only by its neurological aspects. Years later, with the development of treatment, it was recognized that psychiatric symptoms could occur at any point in the course of the disease with or without concomitant neurological symptoms. Most common psychiatric initial presentations (before or together with neurological and/or hepatic symptoms) are psychosis, depression, personality changes and learning disabilities [3]. During the course of the disease, most common presentations are depression, incongruous behavior, cognitive impairment and irritability [4]. Symptoms may either worsen – or be unmasked – or improve with chelating treatment [3]. It has been reported as well how psychiatric interventions can improve not only psychiatric symptoms but also motor symptoms [5].

Functional neurological disorder (FND) is a condition in which the primary pathophysiologic processes are alterations in functioning of brain networks rather than abnormalities of brain structures [6]. The most common presentations of FND are functional seizures (also called dissociative or psychogenic non-epileptic seizures) and functional movement disorders [6]. No single symptom or physical sign is pathognomonic of FND or functional seizures but some positive signs are needed to diagnose; the "gold standard" for diagnosis is recording patients' typical episodes consistent with functional seizures (positive sign) on video EEG (vEEG) without epileptic waves associated [7]. Signs with high sensitivity or specificity for functional seizures are long duration of events, fluctuating asynchronous limb or side to side head movements, pelvic thrusting, ictal eye closure, ictal crying, postictal memory recall [7].

To our knowledge, there have been no reports associating functional neurological disorder and dissociative symptoms (f.e. dissociative identity disorder, functional/dissociative seizure and dissociative amnesia) with WD. Because dissociative symptoms and functional neurological disorder symptoms are usually understood as purely "psychogenic" and WD's has an "organic" physiopathology, we believe clinicians may overlook the possibility of the diagnosis of functional and dissociative disorders in WD cases, in spite of neuropsychiatric literature revealing common comorbidity between functional and dissociative

* Corresponding author.
E-mail address: lucas.dandrea@hc.fm.usp.br (L. D'Andrea).

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symptomatology and organic conditions [8];

Following this theme, we describe a case of WD comorbid with Functional seizures. Functional Seizures (FS) are defined as paroxysmal changes in behavior, consciousness and autonomic function that resemble epileptic seizures but have specific clinical characteristics, called positive signs, and lack the electroencephalographic (EEG) signature of epileptic seizures [4]. Along with the case discussion, we will highlight the difficulty in diagnosing this kind of FND in patients with neurological diseases and the risks associated with misdiagnosis in this type of patient.

2. Case

A 22-year-old woman from a non-consanguineous marriage was admitted to the neurology ward in 2019 presenting with ataxia and falls, drooling, loss of sphincter control and mutism, These symptoms had gradually worsened over two years, beginning in 2017, and were associated with depressive features, with no reported family history of neurological or hepatic diseases. Neurological examination revealed a postural tremor in her upper limbs resembling a wing-beat tremor, limb cerebellar ataxia, Kayser Fleisher rings in both eyes, and phasic dystonia in her mouth muscles described as a Risus Sardonicus. There were no positive signs for motor FND. Serum ceruloplasmin levels were below 3 (normal 20–35 mg/dL), and brain MRI showed low T1 signal intensity in both lentiform nuclei and the midbrain, with high T2 signal intensity in the same areas, without enhancement post-gadolinium injection. Ultrasound of the abdomen showed a liver with irregular surface, semi edges blunt, altered echogenicity and echotexture representing chronic liver disease, cirrhosis pattern and signs of portal hypertension. Wilson's Disease was diagnosed clinically, as genetic testing was unavailable at the time, and treatment with penicillamine was initiated. While her neurological symptoms improved with treatment, her psychiatric symptoms worsened, and the patient was diagnosed with intellectual disability and an organic personality disorder – personality changes included disinhibition, puerility, impulsivity, and hypersexualization.

During outpatient follow-up, the patient's mother reported the occurrence of transient loss of consciousness (TLOC) episodes associated with movements, starting in 2021.

The episodes initially presented with preserved consciousness and were accompanied by nausea, vomiting, and asynchronous movements involving the trunk, neck, and limbs. This phase was followed by supraversion of the eyes and a transient episode of apparent loss of consciousness with behavioral arrest, characterized by a vacant stare lasting approximately 5 to 10 s. Subsequently, the patient exhibited ictal eye closure with resistance to passive eye opening, during which she either collapsed onto another individual or remained standing. Notably, the patient never fell to the ground or sustained injuries. The episodes further involved the adoption of a tonic limb posture or the presence of asynchronous, out-of-phase movements of the limbs and neck. The duration of these events varied, ranging from 10 to 60 min. Subsequently, the patient would report experiencing disorientation for approximately 10 min, accompanied by muscular discomfort. No episodes of tongue biting or cyanosis were reported by the patient's mother.

Another type of episode described by the mother involved a "divine conversation with god", during which the patient reported visions of deceased loved ones, including her goddaughter who passed away in 2017. Sometimes this presentation would progress to "being possessed by a demon", with marked changes in voice tonality and general behavior (more aggressive) and with prolonged duration, around 40 to 60 min, with full recovery after and no memory of it.

Both of the episodes occurred two to three times a week, worsening to three times a day at times, but did not require hospitalization or invasive procedures to stop them.

Between 2021 and 2023, the patient received epilepsy treatment with various medications, ultimately receiving gabapentin 600 mg/day and lamotrigine 200 mg/day, and there were no changes in reducing the frequency or the duration of the episodes. In 2023, she was referred to our neuropsychiatry group (PROJEPSI) and underwent a 96-hour Video-Electroencephalogram (VEEG) monitoring, read by two experienced epileptologists, during which both reported episodes that occurred without electroencephalographic correlates. Positive signs for FS during the episode were: ictal eye closure with resistance to eye opening, asynchronous out-of-phase limb and neck movements and long episode duration (up to 60 min). Additionally, hypnotic seizure suggestive induction was performed, with the patient and her mother's consent, inducing the occurrence and remission of both episodes, strengthening the hypothesis of FS and dissociative disorder.

Regarding her life background, the patient experienced parental abandonment during childhood, along with sexual, psychological, and physical abuse perpetrated by her mother, alcohol abuse by her father, and psychological abuse from a controlling ex-boyfriend.

In relation to the patient's family tree and family history: There are no reported neurological, psychiatric, or hepatic conditions in the parents, siblings, and grandparents, except for a paternal grandfather who passed away due to hepatocellular carcinoma. Ceruloplasmin levels were also measured in the patient's siblings, parents, uncles, cousins, and grandparents, all of whom presented normal results.

A diagnosis of Functional Seizure (FS) was made, and the patient was referred to our neuropsychiatric clinics for outpatient follow-up and FS treatment. After a 3 month-period of treatment with psychiatric consultation, family psychoeducation and CBT sessions, the episodes of FS reduced to 1 per month. Additionally, after psychiatric and neuropsychological evaluation, the patient was diagnosed with Identity Dissociative Disorder with possessive dissociative episodes, intellectual deficit (IQ assessment below 70) and organic personality disorder related to Wilson's Disease.

3. Discussion

This is to our knowledge, the first report of a comorbid WD and FS and dissociative disorders.

Since WD is a neuropsychiatric condition, it is plausible to assume that seizure would be one of its symptoms. However, it is not as frequent as imagined, with some studies reporting around 6 % of seizures in WD patients [9] and it can occur at any stage of the disease [10]. When compared to the general population, the prevalence of epilepsy in WD is about 10 times higher [11]. The seizure types associated with Wilson's Disease (WD) encompass generalized tonic-clonic seizures, focal onset with or without impaired awareness and focal seizures with progression to bilateral tonic-clonic. Additionally, periodic myoclonus and status epilepticus have been documented, although these occur less frequently [12]. Nonetheless, it is important to suspect that refractory epilepsy cases related to WD with a somewhat atypical semiology for epileptic events could be FS.

While Wilson's disease and functional seizures are distinct conditions, there may be a connection between them stemming from the neurological and psychiatric manifestations associated with WD and because it is observed that individuals with FS often display neuropsychiatric issues and personality changes [13]. Since WD is linked to the accumulation of copper in the basal ganglia, it leads to neurotoxicity and dysfunction of the neurotransmitter systems, particularly the putamen and globus pallidus, affecting emotional regulation [14]. While the exact pathophysiology remains unknown, it is theorized that the dopaminergic system imbalance contributes to psychiatric disturbances, including mood instability, psychosis, and behavioral abnormalities. Additionally, abnormalities in serotonergic and noradrenergic pathways have been implicated in mood disturbances, anxiety, and cognitive impairments [14].

In addition to basal ganglia alterations and the psychiatric comorbidities associated with WD [15], this case presents additional risk factors for the development of FND. These include a history of early-life adversities such as parental abandonment during childhood, exposure to

sexual, psychological, and physical abuse inflicted by her mother, paternal alcohol abuse, and psychological maltreatment by a controlling former partner [16].

Another point of interest is that since intellectual disability is an important known risk factor for developing FS [17], and it isn't uncommon for WD patients to exhibit developmental disability, together with the environmental responses caused by the personality changes, it is of utter importance to consider the phenomenology of the complex interplay between structural and functional symptomatology when assessing such cases. Failure to do so may overlook important psychopathological aspects of patients suffering from WD.

Our case underscores the intricate interplay between organic and psychogenic factors in neuropsychiatric disorders, highlighting the importance of a multidisciplinary approach in clinical care [18]. The patient's history of childhood trauma and interpersonal difficulties underscores the complex interplay between environmental stressors and psychological vulnerability, contributing to the development and perpetuation of FS [19]. Moreover, the coexistence of intellectual deficit and organic personality disorder in the context of WD further complicates the clinical presentation, necessitating tailored interventions addressing both organic and psychosocial aspects of the disease.

4. Conclusion

The presented case underscores the diagnostic and therapeutic challenges associated with neuropsychiatric manifestations of WD, particularly in the context of comorbid functional seizures. Clinicians should maintain a high index of suspicion for FS in patients with WD presenting with seizure-like events refractory to conventional therapy, emphasizing the importance of comprehensive assessment and collaborative care to optimize patient treatment and to avoid iatrogenic events and unfavorable outcomes. Further research is warranted to elucidate the underlying mechanisms linking WD and FS and inform targeted therapeutic interventions for affected individuals.

CRediT authorship contribution statement

Lucas D'Andrea: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Raphael Mosqueira:** Writing – review & editing. **Alcenor C. Miranda Filho:** Writing – review & editing. **Renato L. Marchetti:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

[1] Członkowska A, Litwin T, Dusek P, et al. Wilson disease. Nat Rev Dis Primers 2018; 4:21. https://doi.org/10.1038/s41572-018-0018-3.

[2] Kinnier-Wilson S. Progressive lenticular degeneration – A familial nervous disease associated with cirrhosis of the liver. Brain 1912;34:295–8.

[3] Zimbrean PC, Schilsky ML. Psychiatric aspects of Wilson disease: A review. Gen Hosp Psychiatry 2014;36(1):53–62. https://doi.org/10.1016/j.genhosppsych.2013.08.007.

[4] Jafari A, Rezaei Tavirani M, Parvareshi Hamrah M, Ahmadi Karvigh S, Bashi Zadeh Fakhar H. Psychogenic non-epileptic seizures: A narrative review. Archives of Academic Emergency Medicine 2020;8(1):e10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7286438/.

[5] Antonio Bozutti L, Gallucci-Neto J, Luiz Marchetti R. Electroconvulsive therapy for mania associated with Wilson disease: Improvement in psychiatric and motor symptoms. Clinical Parkinsonism & Related Disorders 2021;4:100090. https://doi.org/10.1016/j.prdoa.2021.100090.

[6] Hallett M, Aybek S, Dworetzky BA, McWhirter L, Staab JP, Stone J. Functional neurological disorder: New subtypes and shared mechanisms. Lancet Neurol 2022; 21(6):537–50. https://doi.org/10.1016/S1474-4422(21)00422-1.

[7] Baslet G, Bajestan SN, Aybek S, et al. Evidence-based practice for the clinical assessment of psychogenic nonepileptic seizures: A report from the American Neuropsychiatric Association Committee on Research. J Neuropsychiatr Clin Neurosci 2021;33:27–42. https://doi.org/10.1176/appi.neuropsych.20060168.

[8] Carle-Toulemonde G, Goutte J, Do-Quang-Cantagrel N, Mouchabac S, Joly C, Garcin B. Overall comorbidities in functional neurological disorder: A narrative review. L'Encéphale 2023;49(4). https://doi.org/10.1016/j.encep.2023.06.004.

[9] Ibrahim W. Coexistence of seizure with Wilson's disease: A systematic review. Prog Neurol Psych 2020;24:24–30. https://doi.org/10.1002/pnp.559.

[10] Shukla R, Desai P, Vinod P. Wilson's disease presenting as status epilepticus. J Assoc Physicians India 2006;54:887–9.

[11] Dening T, Berrios GE, Walshe JM. Wilson's disease and epilepsy. Brain 1988;111: 1139–55.

[12] Prashanth LK, Sinha S, Taly AB, Mahadevan A, Vasudev MK, Shankar SK. Spectrum of epilepsy in Wilson's disease with electroencephalographic, MR imaging, and pathological correlates. J Neurol Sci 2010;291(1–2):44–51. https://doi.org/10.1016/j.jns.2010.01.007.

[13] Perez DL, LaFrance Jr WC. Nonepileptic seizures: An updated review. CNS Spectr 2016;21(3):239–46. https://doi.org/10.1017/S109285291600002X.

[14] Litwin T, Dusek P, Szafrański T, Dzieżyc K, Członkowska A, Rybakowski JK. Psychiatric manifestations in Wilson's disease: Possibilities and difficulties for treatment. Ther Adv Psychopharmacol 2018;8(7):199–211. https://doi.org/10.1177/2045125318759461.

[15] Dening TR, Berrios GE. Wilson's disease: Psychiatric symptoms in 195 cases. Arch Gen Psychiatry 1989;46(12):1126–34. https://doi.org/10.1001/archpsyc.1989.01810120076012.

[16] Fobian AD, Elliott L. A review of functional neurological symptom disorder etiology and the integrated etiological summary model. J Psychiatry Neurosci 2019;44(1):8–18. https://doi.org/10.1503/jpn.170190.

[17] Rawlings GH, Novakova B, Beail N, Reuber M. What do we know about non-epileptic seizures in adults with intellectual disability: A narrative review. Seizure 2021;91:437–46. https://doi.org/10.1016/j.seizure.2021.07.021.

[18] Chahine LM, Chemali ZN. The bane of a silent illness: When Wilson's disease takes its course. Int J Psychiatry Med 2006;36(3):333–8. https://doi.org/10.2190/1A0B-2M98-0VVE-485R.

[19] Popkirov S, Asadi-Pooya AA, Duncan R, Gigineishvili D, Hingray C, Kanner AM, et al. The aetiology of psychogenic non-epileptic seizures: Risk factors and comorbidities. Epileptic Disord 2019;21(6):529–47. https://doi.org/10.1684/epd.2019.1107.