Monocular nystagmus as the presenting sign of Bardet-Biedl syndrome: diagnosis and treatment

Nistagmus monocular como signo de presentación de síndrome de Bardet-Biedl: diagnóstico y tratamiento

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Abstract

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive ciliopathy characterized by retinal dystrophy, obesity, postaxial polydactyly, renal dysfunction, learning difficulties and hypogonadism. Other ocular manifestations of BBS include nystagmus, high astigmatism, strabismus, glaucoma and cataracts. We report the case of a 17-year-old female with acquired monocular nystagmus and oscillopsia with distressing ocular discomfort. She was unsuccessfully treated with clonazepam and memantine, and experienced a pronounced and rapid visual loss, which resulted in referral to our department. After a comprehensive anamnesis and examination, BBS was diagnosed. Nystagmus was successfully treated with botulinum toxin, followed by large recessions of horizontal recti muscles that resulted in complete resolution of oscillopsia.

Key words: Monocular nystagmus. Bardet-Biedl syndrome. Atypical retinitis pigmentosa. Cone-rod dystrophy. Botulinum toxin for nystagmus. Nystagmus surgery. Oscillopsia.

Resumen

El síndrome de Bardet-Biedl (SBB) es una rara ciliopatía con herencia autosómica recesiva que se caracteriza por la presencia de distrofia retiniana, obesidad, polidactilia postaxial, disfunción renal, déficit cognitivo e hipogonadismo. Otras manifestaciones oftalmológicas del SBB incluyen nistagmus, alto astigmatismo, estrabismo, glaucoma y cataratas. Presentamos el caso de una paciente de 17 años de edad con nistagmus monocular adquirido causante de una oscilopsia incapacitante tratada con clonazepam y memantina sin éxito y derivada a nuestro servicio por una rápida pérdida de agudeza visual. Una exhaustiva anamnesis y exploración dieron lugar al diagnóstico del SBB, y el nistagmus fue tratado exitosamente con toxina botulínica seguida de amplias recesiones de los músculos rectos horizontales con la completa desaparición de la oscilopsia.

Palabras clave: Nistagmus monocular. Síndrome Bardet-Biedl. Retinitis pigmentosa atípica. Distrofia de conos y bastones. Toxina botulínica y nistagmus. Cirugía nistagmus. Oscilopsia.

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Introduction

Nystagmus is a repetitive oscillation of the eyes from one side to the other that can be physiological or pathological¹. There are several neurological pathologies associated with nystagmus, and among the pathological nystagmus of ocular etiology, it is necessary to differentiate between those caused by motor disorders or sensory disorders. Any marked visual loss can lead to sensory nystagmus. The vision of the moving world caused by these involuntary movements in acquired nystagmus is called oscillopsia, and is very disabling for the patient².

The success of the different strategies used so far for treating nystagmus is limited². Pharmacological treatment acts at the level of neurotransmitters gamma-aminobutyric acid (GABA) and glutamate³. In acquired pendular nystagmus, gabapentin and memantine are the most commonly used⁴. The use of prisms and other optical therapies is usually ineffective in this type of nystagmus.

Botulinum toxin injection in extraocular muscles or in the retrobulbar space has shown the reduction of nystagmus and improvement of visual acuity (VA) in certain patients³. The disadvantages of its use are the limited duration of the effect (2-3 months), together with the lack of control over ocular alignment and the development of eyelid ptosis. These complications can occur even when performing the injection under electromyography^{2,3}.

Large recessions of the horizontal muscles with retroequatorial insertion have demonstrated the decrease of nystagmus and the improvement of VA². Muscle positioning at the retroequatorial level decreases the leverage effect, causing the innervation received by the muscles to produce a lower rotational effect of the eyeball. This produces a decrease in the amplitude of nystagmus. This procedure has proven safe and does not cause significant motility limitations⁵.

Regarding treatment selection for nystagmus between toxin and surgery, there are circumstances and conditions of the patient that make the use of toxin preferable, but in most cases surgery is the main treatment and the use of toxin is considered an adjuvant treatment that can be used prior to surgery or in combination with it⁶.

Bardet-Biedl syndrome (BBS) is a rare disorder of autosomal recessive inheritance with both clinical and genetic heterogeneity, where the diagnosis is clinical and made by the presence of 4 of its 5 main features: obesity, polydactyly, pigmentary retinopathy, mental retardation and hypogonadism. Other features described

are learning disability, kidney disorders, dental anomalies, diabetes *mellitus*, ataxia, liver fibrosis and language development disorders.

The most frequent characteristic of BBS is retinal dystrophy, which usually occurs as retinitis pigmentosa with early cone involvement and a rapid decrease in central vision. It can also be associated with optic atrophy. Early diagnosis is important for the management of low vision and advice on visual prognosis. Electrophysiology and genetic examination are essential to confirm the diagnosis⁷.

The prevalence of retinitis pigmentosa is of one case per 3,000-5,000 and in most cases (85-90%), retinal dystrophy occurs isolated. The syndromes associated with retinitis pigmentosa have an important genotype and phenotype variability. Its inheritance may be dominant, recessive or X-linked. In typical retinitis pigmentosa, the initial symptom is night blindness and/or visual field constriction (secondary to rod dysfunction), followed by variable central vision alterations (secondary to cone dysfunction), which is usually preserved in many patients. On the other hand, in atypical retinitis pigmentosa, cone dysfunction prevails over rod dysfunction, with early involvement of central vision⁸.

The diagnosis of retinitis pigmentosa is made by ocular examination, campimetry and electrophysiology tests⁷. Typical clinical features are vascular attenuation, pale papilla and bone spicules in the middle periphery that probably represent melanin from pigment epithelial cells that migrated to the internal retina. Visual fields usually correlate very closely with pigment anomalies observed in the fundus. Electroretinogram (ERG) in these patients shows a decrease in amplitude and latency, even years before fundus signs are detected. When retinal dystrophy progresses, it can be detected on macular examination. These patients can, in turn, develop cystoid macular edema, posterior subcapsular cataract and vitreous detachment, and associated refractive defects such as myopia and astigmatism are frequent⁹.

Clinical case

A 17-year-old patient examined for myopia magna follow-up in our department. VA in the right eye (VA OD) was of 0.8, and VA in the left eye (VA OS) was of 0.5. In December 2012, she started with high-frequency and low-amplitude pendular nystagmus in OS. Upon examination, VA OD was 0.8 and VA OS had decreased to < 0.1. No pathological findings were observed in the anterior or posterior pole, so an urgent nuclear magnetic

resonance imaging (MRI) was requested and the neurology department was consulted. The MRI was reported as normal and clonazepam was indicated.

A year later she consulted again due to lack of effectiveness of the treatment. VA OD remained at 0.7 and VA OS at 0.1, but with greater difficulty for fixation. A macular optical coherence tomography was performed that showed no alterations, and a visual field was considered unreliable. Fluorescein angiography (FA) showed macular and equatorial hyperfluorescence due to pigment epithelial atrophy. An ERG and electrooculogram were requested and the patient was referred to internal medicine for treatment assessment.

After 17 months, the patient was under treatment with memantine, but reported a progressive decrease in its effectiveness. The results of the ERG described a moderate functional alteration of the retinal responses in both eyes under scotopic conditions, which were compatible with a cone and rod dystrophy associated with retinitis pigmentosa. Upon examination, her VA had remained stable in OS, and that of the OD was 0.33. The fundus showed filiform vessels, pigment epithelial atrophy and pigmented lesions more prominent on temporal retina. A molecular genetic analysis was requested and the patient was referred to the strabismus department to assess the possibility of nystagmus treatment.

The patient reported that, despite her VA decrease, it was the oscillopsia that most limited her quality of life, so she was informed of the possibility of treatment with botulinum toxin.

Three months later she began with nystagmus in the OD. Upon examination, VA OS was 0.05 and VA OD was < 0.1. A retinography showed a tessellated fundus with pale optic discs, especially in the temporal sector, peripapillary atrophy and vascular attenuation (Fig. 1). There were also bone spicule perivascular pigmentary changes in the midperipheral zone. FA showed a mild diffuse hyperfluorescent ring due to macular and retinal pigment epithelial atrophy (Fig. 2). Autofluorescence showed bilateral symmetric macular lesions with decreased intensity and a surrounding hyperautofluorescent ring (bull's eye maculopathy) (Fig. 3).

We decided to treat with retrobulbar botulinum toxin in the OS for oscillopsia control. The injected dose was 7.5 IU and the postoperative period was uneventful. After a week, the patient developed ptosis and exotropia in the OS, and the frequency and amplitude of the nystagmus, as well as the oscillopsia, decreased. The ophthalmoplegia-inducing effect of botulinum toxin lasted 5 months, with resolution of ptosis and exotropia 4

Figure 1. Retinography: tessellated fundus in both eyes, with pale optic discs, especially in the temporal sector, peripapillary atrophy and vascular attenuation.

Figure 2. Fluorescein angiography, hyperfluorescent ring in both eyes.

Figure 3. Autofluorescence with bilateral symmetric macular lesions with decreased intensity and a surrounding hyperautofluorescent ring (bull's eye maculopathy).

to 5 weeks after injection. After 5 months, the patient's VA had decreased significantly, in the OD it was 0.05 and in the OS < 0.05. The effect of botulinum toxin had disappeared and oscillopsia had become disabling again. Therefore, we decided to perform debilitating surgery of the horizontal rectus of both eyes and, due to delay of genetic testing, the clinical interview was extended.

The presence of atypical retinitis pigmentosa, obesity, polydactyly and learning disability, made us suspect a BBS, and the patient was referred again to internal medicine for the evaluation of possible genitourinary abnormalities.

The surgery performed was a 11-mm retroinsertion of the medial rectus and a 13-mm retroinsertion of the lateral rectus muscles. The patient did not show diplopia in the early postoperative period and oscillopsia disappeared from the first postoperative day. The surgery achieved nystagmus control in the OD and a decrease of its frequency and amplitude in the OS, with complete stops that lasted a few seconds.

Genetic analysis (molecular study by mass sequencing) reported a compound heterozygous retinitis pigmentosa for the mutant alleles p.Cys201Tyr and p.Thr534Ilefs*21 in exon 2 of the *BBS10* gene, confirming the clinical suspicion of BBS. No kidney anomalies or hypogonadism were found in the examination.

In December 2016, the VA our patient was counting fingers in both eyes and she was very satisfied with the result of the surgery due to the total absence of oscillopsia.

Discussion

It is common a delay in the diagnosis of BBS. This is probably due to the lack of awareness about this entity, as well as the absence of manifestations in early-stage retinal involvement, which is the clinical characteristic that leads to diagnosis in most cases. This patient had a mild intellectual deficit that had gone unnoticed and polydactyly at the lower limbs that was not visible on clinical examination and that she forgot to mention. Macular involvement in these cases begins at a younger age compared to typical inherited retinitis pigmentosa, and its progression to legal blindness is faster. The presentation of the disease usually occurs in the first or second decades of life. This was the case of our patient, whose progression to blindness lasted 3 years¹⁰.

The presence of sudden-onset nystagmus suggests the presence of an underlying pathology. After ruling out possible neurological causes, a thorough ocular examination is necessary to guide the diagnosis, requiring on occasions electrophysiology and genetic tests. MRI and neurological examination in our case were reported as normal, and a retinal dystrophy associated with retinitis pigmentosa was suspected despite scarce retinal bone spicules. An ERG confirmed the diagnosis and molecular analysis reported two mutations in one of the genes associated with BBS¹.

Acquired nystagmus is associated with a significant visual limitation caused by excessive movement of retinal images. The inability of the visual cortex to adapt to nystagmus results in oscillopsia, which can be very disabling^{3,11-13}. This patient reported that she assumed

her evolution towards blindness, but that oscillopsia produced a greater disability compared to her low VA.

Non-surgical therapeutic options include optical correction with contact lenses and eyeglasses, gabapentin, memantine and botulinum toxin^{3,4,11}. In this case, the pharmacological response was limited. However, the response to a retrobulbar injection of botulinum toxin was positive despite the fact that the dose used (7.5 IU) was much lower than that considered as the minimum effective dose described by other authors (20-25 IU), and we observed the same complications described with higher doses, that is, ptosis and exotropia with secondary diplopia that resolved in a few weeks^{2,6,12,13}.

Symmetric retroinsertions of the horizontal recti have proven to be a safe and effective procedure in patients with nystagmus, resulting in a decrease in its frequency and amplitude⁵. However, publications on muscle surgery in acquired sensory nystagmus are rare. In this patient there was an objective improvement with a decrease in the intensity of nystagmus, as well as a disappearance of oscillopsia from the first postoperative day.

Conclusions

BBS is a rare disorder and the diagnosis is clinical. Lack of awareness and a delay in diagnosis can have important systemic implications.

Adult-onset nystagmus should make the clinician suspect an underlying pathology. If a neurological etiology is ruled out, electrophysiology and genetic testing should be performed to help confirm a clinical diagnosis, after a thorough history and examination.

Oscillopsia is a sensation of constant movement of the world around us that can become more disabling for the patient than a marked loss of VA. Botulinum toxin can be effective with lower doses than those described so far. Surgical treatment can achieve good results in acquired nystagmus, with complete disappearance of oscillopsia.

Conflicts of interest

The authors declare no conflicts of interest.

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 no patient data appear in this article.

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.

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