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EYE AND RARE GENETIC DISEASES: CASE SERIES AND LITERATURE REVIEW

P. W. Atipo-Tsiba, MD, FEBO, Ophthalmology Department, Head of Clinic, University Hospital of Brazzaville, Congo, Assistant at Marien Ngouabi University of Brazzaville, Congo, Email: atipo.kani@gmail.com

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SUMMARY

Genetic diseases are generally characterised by a multi visceral pathogenesis. Although orphan, these diseases interest many disciplines due to their clinical expression. Eye is sometimes part of the clinical polymorphism of some rare genetic diseases. Ocular signs are in some cases leading to the diagnosis of these pathologies. This work aimed to identify the records of patients seen for a rare genetic disease in our department. Five cases were selected: Bardt Biedl's syndrome, Fraser's syndrome, Leber Plus, Gilles de la Tourette's syndrome, combination Usher's syndrome - Von Recklinghausen's neurofibromatosis. The diagnosis was clinical, except a case of Leber Plus which required a biological analysis to confirm the mutation causing this disease. The ophthalmologist should have a general view of the patient's symptoms in order to diagnose.

INTRODUCTION

The clinical expression of genetic disease is most often characterised by multiple organ involvement. Although they are orphans, these conditions are likely to interest several disciplines due to their clinical polymorphism. We report the ocular five rare genetic diseases seen in our department.

Bardt Biedl's Syndrome (BBS) is a rare genetic disease; its transmission is autosomal recessive (1). Its diagnosis is clinical and is based on the combination of two major criteria (retinitis pigmentosa, obesity, polydactyly; delay learning; sexual abnormalities) and three minor criteria (delay speech, cataract, strabismus, brachydactyly, syndactyly, diabetes insipidus, mellitus, abnormal dentition, congenital heart disease) (2).

Fraser's syndrome (FS) is a rare genetic disorder transmitted in an autosomal recessive mode. Its diagnosis is clinical based on the presence of two major criteria (cryptophtalmia, syndactyly, genital anomalies) and one minor criteria (ear abnormalities, abnormalities of the nose, larynx anomalies and / or palate, skeletal abnormalities, umbilical hernia, renal agenesis, mental retardation), or one major and four minor criteria (3-6).

The Leber hereditary optic neuropathy (LHON) is a rare hereditary disease, caused by a mutation of mitochondrial DNA (7). Three primary mutations are often found: 11778, 14484 and 3460. The most common is the 11778 mutation; it is also the one with the worst visual prognosis (8).

Gilles de la Tourette's syndrome (GTS) is a rare neuropsychiatric disorder, its prevalence is estimated to be approximately from 0.3 to 0.8% in

the general population (9, 10). Clinical expression is very destabilising for the patient and his family (11). The genetic factor is probably the main determining in the occurrence of this disorder. A mutation of histidine decarboxylase gene was demonstrated in two generations of a family of Chinese patients with GTS (12).

Usher's syndrome (US) is defined by the association of congenital sensorineural hearing loss of varying severity, scalable or not and retinitis pigmentosa gradually blinding (13). There are three clinical types according to the vestibular and degree of hearing loss. Type II we are interested in this article is controlled by a gene locus D1S81 the long arm of chromosome 1 (14, 15). Neurofibromatosis is an autosomal dominant disease (16). There are two types. Von Recklinghausen Neurofibromatosis (VRN) described in this work is the type I, and is due to an abnormality of chromosome (17). Its most common ocular signs are represented by the iris Lisch nodules, plexiform neuroma of the eyelid and optic nerve glioma. The coexistence of these two syndromes, US and VRN, in the same person is exceptional. We found no cases in the literature. This observation has aimed to report an US-VRN association in a 40-year-old man from Mauritania born of a consanguine marriage.

MATERIALS AND METHODS

It is a retrospective study over one year (January 2010 - December 2010), conducted in the ophthalmology department of the University Hospital of Brazzaville. It aims to list the records of patients seen during this period and with a rare genetic disease. Five cases were retained. The diagnosis was made based on

the clinical signs, except a case of LHON for which a biological analysis had confirmed the existence of the typical genetic mutation responsible for the disease.

RESULTS

Five files of patients were identified:

File n°1 (BBS)

A 12 year old child was seen for a bilateral blurred vision evolving for nearly 2 years.

His eye examination noted on both sides: a visual acuity limited to counting fingers at 30 cm, a retinitis pigmentosa.

The general review noted: an obesity (Weight = 58 kg, Height = 1.30 m; a Body Mass Index of 34.32, hypogonadism, surgical scars next to each metacarpophalangeal joint witness of a cure of polydactyly (Figure 1), mental retardation (12 years old he was unable to recognise the right and left, and repeat and articulating properly). The renal ultrasound was normal.

File 2 (SF)

A male child, aged 6 months was referred to our service for the management of a right orbital congenital malformation.

Its review noted (Figure 2): incomplete cryptophtalmia (major criteria: the presence of a draft of the upper eyelid, without palpebral fissure and without eye), a scar surgical treatment of labial cleft palate (minor criteria: abnormal palate, abnormality of the nose: minor criteria), bilateral syndactyly (major criteria: the ring and little fingers were merged).

Left eye examination was unremarkable. The general examination was normal (neurology, cardiovascular, renal, musculoskeletal, and endocrine).

File 3 (LHON)

A man aged 45 (Mr BG) had described at the age of 30 years old a right progressive decrease of visual acuity, over a period of approximately 2 years, followed by a complete blindness of this eye. The performed tests were normal (blood culture, blood count, HIV serology, cerebrospinal fluid analysis, orbitofrontal brain scanner). Corticosteroid therapy was instituted thinking retro bulbar optic neuritis, without success. After a grace period of nearly 3 years, a second episode was marked by a low vision of left eye, quite fast installation. In six months, he was unable to move alone. At 35 years old, he was blind. Around the age of 41, had presented monoplegia of the lower right-hand side without fever or pain. A second biological and tomographic balance had been achieved, still unremarkable. An immunosuppressive therapy was instituted in the eventuality of a

demyelinating disease. No improvement was noted. At the age of 45, the clinical signs were enriched by the paralysis of lower contralateral limb in a few months, always in the same context, without fever and pain. His review noted in both sides: no light perception; cornea, aqueous humor and lens were clear, eye pressure 12 mm Hg, papillary atrophy marked by an extreme paleness, the juxta papillary portion of the retinal vessels was "creamy white" and "uninhabited" (Figures 3a and 3b). Two unsuccessful attempts to fluorescein angiography had induced vagal shock. There was a flaccid paraplegia. The cardiovascular examen was normal. The orbitofrontal brain scan, blood count, erythrocyte sedimentation rate, HIV serology, Lyme serology and the analysis of cerebrospinal fluid were unremarkable. The 11778 mutation was identified.

File 4 (GTS)

A man aged 27 was admitted for a right hemi face swelling and pain with homolateral rhinorrhagia. Half an hour before, he violently banged his face against a door. He lost his right eye following self-harm by knife a year before. He is a drug addict (cannabis), and followed for a GTS since the age of 10 years. This followed more or less regular, monthly visit to a psychologist and a prescription of neuroleptics. His review was as follows: a right eye prosthesis, face edema more marked on the right, crackles snow at the bottom right orbital rim (subcutaneous emphysema). The ST-scan noted (Figure 4) - on right: an orbital implant (plasty), sagging of the floor of the orbit with a clean break of the floor-ethmoid junction, a reduction of the light of ethmoidal cells with a liquid level (hemossinus) to horse between these cells and the maxillary sinus.
- on left: normal aspects.

File 5 (US -VRN)

A man (Mr M) aged 40 was admitted for blindness. This blindness began around the age of 21 years old. Bilateral blindness, rapidly progressive, painless, without fever and without impairment of general condition. It was associated with deafness, handicapping quickly, forcing his entourage to speak "hard" for his understanding.

He was born in a family of four children from a consanguineous marriage. His paternal grandfather is suffering from Von Recklinghausen neurofibromatosis, and her maternal grandmother is suffering from retinitis pigmentosa. One of the sisters is albino and another suffers from retinitis pigmentosa. Figure 5 shows the pedigree of Mr M.

The clinical examen of the patient noted on both sides: an absence of light perception, a retinitis pigmentosa, a medium sensorineural hearing loss (loss of 50 decibels) without vestibular dysfunction. Neurofibromas covered his entire body surface area (Figure 6).

REVIEW OF THE LITERATURE

Georges Bardet Biedl and Arthur were the first to describe this syndrome who finally bear their names (17). The molecular and biochemical mechanisms of the BBS is unknown. The gene of the protein called BBS- protein would play a decisive role in this syndrome was located (18). Recent discoveries about SBB-protein shows that it has several subtypes called SBB-some. These different subtypes play an important role in transporting intracellular vesicles (18, 19). It is now accepted that an abnormality in the structure of these BBS-some is partly the cause of BBS (20, 21). Inbreeding appears to be an important risk factor in the BBS (22). Laurence Moon-Bardet-Biedl's syndrome is often confused with SBB, but strictly speaking it associates spastic paraplegia and polydactyly is absent (23). McKusick Kaufman's syndrome may also lend clinically confusion to the BBS; it combines hydrohematocolpos, polydactyly and congenital heart disease (24). Alstrom's syndrome (retinitis pigmentosa, obesity, progressive hearing loss, heart disease, insulin resistance and delayed development) (25) and Biemond's syndrome (coloboma of iris, obesity, post-axial polydactyly and mental retardation) (26) are also differential diagnosis in case of SBB.

FS is relatively easy diagnosis; to date about 200 cases have been described in the literature (3-5). However, the only cryptophtalmie without syndactyly may be a differential diagnosis with two other birth defects. Blepharophimosis syndrome which is a rare congenital orbitofrontal eyelid malformation, autosomal dominant, affecting both sexes. It combines a malformation of the bony orbit (small and depressed, with a flattened upper orbital rim), a malformation of the eye (epicanthal folds, a telecanthus, and ptosis due to the levator muscle hypotrophy associated with short eyelids), characteristics eyebrows (hypertrichosiques shaped), an inconstant ectropion of the outer part of the eyelids (27). The palpebral coloboma, which are defined by a deficit in the eyelid margin. Many pathophysiological hypotheses are mentioned, such as defects of contiguous embryonic bud or mesenchymal tissues. They can be defined according to their size, their seat, their severity, their number and presence of associated abnormalities in soft tissue and skeleton, which will be systematically on the same axis (27).

Mr BG presented a typical clinical and biological status of LHON. The symptoms of the right eye started at the age of 30 years. This result is in agreement with the results of Grenet *et al.* (28) that in a retrospective study of 10 cases had found the first signs appeared between 14 and 47 years. However genotypically proven cases have also been described to extreme ages (29, 30). The 11778 mutation found in this patient is the most encountered, it is present in approximately

60% of affected families (31). Ocular symptoms of this patient was particularly severe, complete blindness without recovery. This table can be explained by the conjunction of two poor prognostic factors, a relatively late start and the 11778 mutation. Indeed, the visual prognosis depends on the age of occurred and the type of mutation. When low vision begins in childhood, it is more progressive with better final functional recovery (32, 33). In case of 11778 mutation, evolution is often pejorative, with over 90% of the final visual acuity less than 1/10 (34, 35). Spruijt *et al* (33) estimated that 64% improved in the final visual acuity with 14484 mutation. The beginning in childhood and the existence of a mutation other than 11778 are factors of good prognosis; visual recovery may be almost complete (36). The installation of paraplegia in this context (11778 mutation) and in the absence of any other etiology proven, the diagnosis of "Leber Plus" was selected.

The GTS is a complex neuropsychiatric disorder described for the first time in France in 1885 (37). Basal gangliocortical dysfunction projectors affecting sensorimotor circuits of the limbic cortex is the assumption that the largest consensus today (38). The genetic factor is probably the main determining in the occurrence of this disorder. A mutation of histidine decarboxylase gene was demonstrated in two generations of Chinese family patients with GTS (12). This syndrome is characterized by the association of motor and vocal disorders. His diagnosis to be placed must meet the following criteria: beginning from 2 to 15 years; presence of fast repetitive movements aimlessly; the involvement of many muscles of the body, vocal tics (screaming, meow ...), duration symptoms than one year (38-40). The motor tics start around the age of 3 to 8 years (10, 39). Eye blinking and facial movements are the most common engines tics. Vocal tics are manifested by hemmages (throat clearing), simple or more complex sounds such as echolalia (repeating words expressed by others) or paralelie (repeating his own words), sometimes with lewd behavior touching on yourself or on others (copropraxia) (39, 40). Self-injury is a frequently encountered in the GTS. Ophthalmologic lesions are dominated by the attempted avulsion of the eye that result in most cases by the orbital hemorrhage, corneal clouding, hyphema, cataracts, retinal detachment, giant retinal tears (39, 41, 42). We have identified a case of dislocation of the lens described by Gaillard MC *et al* (42). The fracture of the orbital walls in a patient suffering from GTS has, to our knowledge, never been published. This patient was reoperated successfully. Followed with a psychiatric have been proposed.

US was first described in 1858 by Von GRAFFE (13). Usher (43) was the first to understand the hereditary nature of this disease association and described as a specific syndrome. It is at the origin

of 3 to 6% of congenital deafness; and represents 50% of the deafblind population in the United States (15). Its prevalence (P1) is 1 birth/1000 (14). Von Recklinghausen (44) was the first in 1882 to describe the neurofibromatosis that will bear his name. VRN described in this work is the type I. Prevalence (P2) is 1 birth / 4950 (16). If we considered a simple mathematical model, * independence in probability theorem (www.medespace.fr/.../probabilité-conditionnelle-independance), the probability (P) for a single individual suffering from these two diseases (US and VRN) can be calculated by the following formula: $P(P1 \cup P2) = P1 \times P2 = 1 \text{ birth}/4950000$. This probability is extremely low. Inbreeding had probably played a role in this association (45). In Britain, a third of children with rare recessive genetic diseases result from a consanguineous marriage (<http://www.bivouac-id.com/mariages-consanguins-et-tares-genetiques/>). In Morocco, diseases related to inbreeding occupy an important place in the health system. The worst of these is Duchenne muscular dystrophy, children die around age 15 (<http://www.maghress.com/fr/leconomiste/34435>). Approximately 50% of marriages are consanguineous in Mauritania (<http://www.bivouac-id.com/mariages-consanguins-et-tares-genetiques/>). Some factors could explain inbreeding. The traditional family structure, geographic isolation, economic conditions, poor marry among themselves and the rich do the same, and the religious isolation. It would be interesting to determine the gene at the root of this association. Mr M refused any blood examen because no treatment would be offered.

*Theorem of independence in probability: considering two independent events A and B. If the probability of occurrence of event A is P (A), if the probability of occurrence of event B is P (B). The probability that both events A and B can appear simultaneously is $P(A \cup B) = P(A) \cdot P(B)$.

In conclusion, the eye is sometimes part of the clinical polymorphism of certain rare genetic diseases. The ophthalmologist should have a general view of the patient's symptomatology in order to make the diagnosis. Inbreeding can be a source of serious diseases, it should be abandoned.

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