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ORIGINAL ARTICLE

Autosomal dominant optic atrophy plus due to the novel *OPA1* variant c.1463G>C

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Abstract

OPA1 variants most frequently manifest phenotypically with pure autosomal dominant optic atrophy (ADOA) or with ADOA plus. The most frequent abnormalities in ADOA plus in addition to the optic nerve affection include hypoacusis, migraine, myopathy, and neuropathy. Hypertelorism and atrophy of the acoustic nerve have not been reported. The patient is a 48yo Caucasian female with slowly progressive, visual impairment since childhood, bilateral hypoacusis since age 10y, and classical migraine since age 20y. The family history was positive for diabetes (father, mother) and visual impairment (daughter). Clinical examination revealed hypertelorism, visual impairment, hypoacusis, tinnitus, weakness for elbow flexion and finger straddling, and generally reduced tendon reflexes. MRI of the cerebrum was non-informative but hypoplasia of the acoustic nerve bilaterally was described. Visually-evoked potentials revealed markedly prolonged P100-latencies bilaterally. Acoustically-evoked potentials were distorted with poor reproducibility and prolonged latencies. Muscle biopsy revealed reduced activities of complexes I, II, and IV. Genetic work-up revealed the novel variant c.1463G>C in the *OPA1* gene. This case provides novel information regarding the genotype of ADOA plus. The novel *OPA1* variant c.1463G>C not only manifests with visual impairment, hypoacusis, migraine, and myopathy, but also with hypertelorisms and acoustic nerve atrophy.

Keywords Optic atrophy · Retinal ganglion cells · Migraine · Hypoacusis · Mutation · Multiple mtDNA deletions

Introduction

Autosomal dominant optic atrophy (ADOA) is most frequently due to variants in the *OPA1* gene (Finsterer et al. 2018). Variants in the *OPA1* gene causing ADOA have been first described in 2000 by Delettre et al. (2000). *OPA1* encodes for a mitochondrial GTPase involved in cristae structure and mitochondrial network fusion (Gerber et al. 2017). OPA1 localises to the inner mitochondrial membrane and is essential for assembly and stability of respiratory chain supercomplexes, cristae organisation, sequestration of pro-apoptotic cytochrome-C-oxidase, and mtDNA maintenance (Spiegel et al. 2016). *OPA1* variants secondarily lead to multiple mtDNA deletions and a mosaic defect of COX (Hudson et al. 2008). ADOA presents as pure ADOA without affection of structures other than the retinal ganglion cells and the optic nerve, or as ADOA plus, which presents as a multiorgan syndrome (Ham et al. 2019). ADOA plus occurs in 20–30% of the patients carrying a *OPA1* variant (Ahmad et al. 2015; Hudson et al. 2008). The minimum prevalence of *OPA1*-related ADOA is 1:25000 (Spiegel et al. 2016). Here we present a patient with ADOA plus due to the novel *OPA1* variant c.1463G>C.

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Case report

The patient is a 48yo Caucasian female, height 175 cm, weight 57 kg, with a history of slowly progressive, visual impairment since the kindergarten, bilateral hypoacusis since age 10y, and classical migraine since age 20y, with a frequency of 9 attacks per year. Her family history was positive for diabetes in her father and mother. She gave birth to two children with an oligohydramnion during her second pregnancy (Fig. 1). The

older of the two girls suffers from visual impairment with reduced visual acuity. She had one miscarriage. The family history was negative for hypoacusis and migraine.

Clinical neurologic exam revealed hypertelorism, visual impairment allowing her to watch television but not to read the newspaper, hypoacusis bilaterally, bilateral tinnitus, weakness for elbow flexion on the right side (M5-) and for finger straddling bilaterally (M5-), and generally reduced tendon reflexes. There was no ptosis or ophthalmoparesis.

Creatine-kinase was 68 U/l (n, <145 U/l). Serum lactate was 1.1 mmol/l and 0.6 mmol/l (n, 0.5–2.2 mmol/l). The HbA1c value was 4.8%. Thyroid function parameters were normal as well as serum levels of folic acid and vitamin B12. Serum parameters for vasculitis were negative. Investigation of the cerebrospinal fluid (CSF) at age 29y was normal, including CSF lactate. X-ray of the temporal bone was normal bilaterally. A CT scan of the cerebrum at age 43y was non-informative as well as high-resolution CT of the temporal bone. MRI of the cerebrum was non-informative but hypoplasia of the acoustic nerve bilaterally was diagnosed. Visually-evoked potentials revealed a P100 latency of 158 ms on the left side and of 143 ms on the right side. Pure-tone audiometry showed marked hypoacusis bilaterally. Acoustically-evoked potentials revealed distorted potentials with poor reproducibility but prolonged latencies bilaterally. Work-up for cardiac involvement was negative. Muscle biopsy revealed complete absence of complex-I activity and reduced activity of complex-II and complex-IV. Genetic work-up by means of Sanger-Sequencing revealed the heterozygous variant c.1463G>C (p.Gly488Ala) in the *OPA1* gene. This novel OPA1 variant is not enlisted in the Exac and gnoAD databases.

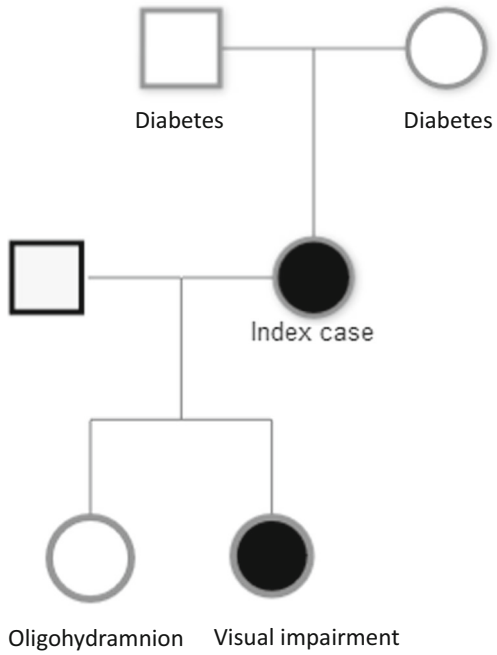

Fig. 1 Pedigree of the described family

Discussion

The presented case is interesting, since ADOA plus was due to a previously undescribed *OPA1* variant and since documented hypoplasia of the acoustic nerve and hypertelorism have not been reported in association with *OPA1* variants. Reduced activity of complexes I, II, and IV of the respiratory chain in the present case suggests that the *OPA1* variant secondarily caused multiple mtDNA deletions. Whether the variant was inherited or de novo remain speculative since the parents of the index case were investigated neither clinically nor genetically. Conceivable is, however, that diabetes in either of the parents represents a manifestation of an *OPA1* variant. However, both did not present with other features of ADOA or ADOA plus. This could be also due to non-penetrance or reduced penetrance of the variant reported in 10–20% of the OPA1 carriers (Spiegel et al. 2016). The detected variant affects the guanosine triphoshatase domain and was predicted to be disease causing by three prediction algorhythms (Mutation Taster: Model: simple_aae, prob.: 0.999999999930694. Polyphen-2, HumVar possibly damaging with a score of 0.725, and PROVEAN as deleterious with a score − 5.416).

Pure ADOA affects only retinal ganglion cells and the optic nerve in form of visual disturbances and optic atrophy but ADOA plus may additionally manifest with a number of other abnormalities of the brain or other organs as listed in Table 1. According to a recent review of 120 patients with ADOA plus due to *OPA1* variants (Ham et al. 2019), the most frequent abnormalities in ADOA plus among 120 patients include hypoacusis, migraine, myopathy of ocular or limb muscles, and neuropathy (Ham et al. 2019). There is significant heterogeneity in the frequency of specific exons involved between pure ADOA and ADOA plus (Ham et al. 2019). Pure ADOA patients tend to have more likely variants in exon 8 and 9 (Ham et al. 2019). ADOA plus patients, on the other hand, tend to have more frequently variants in exons 14, 15, and 17 (Ham et al. 2019). Additionally, individuals with maternally inherited *OPA1* variants tend to have more frequently ADOA plus (Ham et al. 2019), whereas paternally inherited *OPA1* variants more frequently manifest as pure ADOA (Ham et al. 2019). Consecutive generations may manifest with a less severe phenotype or a delayed onset compared to previous generations (negative anticipation) (Ahmad et al. 2015). Occasionally, pure ADOA may be become a multisystem disease with progression of the disease, affecting not only the brain and the eyes, but also the ears, heart, skeleton, and the muscle (Table 1) (Liskova et al. 2013). Interestingly two

Table 1 Clinical manifestations of *OPA1* variants

Organ	Manifestation	Example reference
Brain	Optic atrophy	(Liskova et al. 2013)
	Ataxia	(Liskova et al. 2013)
	Migraine	(Liskova et al. 2013), current case
	Intention tremor	(Liskova et al. 2013)
	Nystagmus	(Liskova et al. 2013)
	Cervical dystonia	(Liskova et al. 2013)
	Spastic paraparesis	(Yu-Wai-Man et al. 2010)
	Myoclonus epilepsy	(Duvezin-Caubet et al. 2006)
	Infantile-onset encephalopathy	(Spiegel et al. 2016)
	Failure to thrive	(Spiegel et al. 2016)
	Dementia	(Carelli et al. 2015)
	Parkinsonsim	(Carelli et al. 2015)
	Abnormal eye persuits	(Spiegel et al. 2016)
	Weak cry	(Spiegel et al. 2016)
	Dysdiadochokinesia, dysmetria, nystagmus	(Nasca et al. 2017)
	Atrophy of acoustic nerve	[current case]
	Central hypotonia	(Spiegel et al. 2016)
	Neurodevelopmental delay	(Spiegel et al. 2016)
	Elevated CSF lactate	(Spiegel et al. 2016)
	Thin corpus callosum, cerebellar atrophy	(Nasca et al. 2017)
	Necrosis of putamina	(Nasca et al. 2017)
Eyes	Cetnral visual loss	(Ham et al. 2019)
	Loss of retinal nerve fibers	(Carelli et al. 2015)
	Impaired colour vision	(Ham et al. 2019)
	Photophobia	(Li et al. 2018)
	Optic disc pallor	(Li et al. 2018)
	Reduced RNFL thickness on OCT	(Pretegiani et al. 2017)
	Dyschromatopsia	(Nasca et al. 2017)
	Centrocecal scotomas	(Nasca et al. 2017)
Ears	Hypoacusis	(Liskova et al. 2013; Santarelli et al. 2015)
Heart	Tachycardia, bradycardia	(Liskova et al. 2013; Spiegel et al. 2016)
	Hypertrophic cardiomyopathy	(Spiegel et al. 2016)
	Myocardial infarction	(Spiegel et al. 2016)
GI tract	Gastrointestinal reflux	(Spiegel et al. 2016)
	Vomiting	(Nasca et al. 2017)
	Hepatopathy	(Nasca et al. 2017)
Nerves	Neuropathy	(Yu-Wai-Man et al. 2010)
Muscle	Ptosis	(Liskova et al. 2013)
	Ophthalmoparesis	(Liskova et al. 2013)
	Myopathy	(Amati-Bonneau et al. 2008; Spiegel et al. 2016)
	Hypotonia	(Nasca et al. 2017)
Skeleton	Hypertelorism	[current case]
	Microcephaly	(Nasca et al. 2017)
	Pes cavus	(Nasca et al. 2017)

CSF cerebrospinal fluid, *GI* gastrointestinal, *RNFL* retinal nerve fiber layer, *OCT* optic coherence tomography

variants of the *OPA1* gene in the same protein domain have been described in patients with a OPA1-plus syndrome complicated by parkinsonism and dementia (Carelli et al. 2015).

In the protein level the Amin acid exchange p.Gly488Ala (p.G488R) has been previously described in two studies (Carelli et al. 2015; Yu-Wai-Man et al. 2010). Despite the identical amino acid exchange, the phenotype of the two families reported by Carelli et al. (2015) was different compared to the phenotype of the present case. Features of Carelli's families not found in the present case included juvenile arterial hypertension, anxiety disorder, ptosis, ophthalmoparesis, Parkinsonism, tremor, dementia, and basal ganglia calcification. Features not described in Carelli's cases were migraine, hypertelorism, and atrophy of the acoustic nerve. In Yu-Wai-Man's study (Yu-Wai-Man et al. 2010), 8 patients carrying the variant c.1462A>G (p.G488R) were described. Manifestations of these 8 patients not present in our case were ataxia, ophthalmoparesis, and epilepsy (Yu-Wai-Man et al. 2010). These findings suggest that the phenotypic expression of the amino acid exchange p.G488R manifests phenotypically with a broad range of different features.

Limitations of the case report are that it has not been investigated if the *OPA1* variant c.1463G>C affected the replication of the mtDNA and caused multiple mtDNA deletions, that the index case has not been investigated prospectively for multisystem disease, that other family members had not been clinically and genetically investigated, and that no functional studies had been carried out to document the pathogenicity of the variant.

Overall, this case provides novel information regarding the genotype / phenotype correlation of the *OPA1* variant c.1463G>C. These findings warrant revised recommandations concerning ADOA plus patients.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

References

Ahmad KE, Davis RL, Sue CM (2015) A novel OPA1 mutation causing variable age of onset autosomal dominant optic atrophy plus in an Australian family. J Neurol 262:2323–2328

Amati-Bonneau P, Valentino ML, Reynier P, Gallardo ME, Bornstein B, Boissière A, Campos Y, Rivera H, de la Aleja JG, Carroccia R, Iommarini L, Labauge P, Figarella-Branger D, Marcorelles P, Furby A, Beauvais K, Letournel F, Liguori R, La Morgia C, Montagna P, Liguori M, Zanna C, Rugolo M, Cossarizza A, Wissinger B, Verny C, Schwarzenbacher R, Martín MA, Arenas J, Ayuso C, Garesse R, Lenaers G, Bonneau D, Carelli V (2008) OPA1 mutations induce mitochondrial DNA instability and optic atrophy 'plus' phenotypes. Brain 131:338–351

Carelli V, Musumeci O, Caporali L, Zanna C, La Morgia C, Del Dotto V, Porcelli AM, Rugolo M, Valentino ML, Iommarini L, Maresca A, Barboni P, Carbonelli M, Trombetta C, Valente EM, Patergnani S, Giorgi C, Pinton P, Rizzo G, Tonon C, Lodi R, Avoni P, Liguori R, Baruzzi A, Toscano A, Zeviani M (2015) Syndromic parkinsonism and dementia associated with OPA1 missense mutations. Ann Neurol 78:21–38

Delettre C, Lenaers G, Griffoin JM, Gigarel N, Lorenzo C, Belenguer P, Pelloquin L, Grosgeorge J, Turc-Carel C, Perret E, Astarie-Dequeker C, Lasquellec L, Arnaud B, Ducommun B, Kaplan J, Hamel CP (2000) Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. Nat Genet 26:207–210

Duvezin-Caubet S, Jagasia R, Wagener J, Hofmann S, Trifunovic A, Hansson A, Chomyn A, Bauer MF, Attardi G, Larsson NG, Neupert W, Reichert AS (2006) Proteolytic processing of OPA1 links mitochondrial dysfunction to alterations in mitochondrial morphology. J Biol Chem 281:37972–37979

Finsterer J, Mancuso M, Pareyson D, Burgunder JM, Klopstock T (2018) Mitochondrial disorders of the retinal ganglion cells and the optic nerve. Mitochondrion 42:1–10

Gerber S, Charif M, Chevrollier A, Chaumette T, Angebault C, Kane MS, Paris A, Alban J, Quiles M, Delettre C, Bonneau D, Procaccio V, Amati-Bonneau P, Reynier P, Leruez S, Calmon R, Boddaert N, Funalot B, Rio M, Bouccara D, Meunier I, Sesaki H, Kaplan J, Hamel CP, Rozet JM, Lenaers G (2017) Mutations in DNM1L, as in OPA1, result in dominant optic atrophy despite opposite effects on mitochondrial fusion and fission. Brain 140:2586–2596

Ham M, Han J, Osann K, Smith M, Kimonis V (2019) Meta-analysis of genotype-phenotype analysis of OPA1 mutations in autosomal dominant optic atrophy. Mitochondrion 46:262–269

Hudson G, Amati-Bonneau P, Blakely EL, Stewart JD, He L, Schaefer AM, Griffiths PG, Ahlqvist K, Suomalainen A, Reynier P, McFarland R, Turnbull DM, Chinnery PF, Taylor RW (2008) Mutation of OPA1 causes dominant optic atrophy with external ophthalmoplegia, ataxia, deafness and multiple mitochondrial DNA deletions: a novel disorder of mtDNA maintenance. Brain 131:329–337

Li H, Jones EM, Li H, Yang L, Sun Z, Yuan Z, Chen R, Dong F, Sui R (2018) Clinical and genetic features of eight Chinese autosomal-dominant optic atrophy pedigrees with six novel OPA1 pathogenic variants. Ophthalmic Genet 39:569–576

Liskova P, Ulmanova O, Tesina P, Melsova H, Diblik P, Hansikova H, Tesarova M, Votruba M (2013) Novel OPA1 missense mutation in a family with optic atrophy and severe widespread neurological disorder. Acta Ophthalmol 91:e225–e231

Nasca A, Rizza T, Doimo M, Legati A, Ciolfi A, Diodato D, Calderan C, Carrara G, Lamantea E, Aiello C, Di Nottia M, Niceta M, Lamperti C, Ardissone A, Bianchi-Marzoli S, Iarossi G, Bertini E, Moroni I, Tartaglia M, Salviati L, Carrozzo R, Ghezzi D (2017) Not only dominant, not only optic atrophy: expanding the clinical spectrum associated with OPA1 mutations. Orphanet J Rare Dis 12(1):89. https://doi.org/10.1186/s13023-017-0641-1.

Pretegiani E, Rosini F, Rufa A, Gallus GN, Cardaioli E, Da Pozzo P, Bianchi S, Serchi V, Collura M, Franceschini R, Bianchi Marzoli S, Dotti MT, Federico A (2017) Genotype-phenotype and OCT correlations in autosomal dominant optic atrophy related to OPA1 gene mutations: report of 13 Italian families. J Neurol Sci 382:29–35

Santarelli R, Rossi R, Scimemi P, Cama E, Valentino ML, La Morgia C, Caporali L, Liguori R, Magnavita V, Monteleone A, Biscaro A, Arslan E, Carelli V (2015) OPA1-related auditory neuropathy: site of lesion and outcome of cochlear implantation. Brain 138:563–576

Spiegel R, Saada A, Flannery PJ, Burté F, Soiferman D, Khayat M, Eisner V, Vladovski E, Taylor RW, Bindoff LA, Shaag A, Mandel H,

Schuler-Furman O, Shalev SA, Elpeleg O, Yu-Wai-Man P (2016) Fatal infantile mitochondrial encephalomyopathy, hypertrophic cardiomyopathy and optic atrophy associated with a homozygous OPA1 mutation. J Med Genet 53:127–131

Yu-Wai-Man P, Griffiths PG, Gorman GS, Lourenco CM, Wright AF, Auer-Grumbach M, Toscano A, Musumeci O, Valentino ML, Caporali L, Lamperti C, Tallaksen CM, Duffey P, Miller J, Whittaker RG, Baker MR, Jackson MJ, Clarke MP, Dhillon B, Czermin B, Stewart JD, Hudson G, Reynier P, Bonneau D, Marques WJ, Lenaers G, McFarland R, Taylor RW, Turnbull DM, Votruba M, Zeviani M, Carelli V, Bindoff LA, Horvath R, Amati-Bonneau P, Chinnery PF (2010) Multi-system neurological disease is common in patients with OPA1 mutations. Brain 133:771–786