ORIGINAL RESEARCH

Are serum levels of trace elements in children with auditory neuropathy within normal limits? – A pilot study

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Abstract

Objectives: To determine whether trace elements that are essential for neural function play a role in the pathophysiology and etiology of auditory neuropathy (AN)..

Materials and methods: Patients diagnosed with auditory neuropathy consisted of eight children (two male, six female). The blood tests including the measurement of sodium, potassium, chloride, calcium, phosphorus, iron, copper and magnesium were done in children with AN during their routine care.

Results: Of the eight children with AN, many had serum levels outside the normal range: one had low sodium, two had low potassium, one had low chloride, two had high

zinc and three had low zinc, two had low calcium and two had higher than normal phosphorus.

Conclusion: Although some serum trace element levels in our patients were higher or lower than normal values, the mean values were within normal limits. Thus, we were unable to detect a relationship between serum trace element levels and AN-. In the future, larger studies should be conducted to confirm these findings.

Auditory neuropathy (AN) is a sensorineural disorder characterized by absent or abnormal auditory brainstem evoked potentials and normal cochlear outer hair

cell function. A variety of processes are thought to be involved in its pathophysiology and the influence of these processes on hearing may be different. People with AN may have normal hearing, or hearing loss ranging from mild to severe, and they always have poor speech-perception abilities. Often, speech perception is worse than would be predicted by the degree of hearing loss. This clinical entity was first reported in the late 1970's as paradoxical findings due to discrepancy between absence of auditory brainstem response (ABR) and hearing threshold presence, and, until late 1970s, was referred to as central auditory dysfunction or auditory neural synchrony disorder. The details of pathophysiological changes in AN was first identified in the 1980s when advanced testing procedures became available to measure the action of the cells in the cochlea.

The prevalence of AN is unknown. It is reported to be present in 0.5% to 15% of patients with sensorineural hearing loss.¹ Recently, it was reported to be found in 22 of 428 (5%) children with hearing loss.² Liang *et al.*³ reported that the prevalence in China was even higher.

Several factors have been linked to auditory neuropathy in children^{2,4}; however, a clear cause and effect relationship has not been proven. Madden and others² described 22 cases of auditory neuropathy from a pediatric otology clinic: 50% had a history of hyperbilirubinemia; 45% had a history of prematurity; 45% had ototoxic drug exposure; 36% had a family history of hearing loss, and 36% had a history of neonatal ventilator dependence. These findings indicate that AN has a multifactorial etiology.

The OTOF gene, encoding otoferlin, is associated with AN. Romanos *et al.*⁵ investigated the contribution of OTOF mutations to AN and to non-syndromic recessive deafness in Brazil. Among the 11 probands with AN, seven had at least one pathogenic mutation in the OTOF gene.

Some children who have been diagnosed with auditory neuropathy experienced certain health prob-

lems as newborns, or during or shortly before birth. These problems include jaundice, premature birth, low birth weight, and an inadequate supply of oxygen to the unborn baby. In addition, some drugs that have been used to treat medical complications in pregnant women or newborns may damage the inner hair cells in the baby's ears, causing auditory neuropathy.^{4,6}

In this study we hypothesized that some elements that are essential for neural function play a role in the pathophysiology and etiology of AN.

Materials and Methods

This pilot study was carried out at the Kirikkale University, Faculty of Medicine, ENT Department and Hacettepe University, Faculty of Medicine, Division of Audiology and Speech Pathology of ENT Department, Turkey. All steps of the study were planned and carried out according to the principles outlined in the Declaration of Helsinki.⁷

Subjects

The patients diagnosed as auditory neuropathy (AN) according to previously established diagnostic criteria⁸⁻¹⁰ were sent from Hacettepe University Faculty of Medicine ENT Department and Division of Audiology to Education Audiology Division. Diagnosis of AN was performed with the criteria of⁸⁻¹⁰:

1. In pure tone thresholds, there was sensorineural hearing loss and/or fluctuant hearing loss,
2. Otoacoustic emissions: normal
3. Middle ear muscle reflexes: ipsilateral: absent, contralateral: absent
4. In ABR: ABR waves were absent (or severely abnormal); and cochlear microphonics were absent.

These patients formed the auditory neuropathy group and this group consisted of eight children (two male, six female). Their mean age was 8.6 ± 6 (range 2-20) years.

Patients' history, including any risk factor for AN and specific auditory behaviors, were taken from parents. All children were included in the study with their parents' agreement by written, informed consent. According to the information obtained from both the parents and the hospital files, children with known risk factors for AN, such as premature birth, low birth weight, intrauterine infections were excluded from the study.

Blood serum levels of sodium, potassium, chloride, calcium, phosphorus, iron, copper and magnesium levels were measured in AN children at Numune State Hospital. The laboratory's normal values were used as the control values for the study.

Statistical analysis

Statistical packet for SPSS (Version 8.0) was used for statistical evaluation. Mean±standard deviation values for each of the trace elements were found.

Results

Childs' gender, age and features of the AN in our eight cases are summarized in Table 1.

Trace element values of children with AN and normal levels are demonstrated in Table 2 and Figure 1.

Of the eight children with AN, one had a sodium level, two had a potassium level and one had a chloride level lower than normal serum values. Serum zinc levels were higher than normal in two children and lower than normal in three. Serum calcium levels were lower than normal in two patients and phosphorus levels were higher than normal in two patients.

Mean hemoglobin values were 13.26 ± 1.14 (Ranged from 11.28 to 14.55) g/dl in AN group. Normal levels were 11.6-13 g/dl. In only one boy was the hemoglobin level lower than the normal values for this age group.

Discussion

Auditory neuropathy is characterized by an abnormal auditory brainstem response and intact (but sometimes disappearing) otoacoustic emissions. Middle ear muscle reflexes are absent, while audiograms are quite variable, ranging from profound to mild.

Starr *et al.*¹¹ described 10 patients, all children or young adults who had AN. Cochlear microphonics

TABLE 1. Features of the Auditory Neuropathy in our eight cases

Case Number	Gender	Age	Features of Auditory Neuropathy		
			Severity of AN	AN Initiation Time	
				Pre-lingual	Post-Lingual
Case 1	Male	4	Very severe	Understands by looking at the face	-
Case 2	Female	8	Very severe	Can not understand speech	-
Case 3	Female	13	Severe	Understands by looking at the face	-
Case 4	Female	3	Severe	Understands by looking at the face	-
Case 5	Female	20	Severe	Understands by looking at the face	-
Case 6	Male	11	Moderate	Understands by looking at the face	-
Case 7	Female	8	Very severe	Understands by looking at the face	-
Case 8	Female	2	Very severe	Can not understand speech	-

TABLE 2. Serum trace element levels in children with AN

Trace Elements	Values			
	Normal	AN group		
		Mean±Standard Deviation	Minimum	Maximum
Na (mmol/L)	136-144	139±2.56	135	143
K (mmol/L)	3.6-5.1	4.13±0.58	3.4	4.99
Cl (mmol/L)	101-111	104.5±2.92	99	109
Zn (µg/dl)	63.8-110	86.67±26.60	51.6	121.76
Cu (µg/dl)	70-150	86.45±35.76	18	135
Ca (mg/dl)	8.9-10.3	9.83±0.75	8.9	11.1
P (mg/dl)	2.4-4.7	4.66±0.70	3.5	5.5
Mg (mg/dl)	1.8-2.5	2.31±0.21	2	2.6
Fe (µg/dl)	45-182	104.57±39.7	56	158

FIGURE 1. Trace element levels: Normal levels versus levels in children with AN

and otoacoustic emissions were preserved in all, but auditory brainstem response were abnormal. Auditory brainstem reflexes were also negative. The shape of the pure tone loss varied, being mainly low frequency in 5, flat in 3, and high frequency in 3. Speech was affected out of proportion to that expected from a pure tone loss, which might lead to some confusion with a central hearing loss pattern. Subsequently eight of these patients developed evidence of a peripheral neuropathy, which was hereditary in three. Starr *et al.*⁶ also reported a variant in three children, in whom transient deafness occurred when the children were febrile. This pattern is reminiscent of the typical exacerbation of neurological symptoms in individuals with demyelinating disease (e.g., MS).

The underlying abnormality affects some combination of the inner hair cells, the nerves of the primary auditory pathway, and the connecting synapses. Both genetic and environmental factors are known to cause AN. Gibson and Sanli¹² studied 39 children with AN and concluded that the more likely mechanism was selective loss of inner hair cells.

Doyle, Sininger and Starr⁶ reported eight pediatric patients having hearing deficits which they attributed to AN. They comment that word discrimination was impaired out of proportion to pure tone performance. Their subject eight also had Friedreich's ataxia, which is an inherited ataxia which is associated with neuropathy. There were no patient with a neurological syndrome in our group, which can be the reason for AN.

Hong *et al.*¹³ examined experimental AN model induced in mice following application of increased dosages of pyridoxine. Pyridoxine-treated mice exhibited an increase in the hearing threshold shift and delayed latency of both ABR and auditory middle latency response (AMLR) in proportion with pyridoxine dosages. Additionally, the extent of auditory nerve fiber loss increased in a dose-dependent manner following pyridoxine intoxication. Coffee or trigonelline treatment ameliorated the hearing threshold shift, delayed latency of the auditory evoked potential, and improved sensory fiber loss induced by pyridoxine

intoxication. The present findings demonstrate that high-dose pyridoxine administration can be used to produce a new mouse model for AN, and coffee or trigonelline as a main active compound of coffee extract can potentially facilitate recovery from pyridoxine-induced AN. As stated in this study, all biological factors effecting neural structures may have a potential role in etiology of AN.

In this study, all patients exhibiting any known risk factor for AN, such as premature birth, low birth weight, intrauterine infections, icterus or hyperbilirubinemia, were excluded from the study.

In this study, we aimed to measure trace element levels in patients with AN - which has not been investigated before. Lower than normal trace element levels in patients with AN could point the way to new therapeutic treatment options.

Although our analysis showed that some serum levels in our patients are higher or lower than normal values, when mean values are evaluated, these were normal limits. Thus, our results did not show a relationship between serum trace element levels and AN.

AN is a rare pathology and the population of the children with AN studied may have been too small to detect any statistically significant differences between AN patients and normal population. Thus, future studies with larger groups of patients evaluating the role of trace elements in NA may demonstrate more valuable data. Our study can be viewed as a pilot study which attempts to investigate the etiology of AN from a new perspective.

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