Association between homozygous c.318A>GT mutation in exon 2 of the EIF2B5 gene and the infantile form of vanishing white matter leukoencephalopathy

Carmen Esmer¹, Gabriela Blanco Hernández², Víctor Saavedra Alanís³, Jorge Guillermo Reyes Vaca⁴ and Antonio Bravo Oro^{2*}

¹Department of Genetics, Hospital Central Dr. Ignacio Morones Prieto; ²Department of Pediatric Neurology, Hospital Central Dr. Ignacio Morones Prieto; ³Department of Molecular Biology, School of Medicine, Universidad Autónoma de San Luis Potosí; ⁴Department of Radiology and Diagnostic Imaging, Hospital Central Dr. Ignacio Morones Prieto. San Luis Potosí, San Luis Potosí, Mexico

Abstract

Background: Vanishing white matter disease is one of the most frequent leukodystrophies in childhood with autosomal recessive inheritance. A mutation in one of the genes encoding the five subunits of the eukaryotic translation initiation factor 2 (EIF2B5) is present in 90% of the cases. The diagnosis can be made by clinical and neuroradiological findings and molecular tests. **Case report:** We describe a thirteen-month-old male with previous normal neurodevelopment, who was hospitalized for vomiting, hyperthermia, and irritability. On examination, cephalic perimeter and cranial nerves were normal. Hypotonia, increased deep tendon reflexes, generalized white matter hypodensity on head tomography were found. Fifteen days after discharge, he suffered a minor head trauma presenting drowsiness and focal seizures. Magnetic resonance showed generalized white matter hypointensity. Vanishing white matter disease was suspected, and confirmed by sequencing of the EIF2B5 gene, revealing a homozygous c.318A>T mutation in exon 2. Subsequently, visual acuity was lost and cognitive, and motor deterioration was evident. The patient died at six years of age due to severe pneumonia. **Conclusions:** This case contributes to the knowledge of the mutational spectrum of VWM in Mexican patients and allows extension of the phenotype associated to this mutation.

Key words: Vanishing white matter disease. EIF2B5 gene. Magnetic resonanc. Leukodystrophy.

Asociación entre la mutación homocigota c.318A>T en el exón 2 del gen EIF2B5 y la forma infantil de la leucoencefalopatía con sustancia blanca evanescente

Resumen

Introducción: La leucoencefalopatía con sustancia blanca evanescente es una de las leucodistrofias más frecuentes. Generalmente inicia en la infancia y presenta un patrón de herencia autosómica recesiva. El 90% de los casos manifiesta mutaciones en uno de los genes que codifican para las cinco subunidades del factor de iniciación eucariótica 2 (EIF2B5). El diagnóstico se realiza por las manifestaciones clínicas, hallazgos en la resonancia magnética cerebral y estudios moleculares confirmatorios. **Caso clínico:** Paciente masculino de 13 meses con neurodesarrollo previo normal. Antecedente de

Correspondence:

*Antonio Bravo Oro

E-mail: neurologobravo@gmail.com

Received: 14-03-2017

Accepted: 03-07-2017

DOI: 10.24875/BMHIME.M17000007

Available online: 18-06-2018

Bol Med Hosp Infant Mex. 2017;74:364-369

www.bmhim.com

2444-3409/© 2018. Hospital Infantil de México Federico Gómez, published by Permanyer México SA de CV, all rights reserved.

internamiento por vómito, hipertermia, irritabilidad y rechazo a la vía oral de 15 días de evolución. Ante la exploración presentó perímetro cefálico y pares craneales normales. Se encontró hipotónico, con reflejos incrementados, sin datos meníngeos ni de cráneo hipertensivo. La tomografía de cráneo mostró hipodensidad generalizada de la sustancia blanca. Egresó sin recuperar deambulación. A los 15 días presentó somnolencia y crisis convulsivas focales después de traumatismo craneoencefálico. En la resonancia magnética se observó hipointensidad generalizada de sustancia blanca. Ante la sospecha de leucoencefalopatía con sustancia blanca evanescente, se solicitó la secuenciación del gen *EIF2B5*, que reportó mutación homocigota c.318A>T en el exón 2. El paciente requirió múltiples hospitalizaciones por hipertermia y descontrol de crisis convulsivas. Posteriormente mostró deterioro cognitivo, motor y pérdida de la agudeza visual. Falleció a los 6 años por neumonía severa. **Conclusiones:** Este caso contribuye a conocer el espectro de mutaciones que se presenta en pacientes mexicanos y permite ampliar el fenotipo asociado con esta mutación.

Palabras clave: Leucoencefalopatía con sustancia blanca evanescente. Gen *EIF2B5*. Resonancia magnética. Leucodistrofia.

Introduction

Vanishing White matter disease (VWM, OMIM#603896), also known as childhood ataxia with central nervous system hypomyelination, is one of the most frequent leukodystrophies in Caucasians^{1,2}. The first case was described by W. Eicke in 1962, in a 36-year-old woman with secondary amenorrhea that, after a mild traumatic brain injury, developed progressive neurological deterioration until her death³.

VWM is a hereditary disease with an autosomal recessive pattern of inheritance. In 90% of the cases, it is associated with mutations in one of the five genes—*EIF2B1* (12q24.3), *EIF2B2* (14q24), *EIF2B3* (1p34.1), *EIF2B4* (2p23.3), *EIF2B5* (3q27)—in charge of codifying the five subunits (α , β , γ , δ , ϵ), which form the eukaryotic translation initiation factor 2 (eIF2B)^{4,5}. Its main function is to initiate translation of the messenger RNA to polypeptides and its regulation in stress states. The factor is activated through cycles of phosphorylation and dephosphorylation coupled with guanosine diphosphate (GDP)/guanosine triphosphate (GTP) in its subunit GEF (guanine nucleotide exchange factor). Cellular stress states that promote phosphorylation of eIF2 α inhibit reactivation by eIF2B; its low intracellular concentration limits reactivation cycles, decreasing global protein synthesis⁶. Although it can be found in different cell lines, glial cells present increased vulnerability to stress while neurons and other cells of the central nervous system (CNS) are protected. This vulnerability leads to alteration of myelin production, characteristic of this illness^{7,8}.

In 1997, van der Knapp et al. defined VNW according to clinical and neuroradiological criteria⁸. The prenatal form of the disease presents with oligohydramnios and decreased fetal movements. At birth, patients present with feeding difficulties, vomit, hypotonia, difficult-to-treat seizures, coma, apnea, microcephaly,

cataract, organomegaly, renal hypoplasia, ovarian dysgenesis, joint contractures and death before one year of age⁹. The childhood form manifests in the first year of life with irritability, stupor, seizures, motor neuroregression, recurrent infections; usually, patients die before two years of age¹⁰⁻¹². There is a late childhood form that presents in two ways: some patients develop ataxia, intention tremor, dysmetria between one and 5 years of age, with a previous period of normal motor and cognitive development, some with motor and mild language retardation. Other cases present with coma after a traumatic brain injury (TBI) or fever, and even though recovery exists, patients develop progressive motor deterioration with gait problems, signs of upper motor neuron disease, dysarthria, seizures, feeding problems and optic nerve atrophy. In these patients, cognitive abilities seem to be preserved, and they later enter a phase of stabilization until they die in a period of 1 to 5 years^{8,13}. The juvenile form starts between 5 and 15 years of age, with slowly progressive spastic diplegia that alternates with periods of stability, and even motor improvement; patients have a long survival¹⁴. In the adult form, cognitive impairment, transient episodes of optic neuritis, hemiparesis, intense headaches predominate. It presents as secondary amenorrhea due to ovarian failure in women often referred as ovarioleukodystrophy^{15,16}. Recent publications have emphasized the presence of movement disorders, such as dystonia and myoclonus, which characterize late onset presentations, but occasionally childhood forms with opsoclonus-myoclonus have been described¹⁷.

Neuroradiological abnormalities are a constant, but they vary according to age and can be present in asymptomatic patients. The study of choice is a brain magnetic resonance (MR). In the neonatal forms, only brain immaturity can be observed, characterized by thick gyri, and white matter with a high-water content. In the childhood forms, the hemispheric white matter is

affected symmetrically and diffusely in T1, T2 and FLAIR sequences (fluid-attenuated inversion recovery), with an intensity that is similar to cerebrospinal fluid (CSF). A fine mesh of remaining tissue can be observed within the affected areas, with a radiated appearance, and in the semiovale center a speckled pattern can be detected in sagittal and coronal slices in T1 and FLAIR; in this stage, atrophy cannot be observed. In later stages the presence of cystic lesions observed in the FLAIR sequence is common. Spectroscopy of these areas show similarities with the CSF, with a decrease in normal metabolites and the presence of lactate and glucose. Cerebellar atrophy varies from mild to severe; the vermis is the first structure to be affected and signal alterations in the midbrain, pons, and occasionally in the spine can be observed. In adults with slow progression of the disease, cortico-subcortical atrophy can also be seen^{1,2,8}.

In this work, we describe the case of the childhood form of VWM caused by a homozygous mutation c.318A>T in the exon 2 of the *EIF2B5* gene. This case contributes to the knowledge regarding the spectrum of mutations that occurs in Mexican patients, which allows broadening the associated phenotype of this mutation.

Clinical case

Thirteen-month-old male patient, young parents, healthy, non-consanguineous. Product of a first full-term pregnancy, without any signs of perinatal asphyxia, normal motor development. He was taken to the emergency room because of vomit, intermittent hyperthermia, irritability, and oral intolerance during the previous fifteen days. At admission, he presented with hyperthermia and periods of somnolence with irritability. On physical examination by the pediatric neurologist, he was found to be irritable, with a normal cephalic perimeter, normal cranial nerves, and fundus, decreased tone in the extremities and increased deep tendon reflexes, without any meningeal signs or evidence suggestive of increased intracranial pressure, abdomen without any organomegaly and no abnormal skin findings. A head computed tomography showed generalized white matter hypodensity. A brain MR showed alterations of signal intensity in the white matter in both cerebral hemispheres on T1 and T2 weighted images. (Figures 1-3). The "U" fiber was not compromised, and there were remains of white matter in the central portions, especially in the semioval centers, and the corona radiata at the periatrinal and frontal level (Figures 2 and 3). On T1 weighted images, atrophy of

Figure 1. T1 Coronal Image. Absence of white matter myelination, atrophy of the corpus callosum with partial myelination, normal brain stem. The cavum septum pellucidum and cavum vergae can be observed.

Figure 2. T1 axial image. Generalized signal changes of the white matter that coexist with remains of white matter at the central portion, preserving the "U" fibers. Loss of myelin in the splenium of the corpus callosum should be noted.

the corpus callosum was observed with signs of hypomyelination (Figure 1). On T2 weighted images, the brain cortex was discretely atrophied, while the basal ganglia and brain stem were normal (Figure 3).

Metachromatic leukodystrophy was discarded based on normal enzymatic activity. The patient was discharged without gait recovery. During the following fifteen days, he presented with focal complex seizures along with fever, an abnormal electroencephalogram with focal paroxysmal activity; he was started on magnesium

Figure 3. T2 axial images. Alteration in the myelination of practically all the white matter of both cerebral hemispheres, respecting the gray matter, although thinning of the cortex due to atrophy can be observed. Several images of remaining white matter in the semioval centers and the corona radiata are detected.

valproate. After a week, he suffered a mild traumatic brain injury. His motor deterioration worsened, and the episodes of somnolence and irritability with vomit and hypotonia recurred. VWM was suspected, and sequencing of the *EIF2B5* gene was indicated. A homozygous c.318A>T mutation in the exon 2 was reported causing a change of a leucine for a phenylalanine at the position 106 of the protein (pLeu106Phe). A heterozygous state in both parents was confirmed. Molecular studies were done at the VU University Medical Center's laboratory, in Amsterdam.

Admissions due to hyperthermia continued, with episodes of uncontrolled seizures and exacerbations of cognitive impairment. At 2 years of age, a gastrostomy tube was placed due to swallowing difficulties. In his last evaluation, at 6 years, he presented with occasional controlled seizures on magnesium valproate and topiramate, a complete loss of visual acuity due to optic nerve atrophy and spasticity in all four extremities. The patient received physical therapy, orthosis, baclofen orally and application of botulinum toxin. He finally died at age six due to severe community-acquired pneumonia.

Discussion

Diseases that affect the white matter are a challenge in the field of both genetics and pediatric neurology. They have a wide clinical spectrum, with presentation ranging from birth to the adult age. They have been classified in two groups with the goal of facilitating diagnosis of these diseases: the classical forms, which are hereditary conditions that mainly affect glial cells, with or without affection of myelination of the peripheral nervous system; they comprise about thirty entities.

The genetically determined leukoencephalopathies, which affect the white matter secondarily by affecting neurons, the vasculature or due to systemic diseases. Among the leukodystrophies, one of the most frequent is VWM^{18,19}.

The present case had an early-childhood onset, with clinical characteristics that evolved according to what has been described for this disease, episodes of neurologic deterioration associated with a TBI and fever. According to this phenomenon, it has been observed that normal oligodendrocytes show hyperactivation of kinases such as GCN2, PERK, PKR and HRI, which phosphorylate eIF2, which inhibits eIF2B in animal models, thus restricting GEF activity and decreasing the reactivation capacity without altering its functions. eIF2B deficiency increases PERK signaling which, by interacting with mutated eIF2B, inhibits protein synthesis in oligodendrocytes and alters its function in stress conditions²⁰⁻²².

In patients with acute neurological deterioration during or after a febrile process, acute disseminated encephalomyelitis or infectious encephalitis should be suspected. When deterioration is subacute or chronic, mitochondrial disease, such as pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency and Aicardi-Goutières syndrome should be part of the differential diagnosis. In X-linked adrenoleukodystrophy, as well as in VWM, neurological deterioration is associated with a TBI. Nerve optic atrophy is observed in Canavan's disease, cerebrotendinous xanthomatosis, and peroxisomal diseases².

Analysis of clinical manifestations, mainly neuroradiological, allowed identification of VWM among these demyelinating diseases. MR findings in this patient are compatible with the imaging criteria for VWM since demyelination affects both cerebral hemispheres, it shows myelin remains at the semioval centers, corona radiata, frontal lobes and periautal regions, compromise of the corpus callosum and discrete atrophy of the cerebral cortex². A normal electroencephalogram is expected at disease onset and progressive slowing of basal rhythms with multifocal paroxysmal activity. Visual and auditory evoked potentials are initially normal, with a progressive increase in latency until they disappear. Unlike metachromatic leukodystrophy, nerve conduction velocities and electromyography are normal²³.

The main neuropathological findings in VWM are cystic degenerations, reactive gliosis, astrocytes with abnormal morphology and scarce myelin.

Initially, Dietrich et al. associated a loss of white matter with dysfunction of astrocytes and their progenitor

cells due to an absence of expression of the glial fibrillary acidic protein (GFAP) mediated by an interference RNA of the EIF2B5 gene²⁴. Later, Dooves et al. found an accumulation of hyaluronic acid, which inhibits proliferation of astrocytes during gliosis. Glial cell affection extends to structures like the cerebellum and retina, explaining some patients' cerebellar and visual dysfunction, including the present case²⁵.

More than 160 mutations have been reported in the five subunits of the eIF2B complex: 64.7% in the eIF2B5 gene, 17% in the eIF2B4 gene, followed by 15% in eIF2B2. In eIF2B5, most amino acid substitutions, such as pArg113His, which is the most frequent in the adult form⁴. The mutation found in this patient is the second most frequent and consists of a change of leucine for phenylalanine at the position 106. It was reported initially in a heterozygous state by Leegwater et al.²⁶. Later, another heterozygous case of a girl with ataxia and hemiparesis was reported²⁷.

In the literature, there have been two other homozygous cases described with a less rapid and severe evolution²³. Some mutations, such as pVal309Leu, consistently show a more severe phenotype while the homozygous state for the mutation p.Thr91Ala can present in asymptomatic adults and also in early-onset cases²⁶. The p.Arg113His mutation is localized near to the one presented in this case, with a less severe course, reflecting that there is no clear correlation between the effect of the mutation over GEF exchange activity of eIF2B and the severity of clinical manifestations²⁸.

Two cases of Mexican patients with VWM were identified after a bibliographical search: one, that debuted at 14 months without a molecular study, and other with a p.Arg299His homozygous abnormality (c.896G>A) of the *EIF2B5* gene. In both cases, manifestations were very similar to the patient herein reported. Patients showed a previously normal neurological development, motor and cognitive deterioration associated with an infectious process, without full recovery of the lost developmental milestones. In the second case, the patient shows a newly-onset neurological deterioration after a TBI^{29,30}. Description of the present case contributes to knowledge of the clinical and molecular epidemiology of this disease. Probably, the fact that both parents are carriers without evidence of consanguinity or endogamy reflects the important frequency of the mutation in Mexico.

Currently, there is no specific treatment for VWM, only interventions to treat seizure, spasticity and feeding difficulties. It is recommended to avoid stressful situations that would lead to deterioration, such as

infections, fever, contact sports, although this is not enough to prevent progression of the disease².

VWM is one the most common leukodystrophies with a worldwide case distribution. In our country, it is probably underdiagnosed, specifically the late and atypical forms of the disease.

The clinical course supports the diagnostic suspicion. Neuroimaging findings are usually characteristic, but DNA studies contribute to confirming the diagnosis. The reported case presented with a previously described mutation, with some clinical discrepancies between the previously described individuals, so a definitive conclusion about the phenotype-genotype correlation of this genetic abnormality is not possible. Given that there is no specific treatment, genetic counseling and informing the family about the natural history of the disease is an important part of the clinical management. When the status of the healthy heterozygous carrier is confirmed in both parents, there a risk of recurrence of 25% in each pregnancy. In this case, reproductive options include a preimplantation diagnosis, prenatal diagnosis, and gamete donation from one of the parents and adoption.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Acknowledgments

To Dr. Merjo van der Knaap for her support in the molecular studies.

Funding

None.

Conflicts of interest

The authors declare no conflicts of interest.

References

- van der Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. *Radiology*. 1999;213:121-33.
- van der Knaap MS, Pronk JC, Scheper GC, van der Knaap MS. Vanishing white matter disease. *Lancet Neurol*. 2006;5:413-23.
- Eicke WJ. [Polycystische umwandlung des marklagers mit progredientem verlauf. Atypische diffuse sklerose?] *Arch Psychiat Nervenkr*. 1962;203:599-602.
- Scali O, Di Perri C, Federico A. The spectrum of mutations for the diagnosis of vanishing white matter disease. *Neurol Sci*. 2006;27:271-7.
- Pronk JC, Van Kollenburg B, Scheper C, van der Knaap MS. Vanishing white matter disease: a review with focus on its genetics. *Ment Retard Dev Disabil Res Rev*. 2006;12:123-8.
- Scheper GC, Proud CG, van der Knaap MS. Defective translation initiation causes vanishing of cerebral white matter. *Trends Mol Med*. 2006;12:159-66.
- Schiffmann R, Elroy-Stein O. Childhood ataxia with CNS hypomyelination/vanishing white matter disease—a common leukodystrophy caused by abnormal control of protein synthesis. *Mol Genet Metab*. 2006;88:7-15.
- van Der Knaap MS, Barth PG, Gabreëls FJ, Franzoni E, Begger JH, Stroink H, et al. A new leukoencephalopathy with vanishing white matter. *Neurology*. 1997;48:845-55.
- van der Knaap MS, van Berkel CGM, Herms J, van Coster R, Baethmann M, Naidu S, et al. eIF2B-related disorders: antenatal onset and involvement of multiple organs. *Am J Hum Genet*. 2003;73:1199-207.
- Francalanci P, Eymard-Pierre E, Dionisi-Vici C, Boldrini R, Piemonte F, Virgili R, et al. Fatal infantile leukodystrophy: a severe variant of CACH/VWM syndrome, allelic to chromosome 3q27. *Neurology*. 2001;57:265-70.
- Fogli A, Schiffmann R, Bertini E, Ughetto S, Combes P, Eymard-Pierre E, et al. The effect of genotype on the natural history of eIF2B-related leukodystrophies. *Neurology*. 2004;62:1509-17.
- Hata Y, Kinoshita K, Miya K, Hirono K, Ichida F, Yoshida K, et al. An autopsy case of infantile-onset vanishing white matter disease related to an EIF2B2 mutation (V85E) in a hemizygous region. *Int J Clin Exp Pathol*. 2014;7:3355-62.
- Schiffmann R, Moller JR, Trapp BD, Shih HH, Farrer RG, Katz DA, et al. Childhood ataxia with diffuse central nervous system hypomyelination. *Ann Neurol*. 1994;35:331-40.
- van der Knaap MS, Kamphorst W, Barth PG, Kraaijeveld CL, Valk J. Phenotypic variation in leukoencephalopathy with vanishing white matter. *Neurology*. 1998;51:540-7.
- Biancheri R, Rossi A, Di Rocco M, Filocamo M, Pronk JC, van der Knaap MS, et al. Leukoencephalopathy with vanishing white matter: an adult-onset case. *Neurology*. 2003;61:1818-9.
- Ohtake H, Shimohata T, Terajima K, Kimura T, Jo R, Kaseda R, et al. Adult-onset leukoencephalopathy with vanishing white matter with a missense mutation in EIF2B5. *Neurology*. 2004;62:1601-3.
- Klingelhofer L, Misbahuddin A, Jawad T, Mellers J, Jarosz J, Weeks R, et al. Vanishing white matter disease presenting as an opsoclonus-myoclonus syndrome in childhood—a case report and review of the literature. *Pediatr Neurol*. 2014;51:157-64.
- Ashrafi MR, Tavasoli AR. Childhood leukodystrophies: a literature review of updates on new definitions, classification, diagnostic approach and management. *Brain Dev*. 2017;39:369-85.
- Kevelam SH, Steenweg ME, Srivastava S, Helman G, Naidu S, Schiffmann R, et al. Update on leukodystrophies: a historical perspective and adapted definition. *Neuropediatrics*. 2016;47:349-54.
- van der Voorn JP, van Kollenburg B, Bertrand G, Van Haren K, Scheper GC, Powers JM, et al. The unfolded protein response in vanishing white matter disease. *J Neuropathol Exp Neurol*. 2005;64:770-5.
- van Kollenburg B, van Dijk J, Garbern J, Thomas AA, Scheper GC, Powers JM, et al. Glia-specific activation of all pathways of the unfolded protein response in vanishing white matter disease. *J Neuropathol Exp Neurol*. 2006;65:707-15.
- Lin Y, Pang X, Huang G, Jamison S, Fang J, Harding HP, et al. Impaired eukaryotic translation initiation factor 2B activity specifically in oligodendrocytes reproduces the pathology of vanishing white matter disease in mice. *J Neurosci*. 2014;34:12182-91.
- Turón-Viñas E, Pineda M, Cusi V, López-Laso E, Del Pozo RL, Gutiérrez-Solana LG, et al. Vanishing white matter disease in a Spanish population. *J Cent Nerv Syst Dis*. 2014;6:59-68.
- Dietrich J, Lacagnina M, Gass D, Richfield E, Mayer-Proschel M, Noble M, et al. EIF2B5 mutations compromise GFAP+ astrocyte generation in vanishing white matter leukodystrophy. *Nature Med*. 2005;11:277-83.
- Dooves S, Bugiani M, Postma NL, Polder E, Land N, Horan ST, et al. Astrocytes are central in the pathomechanisms of vanishing white matter. *J Clin Invest*. 2016;126:1512-24.
- Leegwater PAJ, Vermeulen G, Konst AAM, Naidu S, Mulders J, Visser A, et al. Subunits of the translation initiation factor eIF2B are mutant in leukoencephalopathy with vanishing white matter. *Nature Genet*. 2001;29:383-8.
- Alías Hernández I, Ramos Lizana J, Aguirre Rodríguez J, Aguilera López P, Garzón Cabrera MI, Entrala Bernal C. [Left hemiparesis as a sign of onset of vanishing white matter disease. Identification of a new mutation]. *An Pediatr (Barc)*. 2013;79:46-9.
- Liu R, van der Lei HD, Wang X, Wortham NC, Tang H, van Berkel CG, et al. Severity of vanishing white matter disease does not correlate with deficits in eIF2B activity or the integrity of eIF2B complexes. *Hum Mutat*. 2011;32:1036-45.
- Márquez-Palacios RE, Castellanos-Ayala G, Gómez-Garza G, Dávila-Gutiérrez G. Síndrome de CACH: ataxia infantil con hipomielinización encefálica. *Rev Med MD*. 2014;5:251-7.
- Lauder JR, Dallara AM. Vanishing white matter disease with macrocephaly. *Am Med Stud Res J*. 2015;1:138-43.