

Dysexecutive Syndrome in a Patient with Wilson's Disease

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Clinical Case Report: This paper presents the alterations and deficits in executive functions of a 33 years old man with Wilson's disease, patient at the Hospital Universitario La Samaritana in Bogotá, who in 2011 was diagnosed with cerebellar ataxia, and beginning to show a clinical picture of dysarthria and generalized motor difficulties. The presence of neuropsychological disorders, as well as the results obtained by Magnetic Resonance Imaging (MRI) of the brain and optical exam (Kayser-Fleischer rings) confirmed the diagnosis of Wilson's disease. **Results and Conclusion:** The neuropsychological profile of the patient showed alterations of attention and mnemonic processes associated with frontal functioning, as well as slowing-down of motor activities and low speed in processing information. The assessment of executive functions revealed impairment in cognitive flexibility, impulsivity and disinhibition, as well as difficulties in the process of planning, organizing and monitoring. All of these features indicated the presence of a dysexecutive syndrome in the patient and correlated with the results obtained by MRI.

Keywords: Wilson's Disease; Executive Functions; Neuropsychological Profile; Dysexecutive Syndrome

Introduction

Wilson disease (WD), also known as hepatolenticular degeneration, is an autosomal recessive hereditary disorder that affects copper metabolism causing an excessive accumulation of this chemical in the body (Litwin et al., 2013; Hewlett, 2012; Teleive et al., 2012; Pfeiffer, 2011; Taly, Prashanth, & Sinha, 2009), primarily in the liver, kidney and brain, producing alterations and liver damage, neurological and psychiatric disorders. It has been reported that the incidence of the disease is one in every 30,000 live births (Moller et al., 2011) and affects both men and women, although the neurological manifestations are more common in male patients.

Regarding the symptoms produced by excess metal in the Central Nervous System (CNS), the most affected areas that show degeneration are the lenticular nucleus, putamen, caudate head, globus pallidus, ventral thalamus, dentate nucleus, mid-brain (except for the red nuclei), pons and in some cases there is cerebellar atrophy. It is commonly observed that on magnetic resonance imaging (MRI) these areas are hyperintense on T2, and with the transcranial sonography technique, hyperechoic lesions are found (Svetel, Mijajlovi, Tomiet et al., 2012; Huster et al., 2012; Krysiak, Handzlik-Orlik, & Okopien, 2012; Nagel & Miralles, 2007; Hitoshi, Iwat, & Yoshikawa, 1991).

WD presents a wide spectrum of manifestations depending on the areas affected by the deposition of metal which are: the liver form, the neurological and psychiatric forms and the form with predominance of other organs (Roberts, 2011; Xu et al.,

2010; López & Serrano, 2007; Wilson, Alderman, Burgess, Emslie, & Evans, 2003). Litwin, Gromadzka, Czlonkowska, et al. (2012) conducted a retrospective study of 204 cases with WD and found that the most common type is the neuropsychiatric with 105 cases, followed by the liver type with 67, and by the type with predominance of other organs, with 32 of the 204 cases studied.

The neurological form of the disease, is particularly characterized by abnormal movements, postural and intentional tremor, chorea, athetosis, myoclonus, seizures, ataxia, dysarthria, hypophagia, hypersalivation, pyramidal signs and abnormalities of eye movement (European Association for the Study of the Liver-EASL, 2012; Svetel, Mijajlovi, Tomiet, et al., 2012). As the disease progresses it is common to find a more complex clinical picture (Lorincz, 2010).

With respect to the WD neuropsychological profile there is little information at present. The majority of articles, research and scientific texts make a description of the general aspects of the neurocognitive profile (Carta et al., 2012; Birk et al., 2011; Jacob & Srivatsa, 2011; Levy & Dubois, 2006).

In a study by Hegde, Sinha, Taly & Vasudev (2010), where he presented the cognitive profile of twelve patients contrasting it with MRI diagnostic studies and the signs and symptoms reported, a greater impairment was found in motor speed (73%), verbal working memory and focused and sustained attention (50%), verbal learning (42%), processing speed (33% - 34%), visual memory and verbal fluency (25% - 27%) and verbal recognition (17%).

Schmitt et al. (2011), in a 40 years follow-up study with 36 patients diagnosed with WD reported that 25% of the patients had neuropsychiatric manifestations where the common symptoms were attention deficit, changes in personality, irritability and hypersomnia. Other studies attribute the changes in mood and personality to a dopamine deficit present in the disease (Litwin, Gromadzka, Członkowska, Poniatowska, & Poniatowska, 2013; Günther, Villmann & Hermann, 2011; Schmitt et al., 2011; Popević, Kisić, Đukić, & Bulat, 2011; Hegde, Sinha, Taly, & Vasudev, 2010).

With respect to executive functions (EF) and Wilson's disease, there is no conclusive research but there is an evidence that regarding the relationship between frontal lobes and basal ganglia, a relationship can be established with the presence of alterations in the executive functioning (Pladdy, 2007).

The EF is dynamic processes which have a high degree of dependence and is performed by different domains or neural network interconnections that work as a unit involving a set of cognitive skills related to processes of programming, regulation and planning of the necessary behavior to achieve an adequate level of adjustment and problem solving related to various cortical-sub cortical areas of the Central Nervous System for its correct functioning.

Alterations due to damage or injury of its structures and networks result in the presence of low capacity for self-control or self-direction, emotional lability, increased tendency to irritability and excitability, impulsivity, erratic behavior, stiffness and deterioration in self-care and grooming (Lezak, 1995; Verdejo-García y Tirapu-Ustárroz, 2012).

Several studies have shown that executive functions are not totally dependent on the prefrontal cortex, but there is a network of neural interconnections that interact simultaneously involving other areas of the CNS, especially connections with subcortical structures such as basal ganglia (Suchy, 2009; Elliot, 2013).

Additionally, it has been established that there is an interaction between the basal ganglia and other subcortical structures such as the thalamus, subthalamic nucleus and globus pallidus in the conformation and configuration of circuits that interact with the frontal lobe for generating a regulated, controlled and supervised behavior of executive functions (Verma, Patil, & Lalla, 2012; Verdejo & Bechara, 2010; Suchy, 2009).

Thus, it has currently been established that the Executive Functions depend on the integration of network circuits between the prefrontal cortex and the cortical subcortical structures and not just on one specified region. Lesions in these networks, even without impairment of the frontal lobe, can generate dysexecutive clinical pictures characteristic of prefrontal syndromes as evidenced in progressive supranuclear palsy, multiple system atrophy and Huntington's disease. Therefore, frontostriatal circuits are important in mediating executive function (Elliot, 2013).

This case study aims to show the main changes in cognitive processes presented in a patient with WD, highlighting the alterations or deficits in executive functions and their correlation with neuroanatomical findings obtained by brain MRI. The case study allows us to observe that the impairment in executive functions presented in the WD is not due to injuries in frontal regions as commonly occurs, but to lesions in the intercommunication Prefrontal Cortex-Basal Ganglia—Prefrontal Cortex.

Method

Desing

A single case study was carried out, using a descriptive design and following an analytical empirical methodology. This methodology was applied to a participant to assess his cognitive functions, focusing the process on his executive functions (Hernández, Fernández, & Baptista, 2006).

Participant

Male patient, aged 33, right laterality, with technical professional education level, currently unemployed. He has a history of psychoactive substances consumption, specifically ethanol, with an intake frequency of 3 to 4 times per week which persisted for about 10 years. Consumption is terminated due to the initiation of the major symptoms of the disease. Similarly, there is history of non-abusive social use of cocaine for a year. In 2011 is diagnosed with cerebellar ataxia, initiating a clinical picture of dysarthria and progressive motor impairment.

The patient is admitted to a hospital with a clinical picture of ataxia, dysarthria, hypersalivation, hypophagia and constant mood change. He goes through a multidisciplinary assessment process which found, from the dermatology area, copper accumulation after performing a hyperpigmentation biopsy in lower limbs. In the different diagnostic tests performed by the internal medicine staff, accumulation of this metal is found. The gastroenterology examination gives evidence of liver damage. From the area of ophthalmology, the Kayser-Fleischer rings are found (See Figure 1).

From the neurology area, a brain MRI was performed to the patient. Findings show hyperintense lesions in the basal ganglia (Figure 2) and midbrain (Figure 3), characteristic signs of the disease. The frontal lobes were found intact.

Procedure

This research was conducted in three phases. In the initial phase, an identification of the case was made at medical and neurological level. Intake interview and signature of the informed consent were carried out. In the second phase, the neuropsychological assessment took place. And in the final phase, the analysis of results and preparation of the final document were done.

Instruments

Brief Neuropsychological Battery in Spanish, Neuropsi: This is a screening test. In order to carry out its standardization, it was applied to a sample of 800 neurologically intact subjects aged between 16 and 85 years. The sample was divided into four groups according to age and educational level. Reliability was assessed by the test-retest method, with an interval of three months between each application and marking was done by different assessors. Reliability between examiners was 0.89 to 0.95. This instrument allows assessing a wide range of cognitive functions in patients with psychiatric, geriatric, neurological and various medical problems (Ardila & Ostrosky, 2012).

Trail Making Test—TMT—Parts A and B: It is considered that Part A measures motor, viso-spatial skills of visual search and sustained attention, while Part B, additionally involves mental flexibility and divided attention. The test-retest reliability varies greatly according to the specific study (0.60 to 0.90),

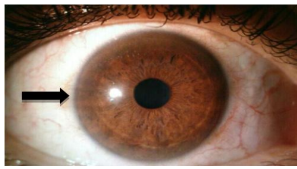


Figure 1.
Kayser Fleischer Ring in the patient.

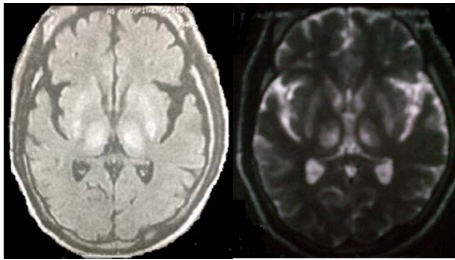


Figure 2.
MRI, hyperintense lesions in basal ganglia.

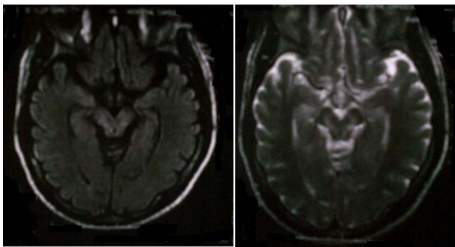


Figure 3.
MRI hyperintense lesions on T2 at midbrain level in patient with WD.

depending on the part or applied version and the pathology (greater variability in schizophrenics, more stability in patients with vascular disease). The temporal stability of the B-A difference is 0.71. The educational level has a significant influence on the scores, especially in Part B. No gender differences were found. According to studies conducted, there is a significant correlation between the test score (both parts) and the degree of atrophy of the caudate nucleus (Ardila & Ostrosky, 2012).

Stroop D-Keys: It is used to assess inhibition in executive functions. The reliability of the test is carried out by the test-retest method, being 0.84. Likewise, it is marked by different assessors and obtains significant correlations (Lopez, Serrano, Llano, Mateos, López, & Sánchez, 2010).

Wisconsin Card Sorting Test, WCST: neuropsychological test used to assess cognitive flexibility. It is especially sensitive to lesions involving the frontal lobes. The reliability was conducted from a test-retest with a correlation of 0.93 for perseverant responses, 0.92 for perseverant errors, 0.88 for non-perseverant errors, and concurrent validity of 70% (Scheres et al., 2004).

Visual-verbal Memory Curve by Ardila: A list of twelve words (animals, fruits, and body parts) is presented in three trials. After each trial the subject is asked to tell all the words he can remember. Also, intrusions and perseverations are recorded, as well as primacy and recency effects (Ardila & Ostrosky, 2012).

Chip Test: the purpose of this test is to assess the understanding of verbal instructions of increasing complexity. The application consists of presenting the chips to the patient and asking him the respective questions which must be made clearly and slowly. Words must not be emphasized. The administration consists of 5 parts, only in Part A and B instruction can be repeated once (Ardila & Ostrosky, 2012).

Wechsler Adult Intelligence Scale, WAIS III: The Wechsler Intelligence Scale for adults consists of a Verbal Scale and a Performance Scale, so that the application provides three scores: a Verbal IQ, Performance IQ or Manual IQ, and a Full Scale IQ. The subtests used were: block design which measures visual-motor coordination, perception, capacity for analysis, synthesis, logic and reasoning. And the matrices subtest, that was used specifically to determine the attention and planning capacity.

Test of emotion recognition in faces by Baron Cohen (Faces Test) and moral dilemmas of the theory of the mind.

Results

It was found that the patient showed slowness in the speed of information processing, disinhibition, hypersexuality, persevering behaviors, cognitive rigidity, difficulty to establish or follow sequences, and failure in the development of strategies for achieving goals. Additionally, he presents emotional lability, low frustration tolerance and impairment in the abstraction capacity, in encoding and recalling both verbal and visual stimuli mediated by his executive functioning. On the contrary, his long term memory both episodic and semantic is preserved (**Table 1**).

These findings account for a clinical picture of dysexecutive syndrome in the patient, which was not the by-product of the damage in the frontal structures, but in the cortico-subcortical connections between basal ganglia and frontal lobes.

Discussion

The alterations found in the patient's cognitive functions, which correspond to a dysexecutive syndrome, may be associated with possible failure in the connections between basal ganglia and frontal lobes. That is why dysexecutive syndrome is a trigger for alterations involving different cognitive areas (Ardila, 2008).

Results of this study are similar to those reported by Clark, Collazo, Ruenes & García (2011) who showed that patients with a neurological form of WD had no major impairment in basal ganglia, but they did in their interconnections, showing poor operating performance on executive functioning, memory, visuospatial processing and verbal and abstract reasoning.

Many years ago, the research by Posner & Raichle (1994), identified the existence of interconnected neural networks to describe attention processes. They suggested that the central control mechanism of the alert system, the orientation system and the executive system forms a dependent circuit, where each one of them is responsible for a specific task in the attention process, but interacting dynamically and integrating into the executive system the interconnected networks of the frontal lobe, the anterior cingulate and the basal ganglia, which makes cognitive functions also interdependent in this process.

In summary, the present case describes a patient who shows neurological involvement both in memory and attention mediated by the executive dysfunction which decreases the possibil-

Table 1.
Results of neuropsychological test.

Neuropsych		
Score	Score Normal	
89	112 - 102	
Trail Making Test A		
Time	Score Normal	
164 seconds	27 - 32 seconds	
Trail Making Test B		
Time	Score Normal	
677 seconds	56 - 69 seconds	
WAIS III		
	Direct Score	Normal Score
Cubes	4 - 8	3
Matrices	11 - 12	8
Wisconsin Card Sorting Test		
	Score	Normal Score
Trials	128	72
Categories	1	5
Corrects	62	67
Perseverative Errors	41 (32%)	(5%)
Conceptual level	40	67
Ardila's Verbal Memory Curve		
	Score	Normal Score
Initial Volume	5	7 ± 2
Maximum Volume	9	10
Trials	10	4
Evocation 3 (20) minutes	9 (5)	10 (8)
Ardila's Visual Memory Curve		
	Score	Normal Score
Initial Volume	5	7 ± 2
Maximum Volume	10	10
Trials	3	4
Evocation 3 (20) minutes	9 (8)	10 (8)
Test of emotion recognition in faces		
Corrects	Errors	
17/20	Guilt—Anger/Boredom—Fear	

ity of making new effective learning, develops appropriate encoding and recalling strategies, inhibits irrelevant information effectively, holds his attention on the tasks and foster flexibility. All of these impairments can be attributed more to a dysfunction in the cortical-subcortical neuronal interconnection which interferes with the proper functioning of cognitive processes.

The research that gives account of affectations on cognitive functions in WD suggests a deficit in different areas of these operations. However, considering the role of basal ganglia—executive functions, it is proposed that the main neuropsychological deficit caused in WD lies in executive functions. In similar profiles to the one reported in this study the other cognitive impairments evidenced are secondary to such a deficit.

Although the description of executive functions and neuropsychological involvement made in this study is similar to the descriptions made by other researchers, it differs that it empha-

sizes the relationship between cortical and subcortical structures in the conformation of the dysexecutive clinical picture present in WD and points out that the impairments in other domains are secondary to this one.

On the other hand, it is important to note that although the patient has a history of chronic alcohol consumption, and that this condition has some effects on the Central Nervous System—CNS—which, in turn, affects cognitive functions, several studies have found a phenomenon that has been called “deficit recovery following abandonment” (Garrido & Fernandez, 2004), which refers to a decline in cognitive functions immediately to cessation of the substance. But after overcoming the withdrawal symptoms and having abandoned consumption completely, patients are able to recover their functions within approximately one month. However, at present, the patient in this case study has been in abstinence for more than two years which leads to relating his clinical dysexecutive syndrome directly with WD and copper accumulation in the basal ganglia (Bidaki et al., 2012; Carta, Mura, Sorbello, Farina, & Demelia, 2012; Di Stefano, Lionetti, Rotolo, La Rosa, & Leonardi, 2012; Castañeda, Ubilluz, Ávalos, Escalante, & Nicoll, 2002).

Finally, it is important to note that the projections and circuits between and from the basal ganglia to the cortex have been extensively described in the literature. It is now known that in addition to their circuits and projections with the frontal lobes there are also connections with other cortical areas. Target projections of the thalamic nuclei, superior colliculus, reticular formation and pedunculopontine nucleus are located toward the temporal and parietal areas. Furthermore, it has been reported that such nuclei have a strong participation in the modulation of behavior (Peng, Lutsenko, Sun, & Muzik, 2012; Cheon et al., 2010; Stocco, Lebiere & Anderson, 2010; Bernal & Calle, 2007). This explains the wide variety of cognitive symptoms present in the clinical case shown in this article and the dynamism and complexity of executive processes in the CNS.

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