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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.

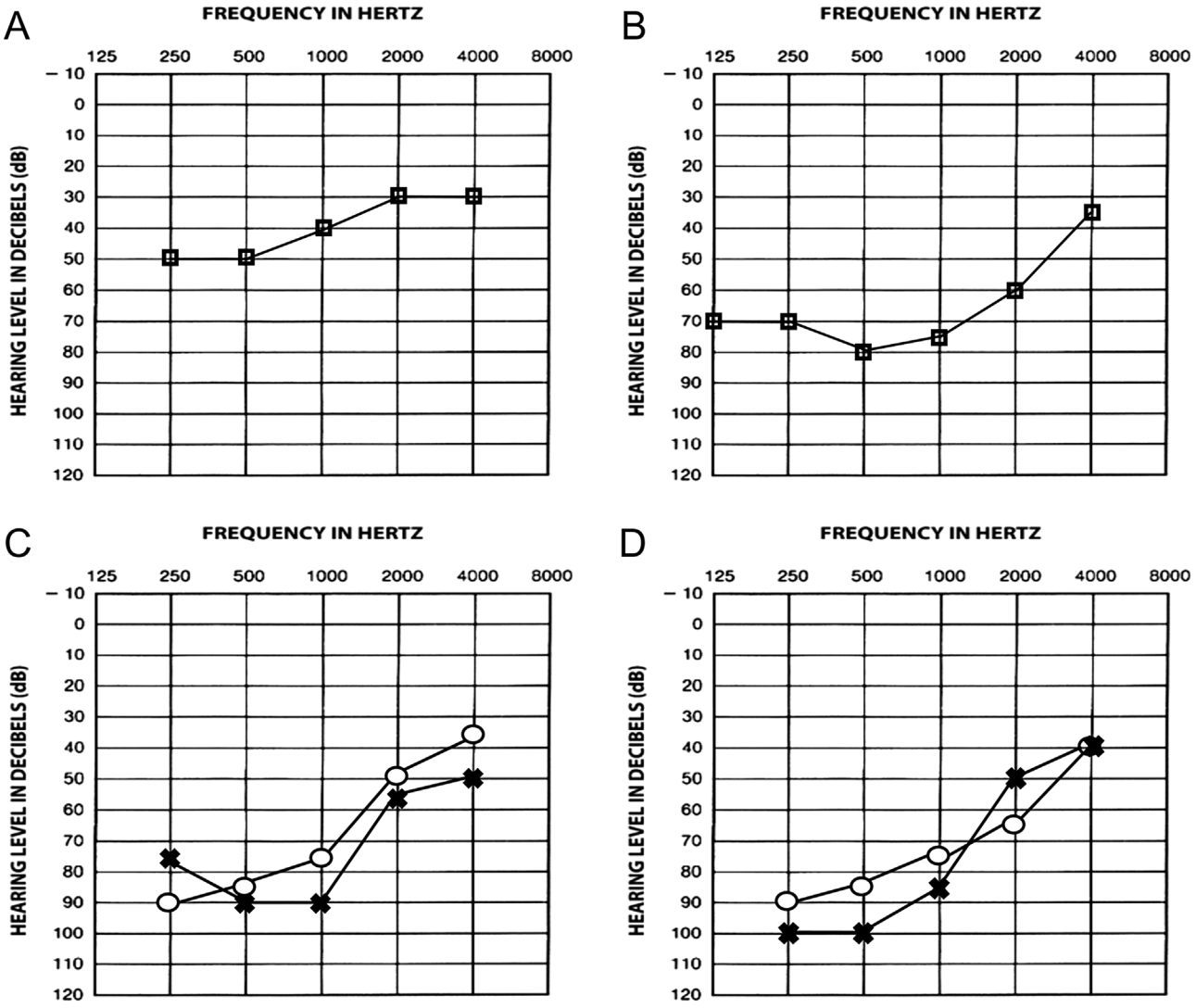

Fig. 1. A–D: First free-field pure tone audiometry with binaural air conduction thresholds at the age of 4 years (A) and four months later (B). Pure tone audiometry with earphones in both left (x) and right (0) ears, five months after the initial assessment (C) and two years later (D).

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