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Familial Alström syndrome: a rare cause of bilateral progressive hearing loss☆,☆☆

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KEYWORDS
Alström syndrome;
Sensorineural hearing loss;
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Retinitis pigmentosa

Abstract
Introduction: Alström Syndrome is a rare disease caused by mutations in ALMS1 gene. It is characterized by a progressive degeneration of sensory functions, resulting in visual and audiological impairment, as well as metabolic disturbances such as childhood obesity, hyperinsulinemia, and diabetes mellitus type 2.
Objective: To report and discuss the genetic and audiological findings in two siblings with Alström syndrome.
Methods: This was a prospective, analytical and descriptive study, using questionnaires, serial audiograms, otoacoustic emissions, and auditory brainstem response analysis, as well as molecular genetic analysis.
Results: Both patients presented childhood-onset bilateral sensorineural hearing loss, which progressed to moderate impairment in the first case and severe hearing loss in the second. Otoacoustic emissions were absent, and auditory brainstem responses were bilaterally normal in both cases.
Conclusion: In the present patients, Alström Syndrome began with a neurosensory hearing loss in early childhood that progressed to a profound loss in ten to twenty years. The auditory lesions were cochlear in origen according to the otoacoustic emissions and auditory brainstem responses.

PALAVRAS-CHAVE
Síndrome de Alström;
Perda auditiva neurossensorial;
Obesidade infantil;
Diabetes *mellitus* tipo 2;
Retinite pigmentosa

Síndrome de Alström familiar: uma rara causa de perda auditiva progressiva bilateral

Resumo
Introdução: A Síndrome de Alstrom é uma doença muito rara, causada pela mutação no gene ALMS1, que apresenta uma degeneração progressiva das funções sensoriais, resultando em deficiências visuais e auditivas, além de distúrbios metabólicos como obesidade na infância, hiperinsulinemia e diabetes tipo II.
Objetivo: Apresentar o perfil audiométrico de dois irmãos da mesma família afetados pela Síndrome de Alström.

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Método: Estudo prospectivo, analítico descritivo, os pacientes afetados foram submetidos a um questionário previamente testado, audiometria tonal e vocal seriadas, análise de emissões otoacústicas, e de respostas de potencial evocado auditivo de tronco encefálico, além de análise genético-molecular para comprovação diagnóstica.
Resultados: Ambos os pacientes apresentaram perda auditiva bilateral com o início na infância e progressão lenta para perda auditiva neurosensorial severa no primeiro caso e, profunda, no segundo. As emissões otoacústicas estavam ausentes, e o potencial evocado auditivo de tronco encefálico estava normal em ambos os pacientes, bilateralmente.
Conclusão: A Síndrome de Alström apresenta início precoce de perda auditiva neurossensorial, antes da adolescência, 10 a 20 anos para desenvolver perda auditiva severa a profunda. A lesão auditiva é essencialmente coclear, de acordo com os resultados dos testes de emissões otoacústicas e de potenciais evocados auditivos de tronco encefálico.

Introduction

According to Alström et al.,[1] Alström syndrome is a genetically transmitted disease with a variety of symptoms that include progressive sensory degeneration, resulting in visual and auditory deficits, as well as obesity. Metabolic, endocrine, renal, cardiac, and hepatic dysfunctions are also observed.

Descriptions of clinical cases of Alström syndrome are scarce. The first significant scientific article was published by Eggitt Russell et al.,[2] who performed a longitudinal study of 22 cases of Alström syndrome, focusing on the histopathology of affected organs and other factors that led to the death of the affected patients. Marshall et al.[3] studied 182 cases of the syndrome. According to Welsh et al.,[4] the genetic factor that causes the syndrome was a reciprocal translocation in a novel gene of unknown function, ALMS1, located on chromosome 2p13.

Even though Alström syndrome has been described as a homogeneous alteration resulting from a mutation in a single gene, families have been described with variable clinical presentations. Cardiomyopathy, hepatic dysfunction, hypothyroidism, and hypogonadism can occur. These symptoms vary in individuals from the same family, due to the interactions of genetic modifiers.[1] Collin et al.[5,6] indicated that the phenotype of Alström syndrome is due to an altered function, rather than inadequate organ development.

Alström et al.[1] reported the onset of hearing loss in patients affected by the syndrome before the age of 10 years and noted subsequent progression. Michaud et al.[7] confirmed that deafness began in the first decade of life. Marshall et al.[3] indicated that hearing loss appeared during childhood and that the mean age of onset was 5 years. Coincidentally, chronic serous otitis media was observed in 42% of their patients, adding a conductive component to the already described sensorineural loss.[7] Russell-Eggitt et al.[2] reported that only two of their 22 cases had normal hearing after 12 years of age.

The present study aimed to perform an extensive literature review and to present a complete clinical-audiometric profile, and molecular genetic analysis of two siblings, the only two cases reported to date in South America, in order to provide a better understanding of this very rare disease.

Material and methods

A prospective, descriptive analytic study of the phenotype of a Caucasian Brazilian family with members affected by Alström syndrome, was conducted. Data were collected through a long-term clinical evaluation of patients, chart review, and a questionnaire answered by family members.

Patients underwent a complete otorhinolaryngological assessment with audiological examination with pure-tone and speech audiometry, acoustic immitance testing, distortion-product otoacoustic emissions (DPOAE), transient-evoked otoacoustic emission (TEOAE), and auditory brainstem response (ABR) testing.

Pure tone audiometry by air conduction was performed, at frequencies from 250 to 8,000 Hz, and by bone conduction at frequencies from 500 to 4,000 Hz; speech recognition and speech reception thresholds were measured using GSI68 equipment, equipped with TDH-39 earphones. Tympanometry was performed using GSI38 equipment. The criteria proposed by Russo and Santos were employed for this assessment.[8]

DPOAE and TEOAE were performed using a Biologic equipment (Scout model). Amplitudes and signal/noise ratio were evaluated in both ears, based on the criteria described by Figueiredo[9] and by Gorga.[10] ABR was performed in a Biologic equipment (Navigator-Pro model). The electrodes were placed according to the international electrode system:[11] the active electrode on the vertex (Cz); the ground, on the forehead (Fz); and the reference electrodes on the lobes of the right and left ears (A1 and A2). The headphone used in the test was the TDH-39. The type of stimulus was a click with an intensity of 80 dB HL. Absolute latencies of waves I, III, and V were measured, as well as interpeak intervals of waves I-III, III-V, and I-V, and binaural comparison of wave V latencies. The Hood criteria were used for this assessment.[12]

To perform the molecular genetic diagnosis, an informed consent was obtained from all patients involved in the study and their parents/guardians. This study was approved by the research ethics committee of the institution, under protocol number 1112000005. Genomic DNA, isolated from peripheral blood according to the standard method, was amplified using the polymerase chain reaction (PCR) protocol, as previously described.[10] Sequences of primers and amplification conditions are available at request. PCR amplicons of exons 8, 10, and 16 of ALMS1 gene were purified, directly sequenced, and