



SCIENTIFIC LETTERS

Neuronal ceroid lipofuscinosis and Bardet-Biedl syndrome in patient with retinitis pigmentosa[☆]



Lipofuscinosis neuronal ceroidea y síndrome de Bardet-Biedl en paciente con retinosis pigmentaria

Dear Editor:

Retinitis pigmentosa is one of the leading causes of loss of vision in children and is characterised by progressive retinal degeneration resulting in severe bilateral visual impairment. It may be caused by different ocular and/or systemic disorders, chief of which are Bardet-Biedl syndrome (BBS) and neuronal ceroid lipofuscinosis (NCL).^{1,2}

Bardet-Biedl syndrome and NCL are autosomal recessive genetic disorders manifesting with bilateral retinal degeneration. In addition, BBS manifests with intellectual disability, hypogonadism, obesity, renal abnormalities, spastic paraparesis and dysmorphic extremities, and NCL with progressive encephalopathy with an early onset (ages 2–11 years), epilepsy and intellectual and impaired cognitive and motor skills.^{3,4}

The diagnosis of 2 genetic disorders in a single patient is rare, and consanguinity is the main risk factor for this outcome.⁵

We present the case of a boy with healthy nonconsanguineous parents and a healthy older brother. The patient had congenital polydactyly with a full supernumerary digit emerging from the first phalanx of the 5th toe of the left foot, which was surgically removed at age 2 years, and early-onset vision abnormalities. At age 3 years, the patient received a diagnosis of retinitis pigmentosa with bilateral total blindness and underwent microarray-based genotyping (Asper Biotech[®]) for screening of 347 mutations in 16 genes involved in syndromic retinal dystrophy (*BBS1-BBS13*, *PHF6*, *ALMS1*, *GNAS1*). The results revealed the presence of the homozygous variant c.1169 T > G (p.Met390Arg) in gene *BBS1*, described as pathogenic in the *ClinVar* database (<https://www.ncbi.nlm.nih.gov/clinvar/>). Since the variant was found in both alleles, it was disease-causing.

During the follow-up, the patient exhibited psychomotor retardation and cognitive impairment, predominantly in language. At age 8 years, he experienced regression of motor skills accompanied by impaired balance, ataxic gait and loss of muscle tone. Concurrently, the patient developed myoclonic seizures in the context of progressive myoclonic epilepsy. The clinical picture was consistent with neurodegenerative disease, which led to performance of molecular tests for identification of lysosomal storage diseases.

Massive sequencing of the main genes involved in lysosomal storage diseases (Table 1) was performed using the Ion S5 system (Ion Torrent[®]). Sequencing evinced the presence in heterozygosis of the following variants in the *CLN5* gene associated with NCL: point variant c.335 G > C (p.Arg112Pro), described as a pathogenic variant in *ClinVar*; point variant c.835 G > A (p.Asp279Asn) described as possibly pathogenic in *ClinVar*; and frameshift insertion c.291_292insC (p.Ser98fs) that is likely pathogenic.

Neuronal ceroid lipofuscinosis has an autosomal recessive pattern of inheritance, so heterozygous variants do not cause disease unless they are found in both alleles, a pattern known as compound heterozygosity. Parental testing was performed, since confirming compound heterozygosis requires detection of one of the variants in the maternal allele and another in the paternal allele. Variants c.835 G > A (p.Asp279Asn) and c.335 G > C (p.Arg112Pro) were found in heterozygosis in the mother and insertion c.291_292insC (p.Ser98fs) in heterozygosis in the father. Parental testing confirmed the compound heterozygous pattern, as the parental variants in the *CLN5* gene affected both alleles in the proband. Both heterozygous variants detected in the mother were also detected in the proband, proving that both were located in the same allele and ruling out compound heterozygosis in the mother. The brother of the proband also underwent testing that revealed the presence of insertion c.291_292insC (p.Ser98fs) in heterozygosis (Table 2).

These results led to the conclusion that this patient, previously given a diagnosis of BBS on account of the homozygous variant c.1169 T > G (p.Met390Arg) in the *BBS1* gene, also had the compound heterozygous variants c.335 G > C (p.Arg112Pro), c.835 G > A (p.Asp279Asn) and c.291_292insC (p.Ser98fs) in the *CLN5* gene, which accounted for the molecular aetiology of NCL. The mother, father and brother were each carriers of at least one of these variants.

The presence of early-onset severe retinal dystrophy combined with the development of manifestations characteristic of neurodegenerative disease was not explain in full by the diagnosis of BBS in isolation, which led to the perfor-

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Table 1 Main genes involved in lysosomal storage diseases.

[0,1–2]Lysosomal storage disease	Involved genes
[2,0]Mucopolipidosis	Type II (I-cell disease) <i>GNPTAB</i> Type III (pseudo-Hurler polydystrophy) <i>GNPTG</i> Type IV <i>MCOLN1</i>
[6,0]Mucopolysaccharidosis	Type I (Hurler syndrome) <i>IDUA</i> Type II (Hunter syndrome) <i>IDS</i> Type III (Sanfilippo syndrome) <i>SGSH</i> (IIIA), <i>NAGLU</i> (IIIB), <i>HGSNAT</i> (IIIC), <i>GNS</i> (IIID), <i>ARSG</i> (IIIE) Type IV (Morquio syndrome) <i>GALNS</i> (IVA), <i>GLB1</i> (IVB) Type V (Maroteaux-Lamy syndrome) <i>ARSB</i> Type VII (Sly syndrome) <i>GUSB</i> Type IX (Natowicz syndrome) <i>HYAL1</i>
[7,0]Glycogenosis	Type I (von Gierke disease) <i>G6PC</i> Type II (Pompe disease) <i>GAA</i> Type III (Cori-Forbes disease) <i>AGL</i> Type IV (Andersen disease) <i>GBE1</i> Type V (McArdle disease) <i>PYGM</i> Type VI <i>PYGL</i> Type VII (Tauri disease) <i>PFKM</i> Type IX <i>PHKA</i> , <i>PHKG2</i> , <i>PHKB</i>
[6,0]Sphingolipidosis	Niemann-Pick disease <i>SMPD1</i> , <i>NPC</i> Gaucher disease <i>GBA</i> , <i>PSAP</i> Fabry disease <i>GLA</i> Krabbe disease <i>ARSA</i> Tay-Sachs disease <i>HEXA</i> Landing (gangliosidosis 1) <i>GLB1</i> Sandhoff disease (gangliosidosis 2) <i>HEXB</i>
[3,0]Lipidosis	Wolman disease <i>LIPA</i> , <i>LIPB</i> Infantile NCL <i>CLN5</i> Juvenile-onset NCL <i>TPP1</i> , <i>CLN3</i> , <i>CLN8</i> Adult-onset NCL <i>CLN6</i> , <i>DNAJC5</i>

NCL, neuronal ceroid lipofuscinosis.

Table 2 Variants in the *CLN5* gene found in the family.

Variant	Proband	Father	Mother	Brother
c.335 G > C (p.Arg112Pro)	Heterozygous	Absent	Heterozygous	Absent
c.835 G > A (p.Asp279Asn)	Heterozygous	Absent	Heterozygous	Absent
c.291_292insC (p.Ser98fs)	Heterozygous	Heterozygous	Absent	Heterozygous

mance of additional molecular tests and diagnosis of NCL, diseases with overlapping phenotypes. The association of BBS and NCL in a single patient is an exceptional finding and is the first such case to be described in the medical literature.

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Use of ivabradine in pediatric post-operative junctional ectopic tachycardia[☆]



Uso de ivabradina en el tratamiento de la taquicardia ectópica de la unión tras cirugía cardiaca

To the Editor:

Junctional ectopic tachycardia (JET) is one of the most frequent arrhythmias that develop after surgical intervention of congenital heart disease. It is characterised by abnormal automaticity within the auriculoventricular (AV) node manifesting as narrow QRS tachycardia, usually associated with AV dissociation and haemodynamic instability. Conventional management consists of the rational use of inotropes, moderate hypothermia, correction of electrolyte abnormalities, optimization of sedation/analgesia, restoration of atrioventricular synchrony with a pacemaker and antiarrhythmic drugs. In general, treatment protocols include amiodarone as the first-line drug.¹ In refractory cases, a second drug may need to be added and, in some cases, low cardiac output may require support with extracorporeal membrane oxygenation (ECMO).

Ivabradine is a drug that acts on the I(f) (“funny”) current by blocking hyperpolarization-activated cyclic nucleotide-gated (HCN) channels at the sinus and AV nodes,² reducing their intrinsic automaticity and without a negative inotropic effect. It has been used successfully for treatment of inappropriate sinus tachycardia and of patients with dilated cardiomyopathy and chronic heart failure resistant to beta-blockers. It has also proven effective for treatment

of congenital JET,^{3,4} although the evidence on its use for refractory postoperative JET is scarce.^{5,6}

We present 3 cases that illustrate the efficacy ivabradine for treatment of postoperative JET refractory to conventional treatment. **Table 1** presents the characteristics of these cases. Implementation of conventional treatment measures, including antiarrhythmic therapy (amiodarone in all cases, combined with esmolol in one), failed to bring the heart rate (HR) below 170 bpm, which prevented restoration of atrioventricular synchrony with a pacemaker. Ivabradine, delivered through a nasogastric tube, was added at a dose of 0.1 mg/kg/12 h in the context of sustained haemodynamic instability. We defined haemodynamic instability as tissue hypoperfusion despite an increase in the vasoactive-inotropic score and/or volume expansion. It was considered “sustained” when it lasted more than 4 h past the onset of JET (during which the loading dose of amiodarone was administered to prevent adverse events). In a mean time of 180 min following the loading dose, the HR had decreased to a mean of 145 bpm, which allowed restoring atrioventricular synchrony through AV pacing. After implementation these measures, there was a clear improvement in cardiac output. Treatment with ivabradine continued for a mean of 3.3 days, with a mean time elapsed to conversion to sinus rhythm of 64 h. We did not observe any significant adverse effects in any of the patients.

Since ivabradine acts on the pathogenic mechanism of postoperative JET, it may be an effective therapeutic option for management of JET refractory to conventional antiarrhythmic drugs. There is ample experience on its use in adults and the evidence of its use in children is growing. Despite the potential limitation in critical patients of the exclusive enteral route of administration, our experience shows that it can achieve an effective reduction in HR in a mean time of less than 180 min (range described in the literature: 50–300 min).⁵ Although the initial dose of ivabradine is not well established for the paediatric population, the current literature suggests starting with a dose of 0.05 mg/kg/12 h,^{3,5} and the maximum reported dose of 0.14 mg/kg/12 h. Sinus bradycardia is the most widely documented adverse event associated with ivabradine, a

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