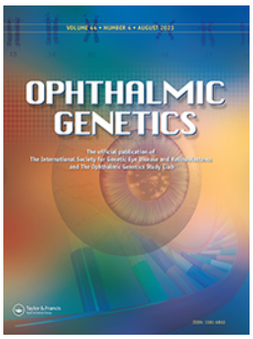

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CASE REPORT



# Neuropathy, ataxia, retinitis pigmentosa: a case of a mother and two siblings

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**ABSTRACT**

**Aim:** We describe the ophthalmic manifestations of Neuropathy, ataxia, retinitis pigmentosa (NARP) syndrome in three related patients.

**Methods:** We examined a mother and her two children, who were carriers of the *mt 8993T>G* mutation. The mother, patient I, is the first known carrier within the family pedigree. Patients II and III are her children from a non-carrier father. NARP syndrome and the heteroplasmy levels were established prior to the first referral of the patients to the Ophthalmology department.

We performed a visual acuity testing, followed by a biomicroscopic and fundus examination, as well as additional multimodal imaging testing: optical coherence tomography (OCT) and fundus autofluorescence (FAF), and functional testing: electroretinogram and visual field.

**Results:** All patients had the clinical manifestations of NARP syndrome, which were variably expressed symptomatically, on the fundus exams, electroretinogram, and visual fields.

**Conclusions:** Once genetically established, NARP syndrome, as other mitochondrial disorders, has a very variable progression with different degrees of severity. A multimodal approach involving both neurological and ophthalmological diagnosis of NARP syndrome is necessary in order to establish the course of the disease and the measures to be taken.

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**KEYWORDS**
Ataxia; retinitis pigmentosa; NARP

## 1. Introduction

Since its initial description in 1990, the neuropathy, ataxia, retinitis pigmentosa (NARP) syndrome has been recognized as a rare hereditary progressive neurodegenerative disorder that typically presents in early childhood, stemming from a disruption in mitochondrial energy generation (1,2).

The disease has been previously documented with varying clinical manifestations, including a cerebellar syndrome associated with ataxia, sensorineural hearing loss, and eventual development of marked lower limb bilateral hyporeflexia and hyposensitivity (2). Other reported symptoms include reduced visual acuity (3), nyctalopia (2,4), nystagmus (4), and dysarthria (4,5).

Patients with NARP are usually referred to ophthalmology departments due to deteriorating visual acuity or nyctalopia, described subjectively as increasing difficulty in low light conditions (2–4). While NARP has been studied for its genetic etiopathogenesis and neurological progression, its retinal manifestations have not been as widely reported in the literature.

Furthermore, phenotypic variability among affected individuals within the same family has been infrequently documented.

This case report details a family with a mutated *MT ATP-6* gene on the 8993 codon, including a mother and her two children **of middle eastern origin**, who are carriers of the mutation. The mother, patient I, is the first known carrier within the family pedigree. With a non-carrier father, she has seven offspring, five of whom carry the mutation, and three of them, two brothers and one sister, who died within the first year of their lives (Figure 1).

Genetic testing was performed on the patient secondary to her child's death.

Her daughter, patient II, is the second known carrier and exhibits 74% heteroplasmy in peripheral blood. She is the mother of two offspring with a non-carrier father, both of whom carry the mutation with 14% and 64% heteroplasmy in chorionic villus sample (CVS). Patient III is the son of Patient I and the brother of patient II. He is a carrier with 86% heteroplasmy in peripheral blood.

## 2. Non-ocular symptoms of NARP syndrome

One of the most commonly reported is a cerebellar syndrome associated with ataxia. Other reported neurological symptoms of NARP are: lower limb hyporeflexia and hyposensitivity, proximal muscle weakness, dysdiadochokinesia, tremor, gait imbalance and sensorimotor axonal polyneuropathy. (2,5)

Other features reported are epilepsy, cognitive impairment, verbal fluency impairment, dementia, dysarthria, (5) and an associated sensorineural hearing impairment. (4,5)

## 3. Case report I – patient I

Upon initial visit, a 57-year-old female with a history of diabetes and NARP syndrome was found to have a mutation on the 8993 codon of the *MT ATP-6* gene.

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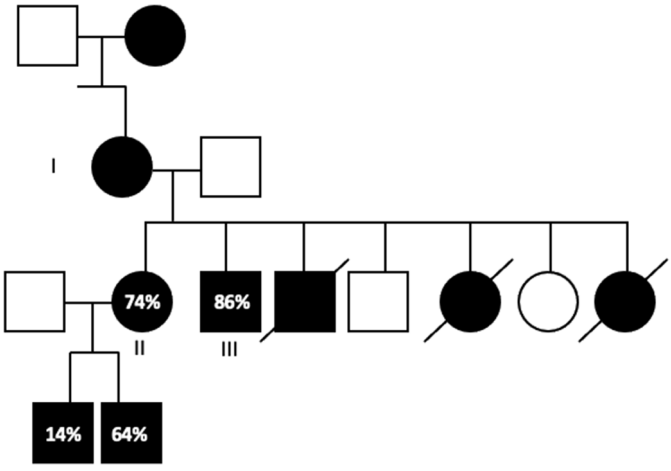


**Figure 1.** Pedigree analysis with heteroplasmic percentage of the MT-ATP 6 8993 mutation.

The patient is a mother of seven siblings, three of whom passed away in early childhood.

No history of consanguinity was reported and genetic testing was done following the children's deaths.

**The patient did not exhibit any signs of diabetic retinopathy despite poor glycemic control (HbA1C 8%). Mild hearing impairment was reported without formal auditory testing at the time**, but no neurological symptoms were reported. During the first consultation in 2012, the patient only had a slight decrease in visual acuity, with an initial visual acuity of 20/25 in both eyes.

The slit lamp examination was unremarkable, and fundus examination showed no signs of diabetic retinopathy or macular alterations.

However, spectral-domain optical coherence tomography (SD-OCT) scans revealed outer retina atrophy with foveal sparing, corresponding to a bull's eye pattern of hypo- and hyper-autofluorescence (FAF). (Figure 2)

Humphrey 24–2 visual field demonstrated a bilateral arcuate scotomatous ring formation (Figure 3).

Full-field electroretinography (ffERG) showed rod dysfunction with preserved cone function (Figure 8).

In April 2017, despite maintaining the same visual acuity, the patient exhibited pigmentary bone-spicules in the mid-periphery, with perifoveal atrophy. FAF showed a perifoveal ring-shaped hyperautofluorescence.

The visual field examination revealed an annular scotoma with residual tubular vision, which progressively worsened until the end of 2018. Subsequently, the patient's visual acuity deteriorated to 20/32 in the right eye and 20/40 in the left eye.

On fundus examination, the previously observed bone-spicules became more prominent around the vascular arcades and peripheral retina. SD-OCT demonstrated a stable aspect, while FAF revealed additional hypoautofluorescence in the vascular arcades.

The patient's binocular visual field showed a peripheral island of vision.

In 2019, the patient, who had previously experienced only hypoacusia without any other neurological symptoms, suffered a hemorrhagic stroke with left hemiplegia. Subsequently, the patient did not continue follow-up in our department since 2020 due to physical disability.

## 4. Case report – patient II

A 38-year-old female was referred to our ophthalmology department due to a deteriorating visual acuity following her fifth uneventful delivery in 2015, along with migraine. The patient had previously undergone genetic testing at 20 years of age in the context of her siblings' deaths, which revealed

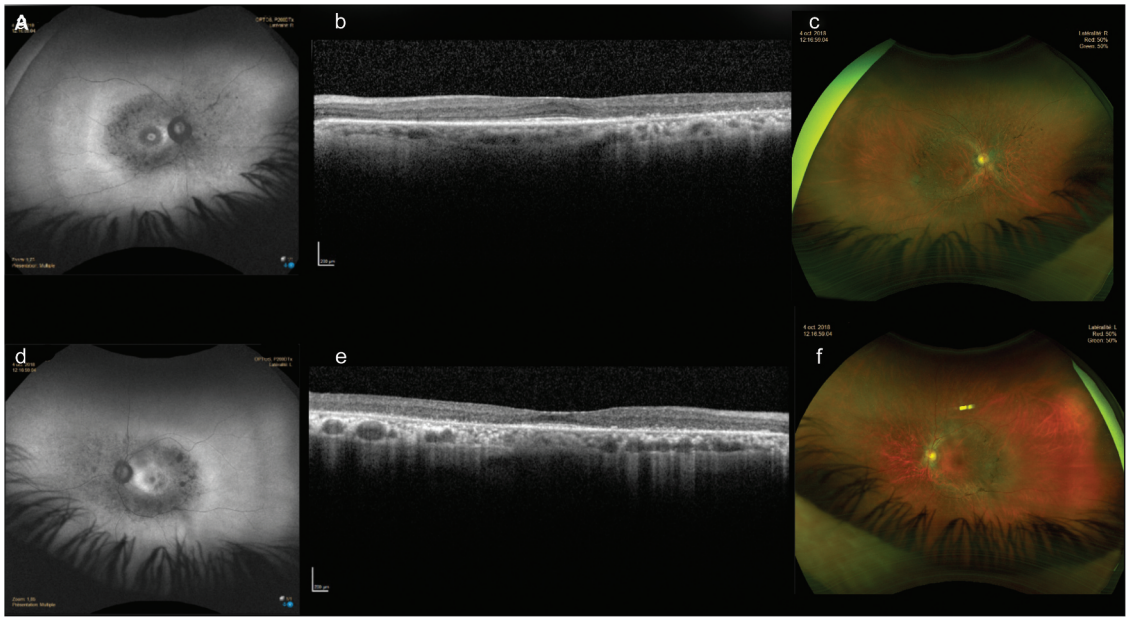


**Figure 2.** (a) and (d) fundus autofluorescence: a bull's eye pattern of hypo- and hyper-autofluorescence. (b) and (e)- OCT: atrophy of the external retinal layers with relative foveal sparing. (c) and (f) ultra wide field retinophotography: no pigmentary changes or macular alterations at this point.

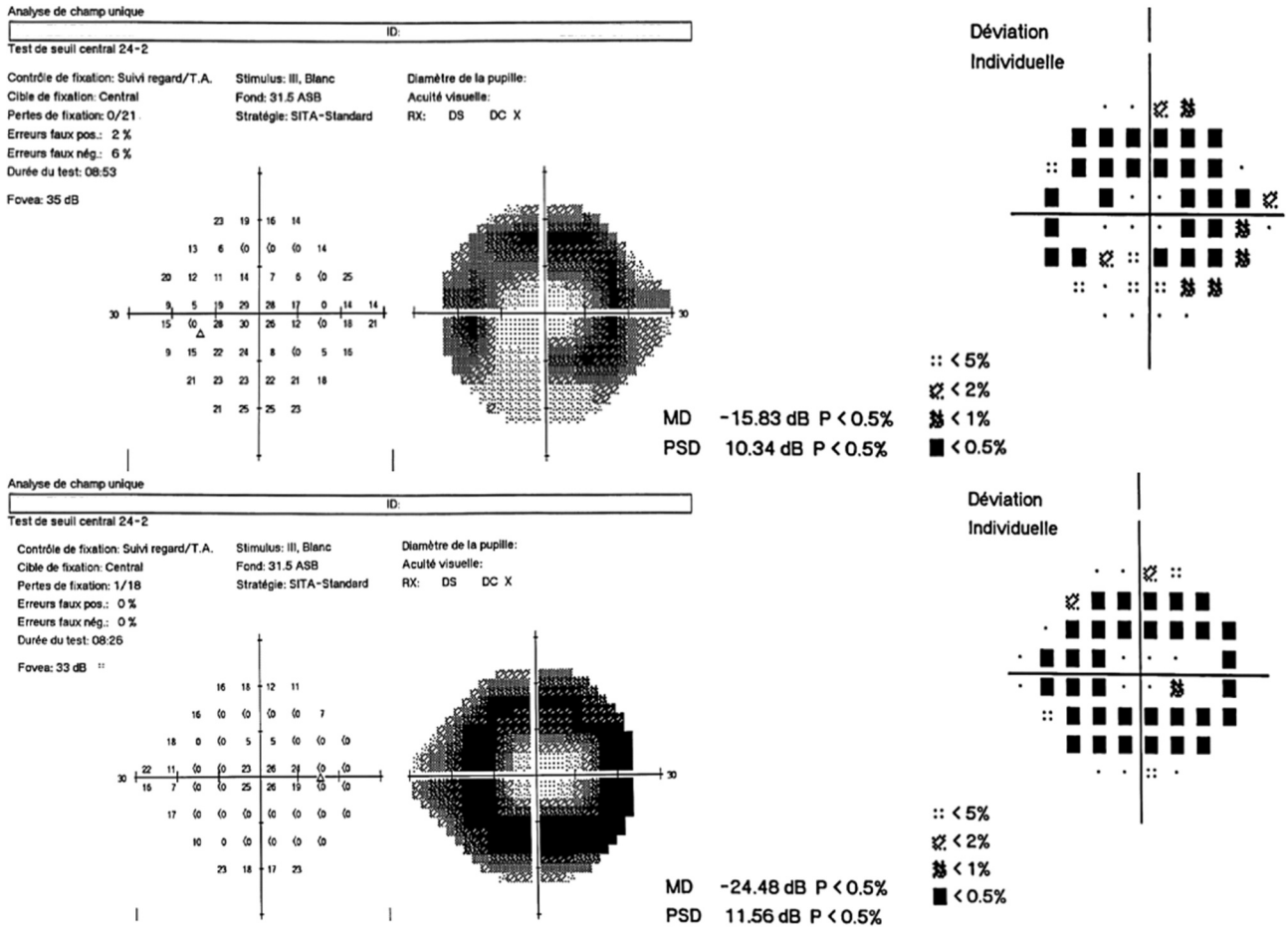


**Figure 3.** Humphrey perimetry (upper- left eye, lower- right eye) demonstrating a bilateral arcuate scotomatous ring.

NARP syndrome with a mutation in the *MT ATP-6* gene on the 8993 codon.

At the time, she had no major neurological disorder, **only a minor distal lower limb sensory deficit was reported by her neurologist**.

During her first visit to our department in 2016, the patient reported a progressive loss of vision, with visual acuity measured at 20/50 in the right eye and 20/40 in the left eye. Over time, she developed prosopagnosia and nyctalopia.

The biomicroscopic examination revealed bilateral punctiform opacities on the crystalline lens that remained unchanged throughout follow-up.

Initially, the fundus examination did not reveal any remarkable findings. However, SD-OCT showed thinning of the Outer Nuclear layer (ONL), along with discontinuity of the ellipsoid zone, with partial foveal sparing. FAF confirmed the presence of a hyperautofluorescent ring at the posterior pole.

The ffERG conducted initially demonstrated major dysfunction of both the cone and rod systems with undetectable responses, using the International Society of Clinical Electrophysiology of Vision (ISCEV) standard protocol (Figure 8).

In 2017, a central scotoma rapidly deteriorated over the year, as indicated by Goldmann perimetry (Figure 4), with an eventual visual acuity of 20/100 in both eyes.

The latest SD-OCT showed advanced atrophy of the outer retinal layers, extending to the **perifoveal** region in both eyes. Furthermore, FAF revealed a corresponding annular hypoautofluorescence in both eyes (Figure 5).

Regarding the neurological findings, the patient now presents with left hemiplegia, spatial disorientation, unpredictable loss of muscle tone, dizziness, migraines, episodes of Broca-type aphasia, and left-sided hypoacusia. Magnetic resonance imaging (MRI) revealed atrophy of the vermis and corpus callosum, along with a periventricular "frosted glass" appearance. Additionally, electromyography (EMG) revealed axonal neuropathy of the lower limbs.

## 5. Case report – patient III

The brother of patient II, a 30-year-old individual with NARP syndrome and the same *MT-ATP 6* mutation, has presented with memory problems and visual impairment since the age of six. The individual was diagnosed with retinitis pigmentosa at 15 years of age, ten years prior to his initial presentation to our department in 2017.

The patient's initial visual acuity was 20/100 in the right eye and counting fingers in the left eye. He also reported experiencing nyctalopia and photophobia, in addition to exhibiting muscular weakness and a lack of equilibrium without ataxia. In addition, the patient exhibited a significant stuttering.

The biomicroscopic examination did not reveal any abnormalities. However, the fundus examination demonstrated macular abnormalities and peripheral bone spicule

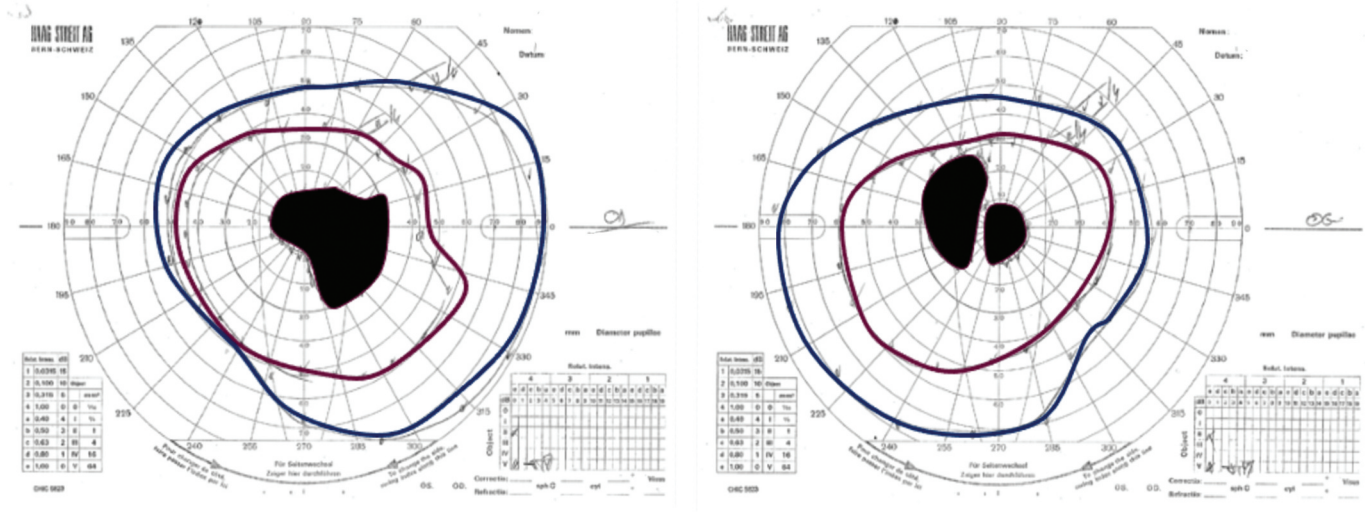

**Figure 4.** A large scotoma and a preserved peripheral visual field on the right eye (left) and left eye (right).

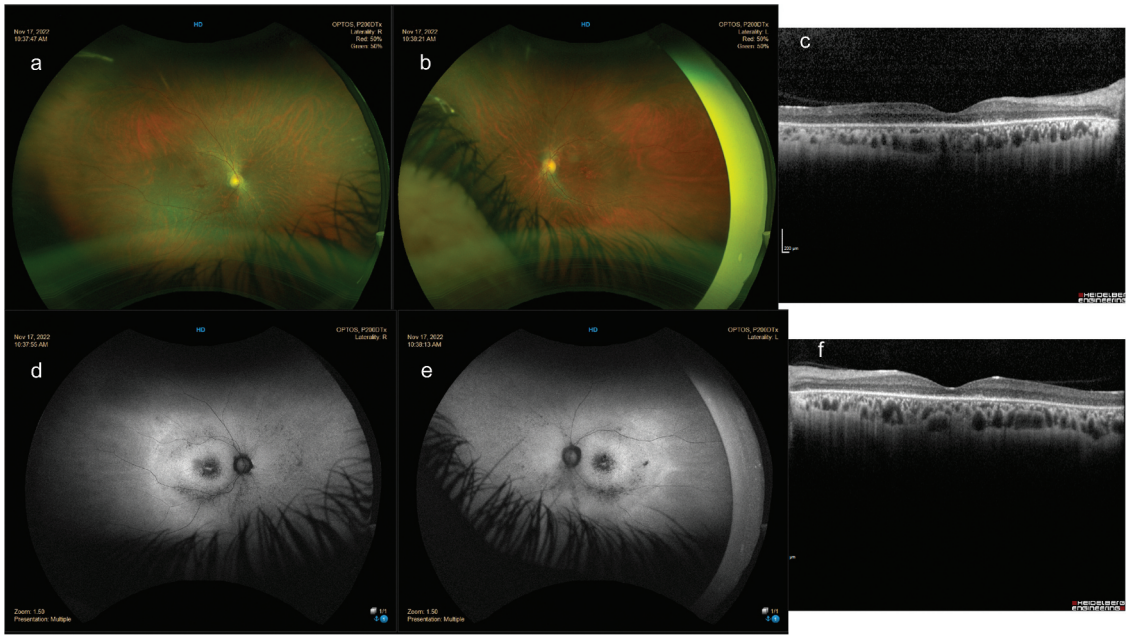


**Figure 5.** (a) and (b) fundus exam: no pigmentary changes or macular alterations at this point, still vessels have small caliber and the optic nerve is pale. (c) and (f)- SD OCT : advanced atrophy of the outer retinal layers, but architecture of the inner retinal layers is preserved. (d) and (e)- FAF: a hypoautofluorescent ring at the posterior pole and heterogenous perimacular annular lesion close to temporal vessels.

formation was little. FAF findings corresponded with the fundal changes, exhibiting a similar hypoautofluorescent ring bilaterally (Figure 6).

Goldmann perimetry revealed a scotoma in the right eye, while in the left eye, the central scotoma was wider, corresponding to a lower visual acuity.

The ffERG demonstrated advanced rod-cone dysfunction with a persistent 30 Hz flicker response (Figure 8).

In 2018, the patient exhibited worsening saccadic movement and slowing of pursuit movements. The SD-OCT remained stable since their initial presentation, showing perifoveal atrophy of the photoreceptor line.

Currently, the patient reports a subjective worsening of his vision over the years, with a stable visual acuity of 20/200 and 20/400 in the right and left eyes, respectively. He continues to be supported by low vision-aids. Presently, the patient does not exhibit any major motor deficit and is not under neurological surveillance.

## 6. Discussion

NARP, or Neuropathy, Ataxia, and Retinitis Pigmentosa, is a rare genetic disorder that affects multiple systems in the body. When it comes to ophthalmological evaluation, there is a wide range of signs that can be observed in individuals with NARP. However, due to the lack of specific diagnostic criteria, it can be a challenging condition to diagnose accurately.

One of the most notable ocular symptoms associated with NARP is the development of a slowly progressive bilateral concentric visual field loss. This loss is typically related to the

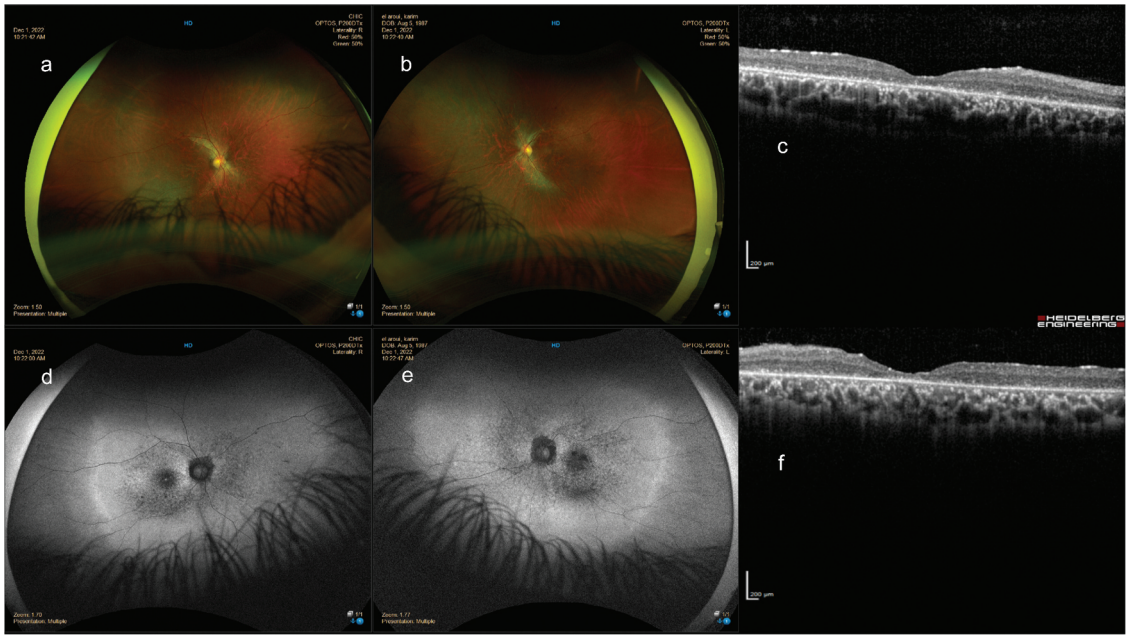


**Figure 6.** (a) and (b) fundus exam: wide-field. (c) and (f)- OCT: retinal and foveal atrophy. (d) and (e) FAF: hypoautofluorescent ring bilaterally.

development of a maculopathy with associated characteristic tardive bone spicule formation, such as for our patients (Figure 7), or even a bull's eye pattern (6,7). Genetic testing is crucial for confirming the diagnosis. There are several different genetic mutations associated with NARP, and testing can identify these mutations in affected individuals (8).

Following a thorough patient history, the ophthalmological evaluation may include visual acuity testing, which can reveal variable degrees of deterioration that may begin in early childhood (2,3).

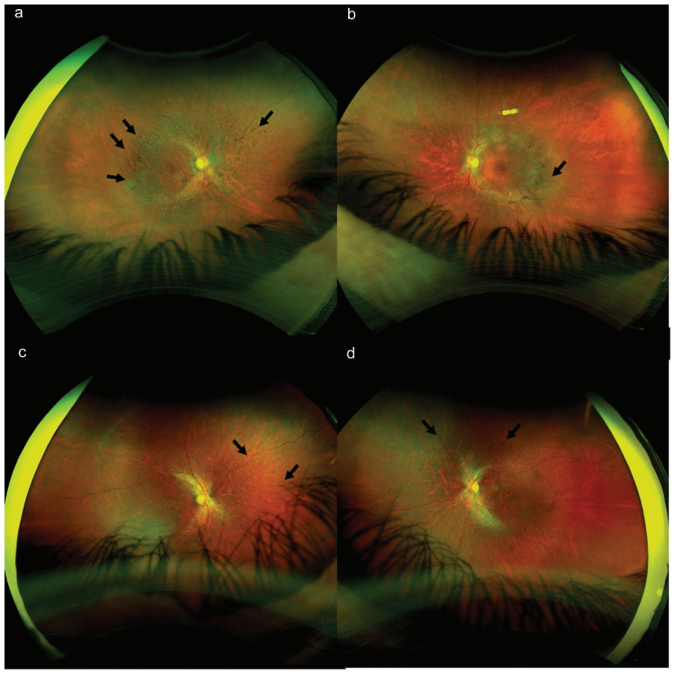


**Figure 7.** Bilateral bone spicule formation on wide-field of the right and left eyes of patient I (a,b), and patient III (c,d), respectively.

Biomicroscopic examination can show varying degrees of retinal dystrophy, ranging from mild maculopathy to typical retinitis pigmentosa (3,7–9).

There are currently many retinography and OCT based reports on the variability of the maculopathy. Some reported heterogeneous zones of neuronal loss in the inner and outer retinal layers, with the outer limiting membrane remaining intact (10). Others have demonstrated a thin outer nuclear layer (ONL), photoreceptor inner segment layer (ISL) and outer segment layer (OSL) with attenuation of the macular Retinal Pigment Epithelial (RPE) layer, corresponding to an RPE mottling surrounding a small central island of preserved RPE seen on retinography (11). Additional OCT findings were an Ellipsoid zone defect (EZ) (2).

In our report, the OCT scans of patient I demonstrated a retinal atrophy with foveal sparing. Patient II had a an ONL thinning and a partial foveal sparing, while patient III had a largely stable OCT that demonstrated perifoveal atrophy.

Visual field testing is an essential component of the evaluation. At earlier stages, visual field testing may demonstrate a normal visual field.

However, as the condition progresses, visual field testing may reveal a constricted field with a concentric decrease (2–4,6). In addition to this, the presence of paracentral scotomas has also been reported (3,11).

In our report, Humphrey Perimetry of patient I exhibited a bilateral arcuate scotomatous ring, while Goldmann perimetry for patient II and III showed an increasing central scotoma.

FAF has been shown to exhibit hyperautofluorescence and hypoautofluorescence granular patterns in the posterior pole and vascular arcades (2). All the patients in our report exhibited a hypoautofluorescent bilateral ring on FAF.

FA shows a variable presentation in patients with retinal dystrophy. In some cases, FA may show multiple peri-macular hyperfluorescent spots in the arteriovenous phase, in addition to dark spots of pigment and arteriolar narrowing. In other

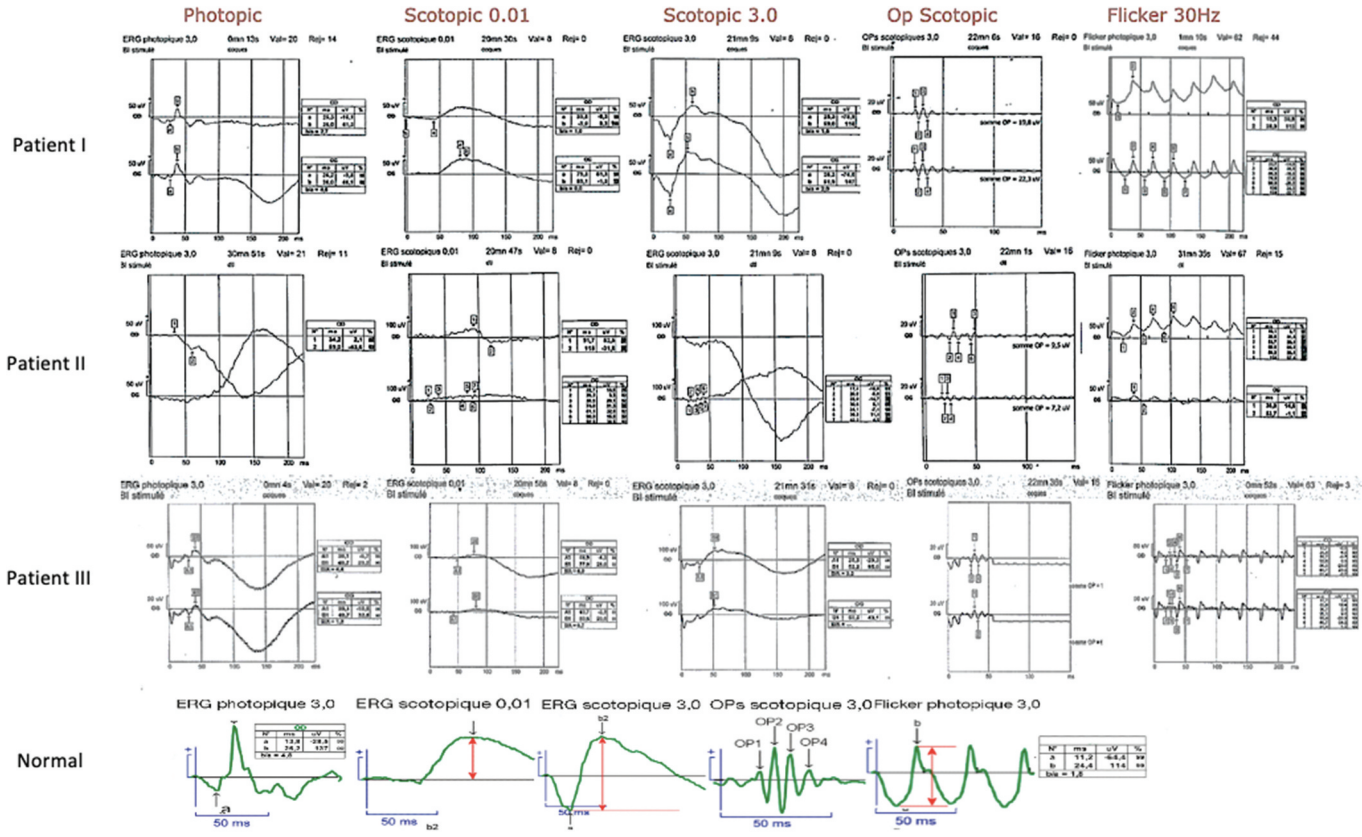


**Figure 8.** A comparative display of full field electroretinogram ERG, following ISCEV protocol. The first line represents the ERG response of the mother with a moderate rod cone dysfunction. Both rods and cones function are altered with diminished amplitude. The second line, representing the daughter's ERG, the rod response is not discernible from noise. The cone response is still distinct, with normal morphology but lower amplitudes compared to normative data. The third line, the brother's ERG, the responses are not easily discernible from noise neither for rod and cone systems. Fourth line, represent normative data, with different kinds of stimulation.

cases, FA may reveal a silent choroid in the center with a perimacular hyperfluorescent ring (3).

Regarding the electrophysiological evaluation, the literature showed that full-field Electroretinogram (ERG), which is often used in the setting of NARP, exhibited variable results, such as a normal cone-rod response (in macular dystrophy), a decreased amplitude of photopic "b" wave (3), or a reduction of both "a" and "b" wave amplitudes (in cone and rod-cone dystrophy) (2). Some reported prolonged rod-mediated and cone-mediated implicit time with severe reduction of multifocal ERG in the central macula (11). Figure 8 provides a comparative analysis of ERG for the three patients, demonstrating variable ERG modifications.

The ERG of patient I, the mother, shows a moderate rod cone dysfunction. Both rods and cones function are altered with diminished amplitude. On her daughter's ERG, that of patient II, the rod response is not discernible from noise. The cone response is still distinct, with normal morphology but lower amplitudes. That of patient III shows both rod and cone responses that are not easily discernible from noise.

In addition, less frequently reported, the fundus-guided microperimetry showed central sensitivities that were lower than normal (11).

In addition to the ophthalmological assessment, the clinical neurological stigmata of NARP syndrome may include proximal muscle weakness, axonal neuropathy, and cerebellar ataxia.

Other features reported were epilepsy, cerebral or cerebellar atrophy, optic atrophy, cognitive impairment, dementia, sleep apnea syndrome, and an associated hearing impairment (12).

Both Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) of the brain have demonstrated cerebral and cerebellar atrophy as well as abnormalities in the basal ganglia (13). Furthermore, electromyography and nerve conduction studies may have the potential to reveal signs of peripheral neuropathy (14).

**NARP syndrome is a mitochondrial disorder due to variants in *MT-ATP6* gene, most of which are missense variants. The most commonly found variant reported in association with NARP syndrome was the *mt 8993T>G as in this family*** (12,15,16).

The authors not only identified a T-to-G change at this position using polymerase chain reaction (PCR), but also noted that heteroplasmy can vary within the same family, potentially producing the variable clinical phenotype of ataxia and retinitis pigmentosa (15,16).

**Additional descriptions of *mt 8993T>G* mutation associated with hearing loss were reported, more precisely with retrocochlear and cochlear nerve lesions**. (17) To the best of our knowledge, due to the rarity of existing reports, coexisting auditory problems were not yet found to be prognostically relevant in the likelihood of developing the aforementioned retinal changes.

Previous reports have demonstrated the *mt 8993 T>G* mutation association with varying degrees of symptom severity depending on the mutation loads in affected patients (18). However, for other mtDNA variants pigmentary retinopathy was found to be less marked in patients without hearing loss (19).

Genetic heteroplasmy can help explain some of the clinical variability observed, as greater degrees of heteroplasmy tend to lead to more severe clinical manifestations (20,21).

In the case of NARP Syndrome, the risk of severe disability substantially increases beyond a threshold of > 60–70% blood heteroplasmy for the *mt 8993T>G ATPase 6* mutation (13).

A case of a de novo mutation of *mt 8993T>G* in an asymptomatic mother and her phenotypic son was previously reported. The authors suggested that a de novo mutation appeared during oogenesis. The healthy mother exhibited mosaicism for the mutation that was restricted to her oocytes (22).

Prenatal diagnosis may be of use in the segregation of this mutation, either from fetal tissue or chorionic villus sampling (CVS) (23). It was suggested as a preventive approach, in which parents with the mutation may select a termination of the pregnancy (24).

The aforementioned neurological severity has been found to be analogous to the severity of retinitis pigmentosa (21). However, to the best of our knowledge, the literature has not yet established a purely retinal severity scale in relation to the extent of heteroplasmy.

## 7. Conclusion

Once genetically established, NARP, as other mitochondrial disorders, has a very variable progression with different degrees of severity. A multimodal approach involving both neurological and ophthalmological diagnosis and care may improve the patient's quality of life.

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