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Case Report

Childhood hearing loss is a key feature of CAPOS syndrome: A case report

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ABSTRACT

CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss) is a rare neurological disorder, recently associated with the c.2452G > A hotspot mutation in the *ATP1A3* gene, with sensorineural hearing loss as a prominent feature. We herein report on a girl who has experienced hearing loss for three years following an initial encephalitic episode when aged 15 months old. CAPOS was diagnosed only when she was six years old by targeted testing whilst she displayed optic atrophy, cerebellar signs and areflexia. CAPOS syndrome should be considered in the differential diagnosis of acquired childhood deafness, prompting clinicians to search for associated neurological features.

1. Introduction

CAPOS syndrome, named after its symptoms (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss) (OMIM #601338), is a rare disorder so far described in only eight families [1–6] since its initial description in 1996 [7]. The typical CAPOS phenotype is characterized by acute neurological deterioration manifesting in infancy and triggered by stressful episodes, such as a febrile illness. These episodes may be recurrent and accompanied by symptoms that may partially disappear thereafter, including ataxia, acquired areflexia, ophthalmoplegia, hypotonia, weakness, lethargy, and comatose state suggestive of encephalitis. Sensorineural deafness and optic atrophy may develop at that time or appear after the acute event and progress slowly over time. Acute episodes of deterioration on top of slowly progressive hearing loss have also been described. In all known cases so far, affected patients have been found to harbor the specific heterozygous mutation c.2452G > A in exon 4 of the *ATP1A3* gene, the recurrence of which creates the "genetic homogeneity" of CAPOS syndrome [5]. We herein describe the first patient of Belgian origin whose acquired sensorineural impairment represented a key feature aiding the clinicians in reaching this challenging diagnosis.

2. Case report

The patient is a six-year-old female, being the first child of non-consanguineous Belgian parents. She was born full term after an uneventful pregnancy. She had normal development and medical history up to age 15 months, when she began walking nearly independently. At that time, she suffered from a febrile gastroenteritis that rapidly evolved into generalized hypotonia and lethargy. Her neurological condition deteriorated, and she became highly confused, requiring intensive care support. On this acute episode, strabismus, horizontal nystagmus, and uncoordinated eye movements were noted. Deep tendon reflexes were absent. A probable diagnosis of post-infection rhombencephalitis or the Miller Fischer variant of Guillain-Barré syndrome was suggested [8–10] despite normal cerebrospinal fluid (CSF) analyses and nerve conduction velocity. No infectious agent was found either in the blood or CSF (Table 1). An electroencephalogram revealed transient slow background rhythm, and the brain MRI was unremarkable. The optic fundus was normal. Antibiotics, acyclovir, and steroids were administered, resulting in partial recovery.

During the next weeks, global hypotonia persisted with residual mild balance difficulties and esotropia. Deep tendon reflexes could be weakly elicited. The patient walked unaided at age two years, yet following a bout of influenza, she once more needed further support. She continued to exhibit progress thereafter yet displayed motor delay, eventually resuming walking unaided at 3.5 years. Neurological examination revealed a broad-based gait and mild dysmetria consistent with cerebellar dysfunction. A brain MRI was repeated three years after the initial acute encephalitic episode, with only normal findings.

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Table 1
Laboratory investigations performed on the proband.

Blood	Glucose, lactate, pyruvate, blood cell count, ionogram, urea, creatinine, uric acid, liver enzymes, creatine kinase, ammonia, isoelectric focusing of serum transferrin, thyroid hormones, immunoglobulins, electrophoresis of proteins, α-foetoprotein, copper, ceruloplasmin, vitamins E, B12, B9, hemostasis Amino acids, acylcarnitines, very long chain fatty acids, pristanic acid, phytanic acid, pipecolic acid Antinuclear and anti-phospholipid antibodies, ANCA and ASCA Antibodies for Mycoplasma Pneumoniae, EBV, CMV, Borrelia, HSV1-2, HZV, and Parvovirus B19 MELAS and MERFF-related mutations Array-CGH
Urine	Amino acids, organic acids, ionogram, glucose, proteins, purine and pyrimidine metabolites, creatine and guanidinoacetate
Cerebrospinal fluid	Glucose, lactate, pyruvate, proteins, immunoglobulins, amino acids, cell count, methyl-tetrahydrofolate, PCR for HSV1-2 and enterovirus

EBV: Epstein-Barr virus; CMV: cytomegalovirus; HSV1-2: Herpes simplex virus Type 1-Type 2; HZV: Herpes zoster virus; ANCA: antineutrophil cytoplasmic antibodies; ASCA: anti-Saccaromyces cerevisae antibodies; CGH: comparative genomic hybridization; PCR: polymerase chain reaction.

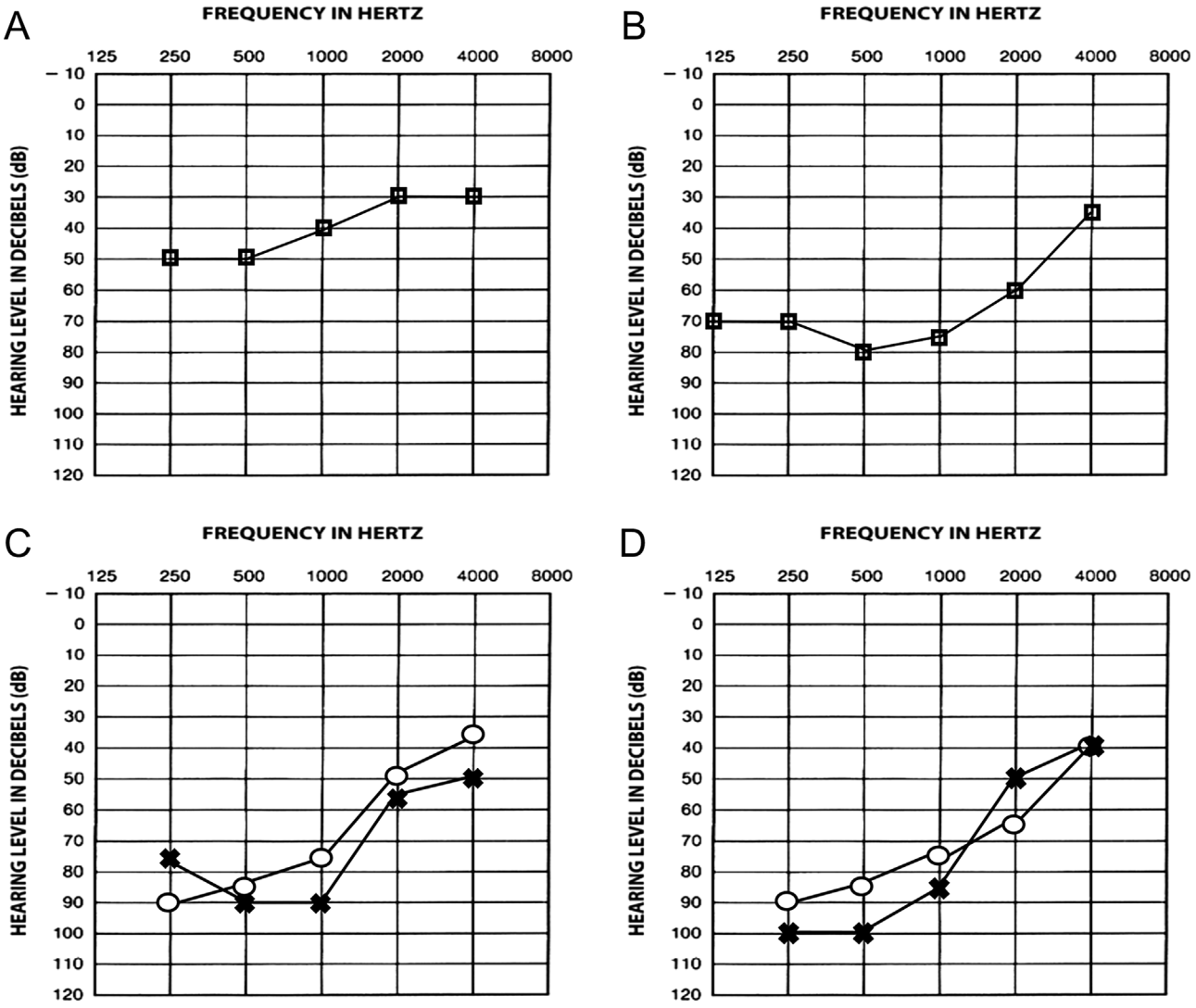

Fig. 1. A–D: First free-field pure tone audiometry with binaural air conduction thresholds at the age of 4 years (A) and four months later (B). Pure tone audiometry with earphones in both left (x) and right (0) ears, five months after the initial assessment (C) and two years later (D).

At age four years, the patient was said to participate less in school activities, and instructions to her had always to be repeated. Hearing loss was suspected then confirmed by audiological assessments. Free-field pure tone audiometry demonstrated deterioration of her hearing thresholds within a few months (Fig. 1A and B). Pure tone audiometry with earphones performed five months after the initial assessment and again two years later confirmed the hearing loss, with relatively similar thresholds recorded for both ears (Fig. 1C and D). Hearing loss was marked for low- and mid-frequency sounds, while high-frequency hearing was better preserved (Fig. 1A–D). Speech audiometry results (audiometer Madsen Astera Otometrics) were obtained with closed set tests using the Word Intelligibility by Picture Identification (WIPI) test [11] in the French language, and indicated reduced discrimination ability over time, with 0% discrimination ability at 90 dB HL for both ears at age four years and eight months. Brainstem auditory evoked potentials demonstrated no detectable synchronized activity beyond 90 dB HL regardless of which ear was tested. At that threshold, only wave I was evident. The cochlear microphonic potential was preserved in both ears. The absence of retrocochlear potentials combined with some preserved endocochlear responses was suggestive of auditory

Table 2
Differential diagnosis of sensorineural hearing loss combined with optic atrophy.

	Diagnostic testing	Other associated clinical signs
Autosomal dominant optic atrophy Type 1 plus and other mitochondrial related diseases	Molecular testing *OPA1* gene	Possible multi-systemic impairment
Biotinidase deficiency, autosomal recessive inheritance	Biotinidase activity in plasma/dry blood spot	Variable developmental delay, periorificial skin rash, alopecia, seizures, leukoencephalopathy
Congenital disorders of glycosylation	Isoelectric focusing of serum transferrin	Possible multi-systemic impairment
Peroxisomal disorders	Plasma with very long chain fatty acid, phytanic acid, pristanic acid	Peripheral neuropathy, retinopathy, liver dysfunction, variable developmental delay and cognitive impairment
Phosphoribosylpyrophosphate synthetase 1 deficiency: Arts syndrome, X-linked inheritance	Molecular testing *PRPS1* gene	Developmental delay, intellectual disability, infection-triggered hypotonia, peripheral neuropathy
Riboflavin transporter defect: Brown-Vialetto-Van Laere syndrome, autosomal recessive inheritance	Molecular testing *SLC52A2* gene	Axonal motor neuropathy, ataxia, progressive upper limb weakness, bulbar impairment, respiratory failure
Deafness-dystonia-optic neuronopathy syndrome, Mohr-Tranebjaerg syndrome, X-linked inheritance	Molecular testing *DDP1* gene	Dystonia, cognitive decline
Congenital cytomegalovirus infection	Polymerase chain reaction (PCR) on neonatal dry blood spot	Microcephaly, developmental delay, seizures, abnormal neuronal migration

neuropathy spectrum disorder [12,13]. The vestibular tests were abnormal bilaterally without any response from the horizontal semicircular canals to caloric and rotatory stimulations. Vestibular evoked myogenic potentials were absent for both ears. A third brain MRI did not demonstrate inner ear or internal auditory canal malformations. The suggestion was made for the child to wear binaural hearing aids. Amplification was used, yet with no clear improvement achieved, and an additional FM device was proposed for school use.

A few months before hearing loss was identified, a routine ophthalmological follow-up had found optic nerve pallor, along with decreased visual acuity and worsening strabismus. Visual evoked potentials from both eyes showed altered visual conduction with flash stimulation. Given the sensory disturbances combined with neurological symptoms, additional investigations were performed in order to detect any metabolic, auto-immune, or infectious diseases (Table 1). However, all results were unremarkable. CAPOS syndrome was suggested when the patient reached 6 years old, with all the symptoms pieced together creating a picture indicative of the specific *ATP1A3*-related disorder. Targeted sequencing confirmed the presence of a heterozygous c.2452G > A (pE818K) mutation, which was not found in either healthy parent, suggesting a *de novo* occurrence.

3. Discussion

Previous descriptions of CAPOS-affected families over the last three years have progressively improved our understanding of the condition. The causal mutation, however, was only identified in 2014, a long time after the initial description [7], with only eight pedigrees reported so far to our knowledge. CAPOS syndrome remains a rare condition, and its underlying pathogenic mechanisms are still not fully understood.

Typically, CAPOS patients exhibit infantile onset fever-induced episodes of weakness, lethargy, cerebellar ataxia, acquired areflexia, and ophthalmoplegia. As was the case for our patient, the acute initial presentation is often suggestive of specific encephalitis, a variant of the Guillain-Barré/Miller Fischer syndrome, or belonging to the rhombencephalitis spectrum [8–10]. The laboratory results, nerve conduction velocity parameters, and brain MRI data yet usually prove unremarkable. Interestingly, neurological impairment has been detected in some patients already prior to the first acute episode, including areflexia, clumsiness, mild ataxia, and motor instability [6]. Hearing loss and optic atrophy were observed after the first paroxysmal event in all cases, except for a recently reported patient who had never experienced acute deterioration [6]. Otherwise, sensorineural impairment may appear either immediately or a long time after the initial acute deterioration. These delayed manifestations, however, are not always connected to the past acute event. In our patient, hearing loss was only noted more than three years after the encephalitic episode, which was initially considered as an independent finding. Audiometry was performed because instructions at school always had to be repeated and the child appeared more distractible. Given that optic atrophy was observed upon a routine ophthalmological examination, a multi-systemic disorder was suspected.

Sensorineural deafness combined with optic atrophy and variable neurological impairment could also be indicative of a mitochondrial disease, especially in the presence of suspected maternal inheritance. Other genetic and metabolic disorders should be considered for the differential diagnosis (Table 2), such as dominant optic atrophy (OPA1) plus syndrome (OMIM #125250), the recently-described dysfunction of phosphoribosylpyrophosphate synthetase 1 (PRPS1) (OMIM #301835) [14], biotinidase deficiency (OMIM #253260), peroxisomal diseases, riboflavin transporter defect (Brown-Vialetto-Van Laere syndrome, OMIM #614707) or congenital glycosylation disorders. It should, nonetheless, be noted that the absence of associated signs like epilepsy, intellectual disability, growth failure, microcephaly, and abnormalities on brain MRI, facilitated the diagnostic approach in our case.

CAPOS syndrome is part of the expanding spectrum of neurological phenotypes related to *ATP1A3* mutations. The other well-defined *ATP1A3*-related disorders (alternating hemiplegia of childhood or AHC, OMIM #614820, rapid-onset dystonia-parkinsonism or RDP, OMIM #128235, known as DYT12) resemble CAPOS syndrome with respect to their paroxysmal neurological symptoms. Paroxysmal febrile induced ataxia has also been described in *CACNA1*-or *FGF14*-related diseases, yet without the typical symptom constellation. Hearing loss in particular was not found in these other conditions, whereas it has been described in all the published CAPOS syndrome patients.

The pathogenic mechanisms underlying hearing deficit in CAPOS syndrome are currently only hypotheses that still require further research. The *ATP1A3* gene encodes the α3-subunit of the transmembrane Na/K-ATPase pump (OMIM#182350) that regulates intra- and extracellular sodium and potassium levels, being implicated in maintaining electrochemical gradients across the plasma membrane [15]. McLean et al. [16] characterized the neuronal expression of the α subunit of the Na/K ATPase pump in the cochlea of rats. These researchers identified the α3 isoform of the Na/K pump within the membranes of the spiral ganglion somata, the Type 1 afferent terminals being in contact with the inner hair cells, and the medial efferent terminals in contact with the outer hair cells. The reason why hearing loss is not found in the other *ATP1A3*-related entities is still unclear, although Heimer et al. [3] proposed investigating these patients further for any hearing deficits. In our patient, hearing loss was marked in low-frequency tones, as frequently described in patients with auditory neuropathy spectrum disorders [12,13]. To date, little data is available on audiological

evaluations performed in previously-described CAPOS patients, yet similar impairment in low-frequency sounds has already been reported for these conditions [1,5,7]. The auditory neuropathy in CAPOS patients could therefore initially involve the cochlear apical turns, where hair cells respond to low-frequency tones. Nevertheless, the neuronal distribution of the α3 isoform of the Na/K pump was also observed in the cochlea's middle and basal turns [15]. Further characterization of the sensorineural hearing deficit in CAPOS patients is now required, however, to confirm this hypothesis. Lastly, acetazolamide has been suggested to prevent neurological deterioration, as has been the case for episodic ataxia. This drug could reduce ionic leakage caused by Na/K pump dysfunction whilst generating metabolic acidosis. The role of medication in CAPOS disease remains unclear. Our patient demonstrated no real improvement by means of an amplification device, and cochlear implantation was discussed. Any potential improvement with hearing aids remains uncertain, since the auditory neuropathy appears to be progressive over time.

4. Conclusion

CAPOS syndrome should be considered in the differential diagnosis of children presenting with acquired sensorineural deafness. From the otorhinolaryngologist's point of view, this case report suggests that clinicians should search for a “hearing loss plus” syndrome, namely for additional neurological features, particularly in the event of a previous unexplained paroxysmal neurological event. Meticulous neurological and ophthalmological examinations are required, given that the hearing deficit is a prominent and permanent feature in all diagnosed CAPOS patients. In addition, conducting a family study in order to detect a likely autosomal mode of inheritance may contribute to the diagnostic approach.

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The authors have no financial relationships relevant to this article to disclose.

Conflicts of interest

None.

References

[1] M.K. Demos, C.D. van Karnebeek, C.J. Ross, S. Adam, Y. Shen, S.H. Zhan, C. Shyr, G. Horvath, M. Suri, A. Fryer, S.J.M. Jones, J.M. Friedmen, the FORGE Canada Consortium, A novel recurrent mutation in ATP1A3 causes CAPOS syndrome, Orphanet J. Rare Dis. 9 (2014) 15.

[2] H. Rosewich, D. Weise, A. Ohlenbusch, J. Gärtner, K. Brockmann, Phenotypic overlap of alternating hemiplegia of childhood and Capos syndrome, Neurology 83 (2014) 861–863.

[3] G. Heimer, Y. Sadaka, L. Israelian, A. Feiglin, A. Ruggieri, C.R. Marshall, S.W. Scherer, E. Ganelin-Cohen, D. Merek-Yagel, M. Tzadok, A. Nissenkorn, B. Ben Zeev, CAOS-Episodic cerebellar ataxia, areflexia, optic atrophy and sensorineural hearing loss: a third allelic disorder of the *ATP1A3* gene, J. Child. Neurol. 30 (2015) 1749–1756.

[4] A. Potic, B. Nmezi, Q.S. Padiath, CAPOS syndrome and hemiplegic migraine in a novel pedigree with the specific *ATP1A3* mutation, J. Neurol. Sci. 358 (2015) 453–456.

[5] R.P.P.W.M. Maas, J.H. Schieving, M. Schouten, E. Kamsteeg, B.P.C. van de Warrenburg, The genetic homogeneity of CAPOS syndrome: four new patients with the c.2452G > A (p.Glu818Lys) mutation in the *ATP1A3* gene, Pediatr. Neurol. 59 (2016) 71–75.

[6] A.D. Rodriguez, M. Prochazkova, S. Santos Santos, O.R. Cabezas, V.C. Extremera Gonzalez-Gutierrez-Solana, Early diagnosis of CAPOS syndrome before acute-onset ataxia- Review of the literature and a new family, Pediatr. Neurol. 71 (2017) 60–64.

[7] P. Nicolaides, R.E. Appleton, A. Fryer, Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS): a new syndrome, J. Med. Genet. 33 (1996) 419–421.

[8] M. Odaka, N. Yuki, M. Yamada, M. Koga, T. Takemi, K. Hirata, S. Kuwabara, Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome, Brain 126 (2003) 2279–2290.

[9] B.R. Wakerley, A. Uncini, N. Yuki, GBS Classification Group, Guillain-Barré and Miller Fisher syndromes–new diagnostic classification, Nat. Rev. Neurol. 10 (2014) 537–544.

[10] Z. Aranyi, T. Kovacs, I. Sipos, D. Bereczki, Miller Fisher syndrome: brief overview and update with a focus on electrophysiological findings, Eur. J. Neurol. 19 (2012) 15–20.

[11] M. Ross M, J. Lerman, A picture identification test for hearing impaired children, J. Speech Hear Res. 13 (1970) 44–53.

[12] T. Moser, A. Starr, Auditory neuropathy–neural and synaptic mechanisms, Nat. Rev. Neurol. 12 (2016) 135–149.

[13] G. Rance, A. Starr, Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy, Brain 138 (2015) 3141–3158.

[14] R. Mittal, K. Patel, J. Mittal, B. Chan, D. Yan, M. Grati, X.Z. Liu, Association of *PRPS1* mutations with disease phenotypes, Dis. Markers 2015 (2015) 127013.

[15] T.H. Holm, K. Lykke-Hartmann, Insight into the pathology of the α3Na/K-ATPase ion pump in neurological disorders; lessons from animals models, Front. Physiol. 7 (2016) 209.

[16] W.J. McLean, K.A. Smith, E. Glowatzki, S.J. Pyott, Distribution of the Na,K-ATPase α subunit in the rat spiral ganglia and organ of corti, J. Assoc. Res. Otorhinol 10 (2009) 37–49.