Early and late brain resonance findings of two siblings with Hunter syndrome

John J. Silvestre-Avendaño, Daniel E. Morales-Vásquez, José R. Muñoz-Zuñiga

Introduction. Mucopolysaccharidosis type II (MPS II) is a lysosomal disease caused by deficiency of the enzyme iduronate-2-sulfatase (IDS), linked to the X chromosome, producing a wide spectrum of clinical manifestations.

Case report. We present the case of two siblings with MPS II of different paternal origin with the same genetic mutation; the age at the time of diagnosis was 5 years of age (case 1) and 8 months of age (case 2). These brethren present different findings in brain magnetic resonance imaging (MRI) with each other, case 1 presented classic findings for age, case 2 presented multiple early findings, such as dilated perivascular spaces up to 9.5 mm, magna megacisterna, among others; without neurological manifestations.

Conclusion. This patient's brain compromise was presented before the year of age and prior to hepatosplenomegaly, thus, MRI becomes an early diagnostic tool for MPS II.

Key words. Colombia. Genetic diseases X-linked. Iduronate sulfatase. Magnetic resonance imaging. Mucopolysaccharidosis II. Sibling relations.

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Introduction

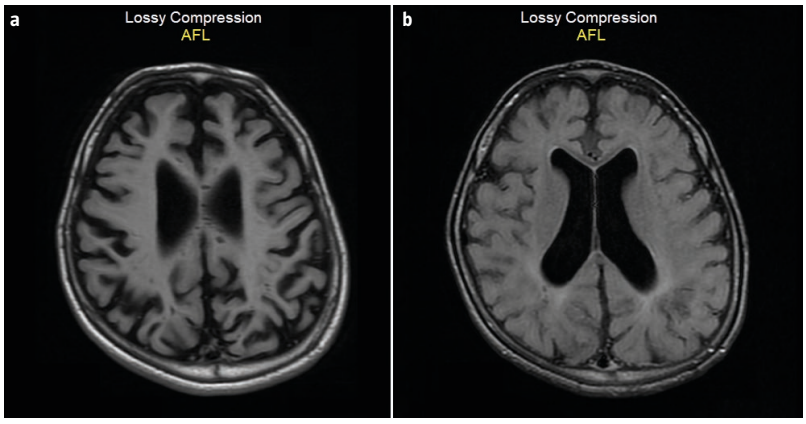
Mucopolysaccharidosis are lysosomal diseases that result from severe deficiency of lysomal hydrolases, responsible for degrading glycosaminoglycans (GAGs); they are inherited in an autosomal recessive pattern, except for type II or Hunter syndrome (MPS II), which is linked to the X chromosome, in the Xq28 locus; the *IDS* gene has 9 exons and codifies a 550 amino acids protein with high rate of mutations. 558 mutations have been recorded, without high recurrences each, and with high clinical heterogeneity, which makes it difficult to associate genotype and phenotype [1]. MPS II is caused by deficiency of the iduronate-2-sulfatase (IDS) enzyme in all cells except mature red blood cells [1]; it is responsible for degrading molecules of the heparan sulfate and dermatan sulfate group; their structure and function has not been completely elucidated [2]. A deficiency of this enzyme leads to accumulation of GAGs in the lysosomes of various organs and tissues including the central nervous system, heart, liver, connective tissue, among others; altering the architecture and function of tissues, producing a wide spectrum of clinical manifestations [3].

Two clinical phenotypes have been identified according to severity: Hunter A (neuropathic or severe phenotype) and Hunter B (non-neuropathic or attenuated phenotype) [1]. Both have systemic manifestations, but type A always presents manifestations in central nervous system while type B neurological manifestations are minimal or absent [2].

Prevalence has been reported to range from 3.4 to 4.5 per 100,000 live births; in Colombia there is no national statistic [2], however, in a regional study of 35 patients with MPS between 1998 - 2007, 8 had MPS II, it was described that the incidence was 0.45 per 100,000 live births [4]. The onset of symptoms between the age of 2 to 4 has traditionally been reported, although in the most severe forms it may occur earlier [1]. In the 2014 Galvis et al [2] study, patients with MPS II 89% of cases are Hunter type A and 11% are Hunter type B, types A had mainly language delay (81.2%) joint stiffness (18.8%) whereas types B reported symptoms such as recurrent pneumonia, visceromegaly and joint stiffness [2]. Other symptoms present in MPS II are: valvular disease, inguinal and umbilical hernia, deafness, carpal tunnel syndrome, cognitive impairment, serious behavioral problems, seizures. Neurological commitments occur in approximately 66% of cases of patients with MPS II [1,3].

Among the main findings in cerebral MRI, using T_1 and T_2 weighting techniques, is the appearance of 'sieve like' in the periventricular and subcortical white substance, and important cortical and diffuse cerebral atrophy which can be symmetrical or asymmetrical, most often seen under the age of 5 years. Such findings in 'sieve like' have also been

Figure 1. a) Dilated perivascular spaces sizing on average less than 5 mm in diameter; b) Mild lateral ventriculomegaly (case 1).



described in the form of multiple cystic lesions or sickle changes in locations such as supraventricular and parietal white substance, callous body and base nodes, which are inversely related to the degree of ventricular atrophy and enlargement [5,6].

Other neurological findings include the 'bee honeycomb' sign in thalamus and basal ganglia which is believed to be caused by the accumulation of glycolypids, GAG and increased fluid in periventricular spaces [5], spindles with increased and decreased signal in callous body's white and, changes in brainstem's gray and white substance, lateral and third ventriculomegalies which may be secondary to hydrocephalus or brain atrophy, irregular areas of hyperintensity in the parietal lobes and enlarged subaracnoid spaces [5,6], infratentorial alterations such as mega cerebellum and mega cisterna magna [7] and enlargement of perivascular spaces [6], which are believed to be caused due to accumulation of GAGs; such spaces can measure between 2 to 8 mm in diameter in healthy individuals of all ages. When they exceed 8 mm they are listed as giant sized and it is considered suggestive for MPS when involving callous body [6].

Case report

The case of two siblings of different paternal origin, with genetic and clinical diagnosis of mucopolysaccharidosis type II, the age at the time of diagnosis was 5 years of age (case 1) and during a family study a second affected member was found to be diagnosed at 8 months of age (case 2). Despite having the same genetic mutation these siblings present different imaging findings at brain imaging.

Case 1

A 5-year-old male patient is brought to consultation with history of repeated tonsillitis during childhood, giant umbilical hernia, and a maternal cousin with neurodevelopment delay of uncertain etiology with early death. On physical examination he has macrocephaly, dysmorphic facial features, giant umbilical hernia, axial joint stiffness with claw hand. In his back the skin has nodular 'pebble' like lesions. At the neurological exam, there was delayed neurodevelopmental milestones, expressive and sympathetic language failures, cognitive deficit, and ataxia. Requested IDS serum levels of less than 0.8 omol/L/h were found to be very low for age. A genetic study of the *IDS* gene reported a hemizygous variant mutation in c.359 C>G; p.Pro-120Arg. Enzyme replacement therapy with idursulfatase was initiated, in accordance with the protocol of the Latin American MPS II guide [3]. Simple brain magnetic resonance imaging (MRI) was requested with findings of dilated perivascular spaces sizing on average less than 5 mm in diameter that compromise white substance in both peritrigonal regions; thinned callous body in its different components with normal signal strength; mega cisterna magna; central and peripheric brain atrophy; mild lateral ventriculomegaly; spinal cord central canal narrowness at cervical level described in figures 1 and 3. Simple column MRI reported discrete multidirectional bulging without additional data.

Case 2

A 8-month male patient, asymptomatic, is brought to consultation due to prior diagnosis of MPS II in his elder brother. On physical examination he presented macrocephaly (SD: +3 → 50 cm), without other alterations. The neurodevelopment milestones were fine compared to age-related peers. Simple brain MRI was requested with findings of multiple hyper-intense ovoid images in T_2 ESF and FLAIR sequences are distributed in the white substance of both cerebral hemispheres with predominance on peri trigonal regions; the largest located on the right side with 8 mm diameter and on the left side of 9.5 mm in diameter. The rest range within an average of 5 mm and are distributed in the other lobes, but none in the infratentorial region;

thinned of the callous body with predominance in the knee; mega cisterna magna; enlargement of arachnoid space in frontotemporal regions; mild lateral ventriculomegaly; craniocervical joint with narrowness in lean foramen with diameter of approximately 15 mm (aprox). The opistion cannot be defined clearly described in figures 2 and 3. Reported IDS levels of less than 2.8 µmol/L/h, being low for age. The genetic study of the *IDS* gene found hemizygous variant c.359 C>G; p.Pro120Arg confirming the diagnosis. No ophthalmological alterations were found; abdominal ultrasound showed no hepatoesplenomegaly, no other clinical or imaging alterations were found.

Discussion

Type II mucopolysaccharidosis compromises multiple systems with characteristic clinical findings and early engagement in central nervous system. For case 1, the onset of symptoms was found within the average diagnostic range [1-3]; however, case 2 presented with macrocephaly without dysmorphic facial features, behavioral changes and without hepatosplenomegaly.

Simple brain MRI was performed in both cases showing central nervous system compromise. These imaging findings have been described in the literature for MPS II [5-7]. For case 1, such findings are within the average for age; however, case 2 presents severe imaging findings given the patients age like multiple dilated perivascular spaces up to 9.5 mm of central and posterior territory, supratentorial ventricular dilation in lateral ventricles, thinning of the callous body with predominance in the knee and magna mega cisterna; but despite the severity of this findings there were no neurological manifestations in case 1, except macrocephaly.

In these cases, two brothers with the same genetic mutation presented with heterogeneous imaging findings and clinical evolution. Case 2 was diagnosed at 8 months and simple brain MRI when 1 year of age was reached already showed great anatomical compromise in the brain without obvious clinical manifestations, suggesting that the brain involvement of patients with MPS II starts at younger ages than expected. Our report allows to establish that a patient at the age of 12 months can already have all the typical findings of MPS II in neuroimaging, including dilated perivascular space [8], mega cisterna magna, callous body thinning, periventricular white substance injury, marked enlargement of arachnoid spaces, among others described above. Although enlarged perivascular spaces are a common finding in children, a size ranging from 5 to 9.5 mm is associated with silent clinical manifestations and should be ruled out as differential diagnosis for MPS II. No marked dilation of the fourth ventricle was observed in our case reports, which coincides with what has been reported in the literature; in addition, no vasculopathy or hematoma was found in images, suggesting that these are rare findings in MPS II [9]. Enzyme replacement therapy does not cross the blood brain barrier which does not prevent progression of neurological engagement [1].

Figura 2. a) Mild lateral ventriculomegaly and dilated perivascular spaces, the largest located on the right side with 8 mm diameter and on the left side of 9.5 mm in diameter; b) Dilated perivascular spaces on average than 5 mm in diameter are distributed in the other lobes but none in the infratentorial region (case 2).

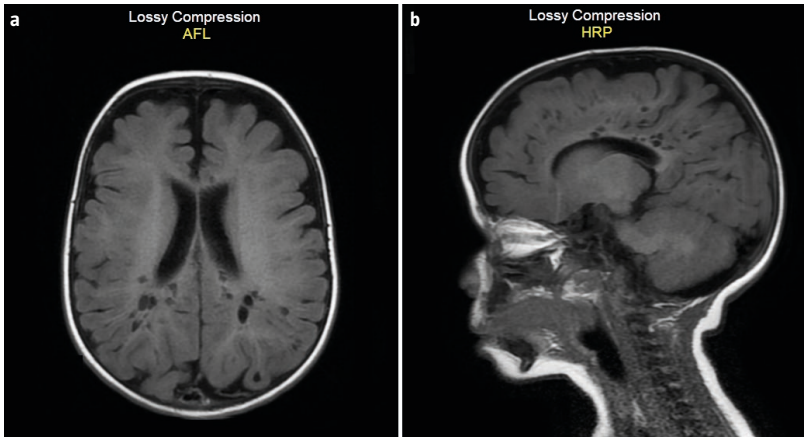
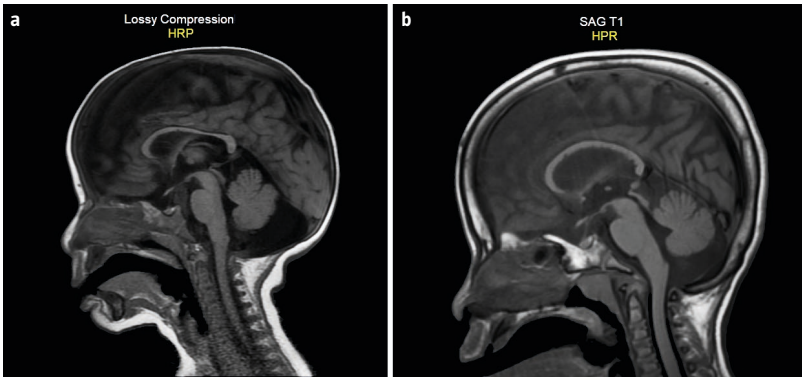


Figura 3. Thinned of the callous body and megacisterna magna. a) Case 1; b) Case 2.



Conclusion

The need to create intrathecal therapies that have the brain as a white organ is left to be considered because the commitment that occurs in the central nervous system is early.

MPS II is associated with great disability and morbidity. In the world there are few documented cases of imaging findings in siblings with MPS II, the Hunter Outcome Survey database is not available to compare data with the clinical cases presented. Variability and clinical evolution are confirmed in patients with MPS II, who have the same genetic mutation. In patients under 1 year of age, with or without neurodevelopmental delay and early macrocephaly, simple brain MRI should be performed as a diagnostic tool for MPS II.

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Hallazgos tempranos y tardíos en la resonancia cerebral de dos hermanos con síndrome de Hunter

Introducción. La mucopolisacaridosis de tipo II (MPS II) es una enfermedad lisosómica causada por deficiencia de la enzima iduronato-2-sulfatasa, ligada al cromosoma X, y produce un gran espectro de manifestaciones clínicas.

Caso clínico. Se presenta el caso clínico de dos hermanos con MPS II de diferente origen paterno con la misma mutación genética; la edad en el momento del diagnóstico fue de 5 años (caso 1) y de 8 meses (caso 2). Dichos hermanos presentan hallazgos diferentes en la resonancia magnética cerebral entre sí: el caso 1 presentó hallazgos clásicos para la edad, y el caso 2 presentó múltiples hallazgos tempranos, como espacios perivasculares dilatados de hasta 9,5 mm y megacisterna magna, entre otros, sin presentar manifestaciones neurológicas.

Conclusiones. La afectación cerebral del paciente del caso 2 se presentó antes del año de edad y previa a la hepatoesplenomegalia. La resonancia magnética se convierte en una herramienta de diagnóstico temprano para la MPS II.

Palabras clave. Colombia. Enfermedades genéticas ligadas al cromosoma X. Iduronato sulfatasa. Imagen por resonancia magnética. Mucopolisacaridosis II. Relaciones entre hermanos.