

Neuropsychiatric symptoms in a patient diagnosed in adulthood with Metachromatic Leukodystrophy: Case report of low incidence and prevalence in Colombia.

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Abstract

Introduction: The metachromatic leukodystrophy (MLD) is a chronic pathology of low prevalence and low worldwide incidence, it is characterized by presenting alterations in the white substance of the central nervous system (CNS), result of a deficiency of the Arylsulfatase A (ARSA) enzyme which is responsible for catalyzing different chemical reactions throughout the organism. It is been found that MLD is clinically related to a deficiency of the neurocognitive functioning, especially in memory tasks (operative memory) and in executive functions (verbal semantic fluency, inhibition, planning and control of the immediate conduct).

Objective: Identify the neurocognitive impairment and the neuropsychiatric symptoms in a patient diagnosed with MLD. Case report of low prevalence and incidence in Colombia.

Methodology: Participant: Sixty aged female patient, single, right handed person and a teacher with a progressive loss of recent memory, accompanied with postural instability, gait disturbance, balance problems and moderate to severe alterations of neurocognitive and affective type.

Results: It is been found that the patient presents executive alterations (frontal lobe) in decision-making, planning, inhibition and in operative memory, correlated to a severe alteration in her basic, instrumental and advanced activities of daily life.

Conclusion: It is necessary to make neuro-rehabilitation functional plans for people diagnosed with MLD, having as a main objective the improvement of their quality of life in individual, social and family aspects.

Keywords: Attention, Neurocognitive Functioning, Executive Functions, Memory, Metachromatic Leukodystrophy.

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Introduction

The Metachromatic Leukodystrophy, (MLD) is a pathology of low prevalence and incidence worldwide; it is characterized by presenting alterations in the white substance of the central nervous system (CNS) and by a deficiency in the Arylsulfatase A enzyme, responsible for catalyzing different chemical reactions throughout the organism. [1,2]. The Arylsulfatase A deficiency is clinically correlated to the damage of the CNS, alterations in the myelination sheath of the neurons and

sometimes the kidneys and the biliary duct. This pathology of a chronic and progressive type worsens the quality of life of the patients, of their families and of their immediate context, generating alterations in their emotional well-being, their daily life activities, in their social support as well as in their neurocognitive functioning. In relation to the neurocognitive functioning, different studies [3,4] have found that MLD patients often present alterations to make and control their conduct, difficulties to inhibit and to process different answers, inability to handle stimuli in different sequential

levels, with regard to the attention levels, the sustained attention is commonly the most affected, the subjects present inability to keep the concentration on a determined stimulus [3]. In other studies [5] a deficiency to control and evocate immediate character information has been found, in this case, it is a deficiency in the operative memory, due to a brain disability in the frontal and superior gyrus and, brain structures in charge of information processing along the brain cortex.

The objective of this article is to identify the neurocognitive damage and the neuropsychiatric symptoms in a patient diagnosed with MLD. We aim to establish a series of functional neuro-rehabilitation techniques in patients with this diagnose in order to improve their quality of life.

Materials and Methods

Participant

The clinical case is focused on a sixty aged single female patient, a right handed teacher with a symptomatology which started in 2006 with persistent objective episodes of vertigo, headache, generalized paresthasias, spine pain and jerking sensation, blurred vision, instable walking, decrease in the recent memory, affective symptoms of depressive and anxious character, insomnia, chronic fatigue and somatomorphic complaints. In the neurological exploration we found that her mental functioning does not present any "alteration". Cranial nerves slow functioning.

Motor-Sensitive System. Bilateral decreasing in the sensitive pressure left facial hypoesthesia, muscular weakening and IV/V paresthasia in the four limbs. Psychomotor slowness, postural instability, walking alteration, balance problems, osteo-muscular reflexes with no alteration.

Absent meningeal signs Slight cerebellar function, bilateral dysmetria and dysdiacokinesia, with left predominance. The metabolic, immune and infectious profile showed normality. With regard to her emotional level, she showed a mixed depressive and anxious clinical profile, which required a hypnotic and pharmacological treatment with inhibitors of serotonin. An evaluative protocol was followed to rule out a neurocognitive damage associated with MLD, and at the same time to make a differential diagnose between the Alzheimer disease and possible corticobasal degeneration.

Materials

Neuropsychological evaluation:

- Mini-Mental State Examination-MMSE: It is a short cognitive detection test which evaluates the cognitive functioning, it consist of 30 sections and it is grouped in five dimensions: orientation (10 points), fixation (3 points), calculus and memory (5y 3 points), language (8 points) and visuoconstructional skills (1 point) [6].
- Montreal Cognitive Assessment-MOCCA: It is a neurocognitive test of a specific type which measures the executive functions, attention, immediate verbal and

deferred memory, visuospatial and visuoconstructional domains. It presents a 90% of more sensibility and specification in comparison to the MMSE [7].

- Wechsler Adult Intelligence Scale: It is a sub-test of the WAIS which has as aim the measuring of the individuals' attention and their immediate verbal memory [8].
- Yesavage's geriatric depression scale: It is a questionnaire that evaluates the depressive symptomatology, it consists of 30 items. The score goes from: 1-9 normal, 10-22 slight depression and from 23-30 severe depression [9].
- Beck's Anxiety Inventory [10]: It is a scale type Likert, which aims to evaluate the symptoms of anxiety, it consist of items, which are divided at the same time in subjective and somatic symptoms. It has a punctuation of four points per question (absolute, slight, moderate, serious), the overall score of its items includes minimum, slight, moderate and severe anxiety.
- Trail making test: Paper and pencil test which has an objective to measure the attention levels (part A). The individual must join the numbers from 1 to 25 consecutively, and the executive functions (part B), which consist of join the numbers from 1 to 25, but this time alternating with letters (1A-2B-3C successively). The individual must do the test as fast as possible [11].
- History of Babcock: This test aims to evaluate the verbal and deferred Memory. This is a listening type test [12]
- Clock Test: It is a neurocognitive test, which evaluates the cognitive functioning in patients with neurological diseases or neurodegenerative diseases.
- It is a test with a high sensibility to detect insanity by Parkinson or Alzheimer [13].
- Frontal Assessment Battery FAB: it is a specific test which measures the executive functioning (frontal lobe) or the low neurocognitive performance which is present in elderly people or in people diagnosed with a neurodegenerative disease [14].
- Neuro-Psychiatric Inventory: It is a test that evaluates the intensity and the frequency of alterations of neuro-psychiatric type. The test is divided in the following sub-items: delirium, hallucinations, excitement/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleepiness and appetite. The frequency score in the test goes from 0-4 and of seriousness of 1-3, with an overall score of 144 and of 123 as a cutoff point to determine a neuropsychiatric profile [15].
- Verbal fluency: It is a test which evaluates the information processing speed of the individual. They are asked to say the names of animals and people in a minute. It is also made in a random manner;

the individual must say a word, alternating it with a category asked by the evaluator. Its score is obtained by adding each one of its items.

- **General Health Questionnaire GHQ-28:** This evaluates the self-perception with regards to one self's health. This test is grouped in four sections of seven items (somatic symptoms, anxiety/insomnia, social dysfunction and depression). A score of or over 23 points is a possible indicator of a psychiatric condition [16].
- **Barthel's Index:** It is a questionnaire which evaluates the level of functional independence showed by the individuals when doing basic daily life activities (BDLs) [17].
- **Lawton and Brody's Scale:** It is a questionnaire which evaluates the level of functional independence showed by the individuals when doing instrumental activities in their daily life [18].

Procedure

The evaluation was carried out bearing in mind the following steps:

1. Interview to be familiar with the patient and with her family.
2. A revision of the patient's clinic record and her medical background.
3. Neuro-psychological Evaluation.
4. Neuro-Psychological Report
5. Functional Plan for Neuro-Rehabilitation.

Ethical Aspect

The patient and her companion in agreement with the researchers signed an explicit consent indicating the procedure to be applied for the patient. Their anonymity was warranted. The patient was informed that the test would be made in paper and with a pencil, this way it would not be a risk for her physical well-being. The study was carried out by taking the ethical principles as a reference for the elaboration of researches and experimentation on human beings, in this case, the Declaration of Helsinki, The declaration of Berna and the resolution 008430 of the fourth of October of 1993 of the Social Protection Ministry of the Republic of Colombia concerning to the ethic aspects of research on human beings.

Neuroimaging Studies

A magnetic resonance imaging scan in coronal, sagittal and axial sequence was taken (We only present the axial plane) after the shooting of the contrast media, where it was found that the patient shows multiple confluent hyper intensity of the subcortical white matter and periventricular. A partial affectionation of the posterior limb of the internal capsule (Figure 1), as well as right cerebellar hyper intensities laterals to the fourth ventricle (Figure 2). These findings are clinically

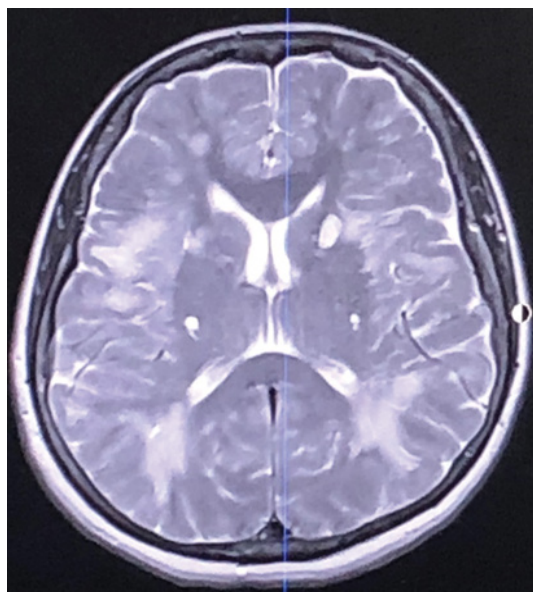


Figure 1. White matter hyper intensities to a subcortical level in patient diagnosed with MLD.

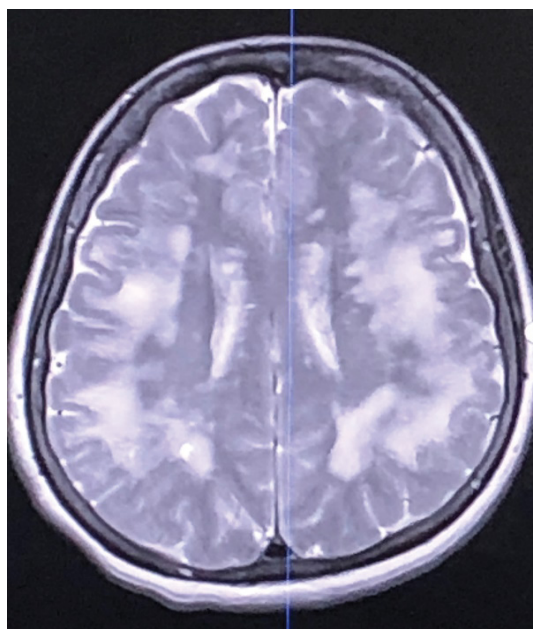


Figure 2. White matter Hyper intensity to the subcortical level in a patient with MLD. Frontal Lobe damage, cerebellum and IV ventricle.

related to a vast involvement of the bilateral white matter compatible with a demyelinating disease as MLD.

Qualitatives Results

Emotional profile: The values of the anxiety and depression scales show that the patient presents a mixed clinical profile of generalized anxiety and depression, with more prevalence of anxiety as a clinical profile of psycho-motor excitement than the depressive one as emotional involvement. Both medical profiles are having influence on the patient's quality of life deterioration (Table 1). The score of the scales present that we are dealing with a neuro-psychiatric profile which must be treated within a multidisciplinary approach.

Table 1. Resultados de la Evaluación Neuropsicológica en la Paciente con LDM.

Name of the Test	Results
Yesavage's Depression Scales	28/30
Anxiety Scales	54/64
Mini Mental MMSE	21/30
Retention of Digits	
direct order	4/16
inverse order	3/14
TMT Form A	She could not do it
TMT Form B	She could not do it
Babcock's Immediate History	4/21
Babcock's Deferred History	2/21
FAB	10/18
MOCA	14/30
Neuro-Psychiatric inventory NPI	130/144
Verbal Fluency	
- Animals	2
- Persons	4
Clock Test Order	2/10
Clock Test Copy	1/10
Barthel's Index	30/100
Lawton Y Brody's Scale	3/8
General Health Questionnaire GHQ-28	84/84

Mini-mental state examination

The results of the test indicate that the patient is conscient of time and place in a partial manner; in general level neurocognitive alterations in each one of the sub-items of the MMSE. The results of the test tend to indicate a possible dementia, but the signs and the symptoms of the patient suggest the making of a comparative chart with a neuro-degenerative disorder as the MLD, the symptoms of the patient show a high neurological and neurocognitive deterioration which is not clinically correlative to a demential profile of frontotemporal type, Alzheimer, vascular or Lewy bodies in an incipient manner.

Specific Cognitive Functioning

Attention

In the specific Neurological and/or Neurocognitive Functioning test it was evident a moderate-severe deficiency in the sustained attention in the patient. The patient is not in conditions to sustained new information; this alteration is associated with the malfunction, which is present in her executive memory, which disables her to condensate and store immediate information. These data are verified in the test TMT form A, the time it took to the patient to do the test makes us clinically infer that her alterations in attention tasks are a predictive factor for a more advanced alteration in her attention processes, specifically related to frontal subcortical circuits, which could be generating alterations in her motor and punctual behavioral aspects. The data in these tests lead to a possible dysfunction in the superior and medium orbitofrontal gyrus and sulcus, brain structures associated with a suppressing conduct and a deficiency in her executive memory.

Executive functions

In the test applied in this section, it was evident that the patient presents moderate-severe alterations to plan, organize, direct and control her immediate conduct. The patient is disabled to manage in many dimensions at the same time. This is related to neurobehavioral alterations such as depression and anxiety (specially anxiety) causing a low neurocognitive performance in tests which deal with different sequentialities like the TMT form B, the time it took to the patient to do this test, make us infer that there is a possible focused typed alteration in her prefrontal cortex, dorsolateral cortex and the superior and medium orbitofrontal gyrus of her brain; brain areas which have as main components the executive functions and the control of the immediate conduct. The MOCA Test showed the alterations that the patient presents in her registration tasks, information decodification, and a deficiency in the processing of her executive memory. The results obtained from the MOCA make us think that we are dealing with a clinical profile which is not associated with dementia, but with a progressive neurological/neurocognitive deterioration of severe damage in the CNS. The previous data are verified by the FAB test (neurocognitive executive functions test) The patient got a score under the cutoff point, this could associated with a medical profile of a dementia caused by Alzheimer, but in the patient the results only show that the patient does not show a dementia medical profile. What was noticed is that a deterioration of her executive functions are a predictive factor for a medical diagnose of dementia caused by Alzheimer which can overlap with a corticobasal degeneration or if possible with a secondary type of Parkinsonism. In verbal fluency tasks, the patient is not able to evocate information, alterations associated with a language problem is noticed, her speech is not fluent, from time to time it seems to be coherent, but she loses in her immediate context, these data can be associated with a brain dysfunction in the Broca's area, specifically the one to produce language.

Memory

In this section, a little ability to consolidate, storage and evocate information was noticed in relation to immediate verbal memory (Babcock's history), this is clinically associated with a possible malfunction in the cellular wall of the hyppocampus and brain structures such as the alveus and the fimbria, the data obtained in these scales show that the patient is presenting a moderate-severe neurocognitive deterioration associated with her current MLD medical diagnose.

Visuospatial functioning/Visuo-constructional

In this neurocognitive domain it was noticed that the patient presents severe difficulties to process mental and/or spatial information, she cannot process nor control information in different contexts. The results of the test regarding to this field (the clock test) show what we have inferred in the section on the executive functions, the deterioration in her visuospatiality is related to a deficiency present in her

executive functions, specifically in her frontal lobe, where it is necessary an appropriate treatment because the tests show that in a medium-term, the patient can suffer from a medical profile of dementia caused by Alzheimer.

Basic, instrumental and advanced daily life activities

The patient presents a grade of a moderate-severe dependency; she is not able to do a great number of her daily life activities. It is necessary to bear in mind that as she becomes more dependent, the probability of developing a medical profile of dementia by Alzheimer is even higher.

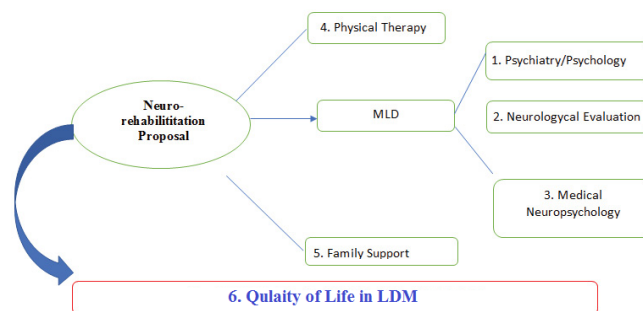
Discussion and Conclusion

The data obtained by each one of the tests, show that the patient with MLD presents emotional alterations such as generalized anxiety and depression. Neuro-conductual pathologies that have impact on the worsening of her quality of life and of her neurocognitive functioning, specifically in her sustained attention tasks, operative memory and her executive functions [3]. Although the scientific literature is little or non-existent on this kind of pathologies, different works [5] have found that the MLD is associated with a deficiency in the processing of information (executive functions) due to the fact that individuals cannot process the immediate conduct which is normally accompanied by an aberrant motor behavior, hostility and a possible disinhibiting conduct caused by a brain dysfunction of the superior, medium and inferior orbital brain gyrus.

In tasks of registration and operative memory, different studies [5] show the lack of consolidation and processing of the information; the malfunction of the frontal-subcortical circuits present in the patients seems to be clinically related to their deficiency in the operative memory and the demyelination of the white matter (Figure 3). The neurological deterioration in this type of patients is of a severe and progressive, unfortunately there are not lines of intervention with the objective of improving the quality of life of the patients, researches are few, and it takes time and financial support by the entities, family relatives and researches willing to face this situation. However, we propose a functional neuro-rehabilitation proposal for initial stages of the pathology in order to slow down the disease to a medical profile



Figure 3. Coronal plane to the point of the mamillary body. White anterior commissure and the gyrus cingula are identified, brain areas plainly affected in patients with MLD. A process of demyelination in this area has impact on a neurocognitive deficiency and the worsening of the quality of life of patients with MLD. Cited from Corina Brain Research. Digital Application. Medicine School. Universidad Libre- Cali (2019).



Graph 1. Functional Neuro-rehabilitation proposal for the improvement of the quality of life of patients with MLD.

of dementia or of a severe deterioration of their neurological/ neurocognitive functioning.

Functional neuro-rehabilitation proposal for patients with MLD

1. It is necessary for the patient to receive therapy in medical psychology and psychiatry in order to generate strategies so that the patient can re-establish a total balanced emotional conduct. That is to say, the control of alterations like anxiety and depression is going to permit an appropriate process of assertiveness in the patients, their family and the immediate staff in charge of their care.
2. The neurological evaluation is important to establish correlations between the medication and the evolution of the disease and the treatment of the individuals diagnosed with MLD.
3. The evaluation by clinical psychology is going to permit the identification of the neurocognitive domains which have been affected in patients with this pathology, but what is really important is the fact that the professional can generate lines of intervention in each one of the neurological/ neurocognitive deficiencies, in order to improve the quality of life of the patients and to slow down to a medical profile of dementia or if possible to a corticobasal degeneration.
4. The physical therapy as a co-assistant in the treatment is going to permit the identification of the etiology of the pain suffered by the patients.
5. The family support is necessary for the patients, due to the fact that as a resilient group, they are going to be able to develop strategies to deal with the disease and their immediate context.
6. Graph 1 represents each one of the steps which must be followed with a patient with MLD. The only aim of this proposal is to improve the quality of life of the patients and slow down the neurocognitive deterioration to a medical profile of dementia.

Dedicated to the memory of this patient which did not survived her diagnose, but who taught us the discipline and the perseverance we needed to continue working and researching to improve the quality of life of patients with neurodegenerative diseases.

Thank you very much to her!

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