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Phenotypical Aspects of a Familial Syndromic Retinitis Pigmentosa

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Abstract

Aim: To report a familial case of syndromic retinitis pigmentosa identified at Aristide Le Dantec Hospital in Dakar and to describe their clinical characteristics ophthalmic. **Observation:** We report a sibling group of nine children, four died at a young age from unknown causes. Three children were affected by retinitis pigmentosa, two cases were syndromic. A history of nyctalopia was found in all three affected children. The mean age of onset of decreased visual acuity was 6.6 years. Patient 1 affected by syndromic retinitis pigmentosa had an extraocular sign of cystic dilation of the main bile duct. Patient 2 had myoclonic epilepsy, psychomotor retardation, and the molar tooth sign on cerebral MRI (highly suggestive of Joubert syndrome). The third child had isolated retinitis pigmentosa. Ophthalmological examinations (fundus examination, electroretinogram, and visual evoked potentials) and pediatric examinations in the remaining two children were normal. **Discussion and Conclusion:** Retinitis pigmentosa is a rare degenerative disease that can be associated with several other malformations, highlighting the importance of screening for associated conditions. It presents a grim functional prognosis and a life prognosis dependent on extraocular manifestations. Molecular biology (karyotyping, next-generation sequencing) could have identified the implicated genes and allowed for a formal diagnosis and genetic counseling.

Keywords

Retinitis Pigmentosa, Syndromic, Heredity, Ciliopathy

1. Introduction

Retinitis pigmentosa (RP) is a hereditary retinal degeneration characterized by dysfunction of the pigment epithelium and loss of photoreceptors associated with deposits of retinal pigments visible on fundus examination [1] [2]. Syndromic forms fall within the scope of a group of genetic diseases, which can be hereditary, belonging to ciliopathies. These refer to a set of syndromes resulting from impairment, either structural or functional, of a cellular organelle, the cilium. RP can be isolated (strictly retinal involvement) or syndromic (retinal and extraocular involvement). The prognosis is often bleak due to the lack of curative treatment associated with the degenerative nature of the lesions, which generally lead to low vision. This condition can jeopardize life prognosis in syndromic forms [2]. We report a case of familial syndromic retinitis pigmentosa followed at the Aristide Le Dantec Hospital Center in Dakar.

2. Observation

This involved a sibling group of nine children, 5 of whom were alive and 4 deceased from unknown causes. The first child (patient 1) was a female twin, aged 8 years, referred by child psychiatry for decreased visual acuity and hemeralopia. Her examination revealed retinitis pigmentosa, which prompted consultation for the other siblings. Ophthalmic examination found limited visual acuity to light perception in both eyes. Fundus examination showed a pale appearance of the retinal field with fine bone spicules diffusely from extreme periphery to near periphery, narrowing of retinal vessel caliber, pale optic disc, and dull macula with loss of foveolar reflex (**Figure 1**). Due to her depressive state and low visual acuity, we were unable to perform the hearing test or ERG. Pediatric examination as well as renal function tests and hepatorenal ultrasound were normal. Her twin sister (patient 2) was being treated in neurology for progressive myoclonic epilepsy. Her ophthalmic examination showed visual acuity assessed at 1/10 in both eyes. Fundus examination revealed a salt-and-pepper greyish appearance of the retinal field with fine bone spicules diffusely from extreme periphery to near periphery, slightly pale optic disc, dull macula with loss of foveolar reflex, and thin retinal vessels. ERG was not performed due to low vision and lack of cooperation. Pediatric and ENT examinations (hearing test) were normal. Abdominal ultrasound showed cystic dilation of the common bile duct (**Figure 2**). Renal function tests were normal. Their older brother (patient 3), aged 12 years, had psychomotor retardation with regression of psychomotor acquisitions since early childhood. He was followed up in neuropediatric for progressive myoclonic epilepsy. Visual acuity was 1/10 in both eyes. Fundus examination showed retinitis pigmentosa in both eyes. The patient's psychomotor state and low visual acuity did not allow us to perform the hearing test or ERG. Orbital-cerebral CT scan showed cerebellar and corticocerebral atrophy confirmed by cerebral MRI with the molar tooth sign (**Figure 3**). Renal function tests, thoracic and abdominal CT scan were normal. The diagnosis of Joubert syndrome was made in

patient 3. Ophthalmic examination and ERG were normal in the remaining siblings as well as in the mother. All patients benefited from low vision orthoptic rehabilitation. Patients 2 and 3 were managed with antiepileptic drugs and neurologic follow-up (See Table 1).

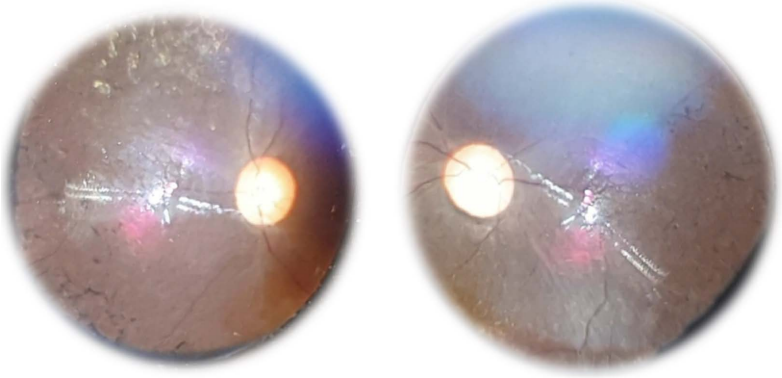

Figure 1. Fundus photographs of patient 1 showing thin retinal vessels, pale optic discs resembling "aspirin tablets", and bone spicules.

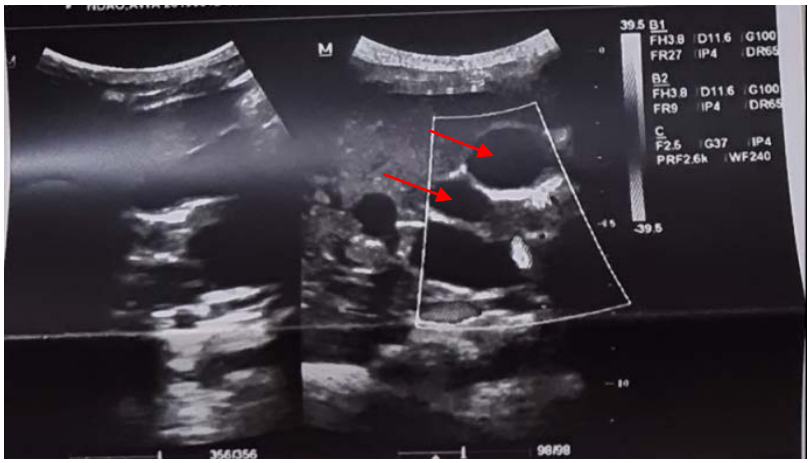

Figure 2. Abdominal ultrasound of patient 2 showing cystic dilation of the main bile duct (red arrows).

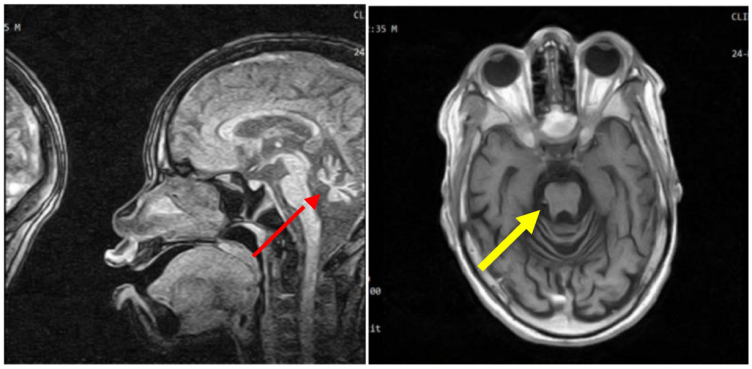

Figure 3. Brain MRI: Cerebellar cerebral atrophy (red arrow). Molar tooth sign (yellow arrow).

Table 1. Clinical and paraclinical signs of 3 patients.

	Patient 1	Patient 2	Patient 3
Age	8 years	8 years	12 years
Sex	F	F	M
Visual Acuity	PL+	1/10	1/10
Fundus	Retinis pigmentosa	Retinis pigmentosa	Retinis pigmentosa
Orbital-cerebral CT/MRI	Normal	Normal	Cerebellar atrophy molar sign
Abdominal echography	Normal	Cystic dilatation of common bile duct	Normal
Other Signs	No	Progressive myoclonic epilepsy	Progressive myoclonic epilepsy psychomotor retardation

3. Discussion

Retinitis pigmentosa remains a rare pathology in ophthalmology with a worldwide prevalence of 1/4000 births. In Africa, we do not have available statistics on the prevalence of RP. In 2015, in Congo, ATIPO TSIBA [3] described the first case of Bardet-Biedl syndrome at the University Hospital of Brazzaville and in Mali in 2017 Sylla [4], described three cases of Bardet-Biedl syndrome. In Senegal, we found two case reports on syndromic RP. These were Bardet-Biedl syndrome by Diagne [5] and Ndongo [6]. The disease can manifest from birth to adulthood. No racial or gender discrimination is noted. Consanguinity is reported in the literature up to the third degree, without being incriminated as a favoring factor [7] [8]. Syndromic retinitis pigmentosa can be grouped into genetic diseases called ciliopathies. The concept of retinal ciliopathy was first mentioned in 1986. It was marked by the observation of patients with X-linked retinitis pigmentosa and Usher syndrome, who presented with abnormalities of sperm tail and motility [9] [10]. Primary cilia are cellular organelles whose specific function is to concentrate and regulate the transmission of sensory or mechanochromic signals into the differentiated cell. Their dysfunction leads to multisystemic phenotypic impairments [11]. The gene involved codes for a protein involved in function or structure explaining clinical and genetic heterogeneity. The significant phenotypic and genotypic overlap between different syndromes explains their grouping into a common entity. Transmission occurs in an autosomal (dominant or recessive) or X-linked or Y-linked Mendelian manner. Transmission can also be due to mitochondrial DNA mutation or digenism [12]. The scarcity of genetic centers in our context and the low socioeconomic level of our patients explain the lack of karyotyping. The most frequent clinical manifestations related to cilium dysfunctions are hepatic and/or renal cystic diseases, neural tube defects, brain abnormalities and intellectual disability, skeletal anomalies, ectodermal anomalies, obesity, situsinversus, infertility, and recurrent respiratory tract infections [7] [13] [14]. They can be isolated or grouped into syndromes. In our case, besides retinal dystrophy, we identified hepatic in-

volvement and nervous system involvement. Brain MRI of patient 3 showed hypoplasia of the cerebellar vermis and middle part of the cerebellum, an abnormally deep interpeduncular fossa, and prominent, straight, and thickened superior cerebellar peduncles. This appearance corresponds to the molar tooth sign characteristic of Joubert syndrome [15]. In patient 2, we could not identify a specific syndrome. Hollanda [16] in a study about 15 patients of syndromic retinis pigmentosa, related 5 cases of Bardet-Biedl syndrome and 3 cases of Usher syndrome. Given the clinical heterogeneity, genetic testing could have provided clarification. Depending on the clinic, molecular genetic testing is possible. These will target the search for mutations in already known genes. The management of syndromic retinitis pigmentosa should be multidisciplinary and symptomatic. Its objective is early support for neurodevelopmental disorders, socio-professional integration, and treatment of various organ impairments to minimize clinical consequences [15]. Genetic counseling is often proposed to parents as part of follow-up and planning for future pregnancies. Mortality is difficult to assess. Genetic therapy remains the most promising approach for the treatment. Therapies can be delivered to the sub retinal space through viral vectors, commonly an adeno-associated virus (AAVs), to provide a functional copy of a gene (augmentation) or to correct a mutation (editing). The retina's immune-privileged environment, as well as its accessibility for surgical procedures, makes it a suitable candidate for this type of approach. In 2017, Luxturna (voretigeneneparvovec, Spark Therapeutics), an adeno-associated virus (AAV2) vector carrying an RPE65 cDNA, became an FDA-approved gene therapy. Designed for the treatment of RPE65-related Leber's Congenital Amaurosis and a small percentage of cases of autosomal recessive RP (~2 percent), the pivotal Phase III clinical trial revealed that the medication met its primary endpoint, improving multi-illuminance mobility testing with adequate efficacy and safety profile after one year [17].

Dempsey [18] described a cohort of 565 patients, 40 of whom died. The majority of patients under 5 years of age died from respiratory failure. Beyond 5 years, causes of death were related to renal failure or hepatic complications.

4. Conclusion

Retinitis pigmentosa is a rare degenerative disease that can be associated with several other malformations, highlighting the importance of screening for associated conditions. It presents a grim functional prognosis and a life prognosis dependent on extraocular manifestations. Molecular biology (karyotyping, next-generation sequencing) could have identified the implicated genes and allowed for a formal diagnosis and genetic counseling.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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