P024

CLINICAL GENETICS

Two cases of auditory neuropathy in children with mutations in TWNK gene

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Introduction

Mutations in TWNK gene were described in patients with Perrault syndrome - autosomal-recessive disease, which includes sensorineural hearing loss, central auditory and speech disorders, cerebellar ataxia, motor and sensory neuropathy, ovarian dysfunction. Only around 100 cases of Perrault syndrome have been described to date. Currently, there are only a few published cases of auditory neuropathy (ANSD) in patients with Perrault syndrome associated with mutations in TWNK gene. Two cases of ANSD, caused by mutations in TWNK gene, are described here.

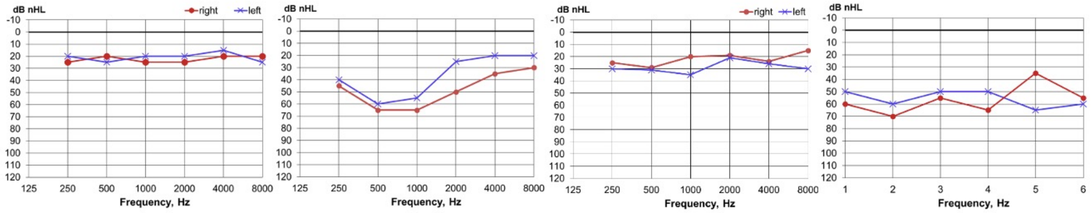


Figure 1. PTA data (1st case)

Patients

The first patient is 13 years old girl. Unstable reactions on sounds, necessity of repeating questions, speech delay since 3 years.

The second patient is 16 years old girl. Hearing loss after 5 years, poor speech intelligibility. Myopia.

Methods

Audiological evaluation: pure-tone and speech audiometry, impedance audiometry, OAEs, ABR, eABR, ECoG, CAEP. Brain MRI, CT of temporal bone. Clinical exome sequencing, Sanger sequencing.

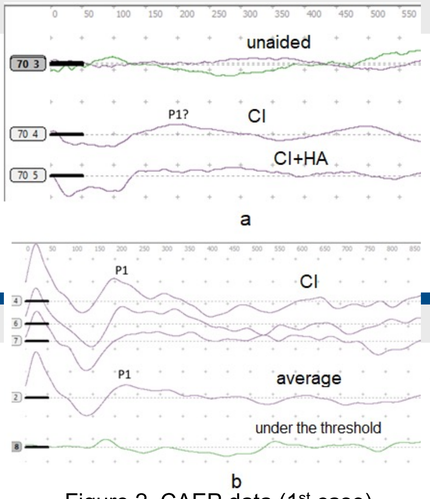


Figure 2. CAEP data (1st case)

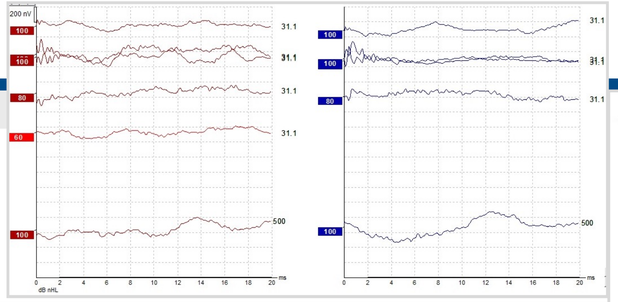
Results

First case: examination in 3 years - normal hearing. The next visit in 8 years: fluctuating hearing thresholds (20-50 dB HL), normal OAE, type A tymp, no acoustic reflexes, no ABR peaks + CM. Normal speech-language development. ANSD was diagnosed. By the age of 9 thresholds elevated up to 55-80 dB HL with high variability (fig.1). Speech understanding degraded. Amplification without any effect. ECoG: registered CM, no compound action potential. In the age of 11,5 unilateral CI was performed. Aided thresholds were stable, 30-35 dB HL, can distinct sounds, words and phrases after first fittings. Despite regular auditory trainings, a gradual regress in speech understanding was observed. CAEP without CI weren't detected. No oblivious CAEP with CI were recorded in 8 month after surgery (fig.2a). Morphologically changed, low-amplitude potentials were recorded in 18 months after CI (fig. 2b). Two mutations in TWNK gene were found. The nucleotide variant c.1523A>G (p.(Tyr508Cys), NM_021830.5) was previously described, another - c.1199G>T (p.(Arg400Leu), NM_021830.5)) is a new one. These variants were confirmed in parents as well. Ovarian dysfunction and debut of the cerebellar ataxia were also revealed in the child.

Second case: mild-moderate sensorineural hearing loss in 12 years, decreased speech intelligibility. Trial amplification was unsuccessful. In the age of 16 ovarian dysfunction was detected. Audiological evaluation: bilateral mild hearing loss (fig. 3), no ABR and CAEP peaks (fig. 4). OAE were present. ECoG: both CM and compound action potentials exist. Speech audiometry: monosyllabic words in quiet - 60%, in noise - 10%. Speech intelligibility with hearing aids worsened. Two mutations in TWNK gene were detected: c.737A>G(p.Arg246Ser, NM_021830.5) and c.1523A>G, which was the same as in the first child. The patient is under observation. MRI, CT data - without any pathological signs in both cases.

Conclusion

The main value of these cases the combination of mutations in TWNK gene (one of them was firstly described) with ANSD phenotype, which has been rarely described in literature and that the hearing loss was the first symptom of the TWNK-related Perrault syndrome. Specificity is also in the progression of hearing loss, ineffective amplification and limited CI effect.



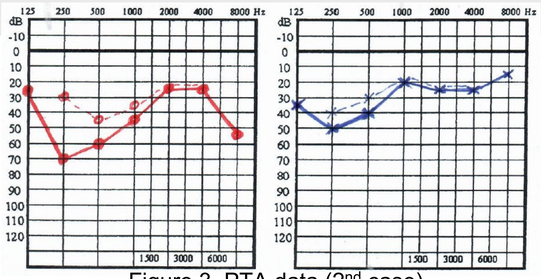
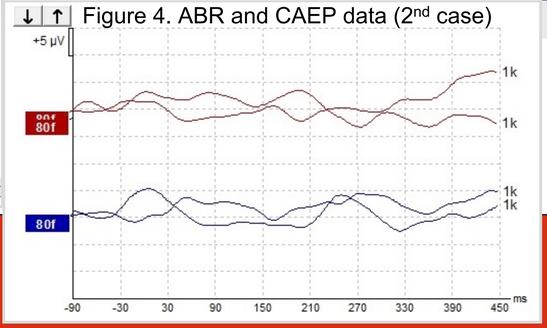


Figure 3. PTA data (2nd case)

Figure 4. ABR and CAEP data (2nd case)



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