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Otorhinolaryngological, audiovestibular and swallowing manifestations of patients with Niemann–Pick disease Type C☆

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ABSTRACT

Objectives: The aim of this study is to evaluate audiovestibular and swallowing impairment of patients with NPC.
Methods: Audiovestibular and swallowing evaluation were performed on patients with Niemann–Pick disease type C (NPC) at Hacettepe University between 20013 and 2015 prospectively. Pure-tone audiometry (PTA), Auditory Brain stem response (ABR), Flexible endoscopic evaluation of swallowing (FEES) test and posturography were done. Hearing, swallowing and balance states were measured.
Results: There were 16 patients (5 male and 11 female, with a median age of 6.5 years old). The most common ABR abnormalities observed were absent waves I and III (%70 absent I waves, %43.75 absent III waves). Twelve of sixteen patients (%75) had an ABR abnormality in at least one ear, of these, four patients had normal hearing and three of them had periferal hearing loss. 12 (75%) patients had complaint of postural imbalance. 11(69%) of patients had peripheral and one (6%) patient had central impairment. Nine of sixteen patients (56.25%) show some degree of dysphagia (either penetration or aspiration). Two patients (12.5%) showed aspiration both liquid and viscous nutrition. Three patients (18.75%) showed aspiration primarily in liquids and two of them had penetration with viscous nutrition. Three patients (18.75%) had penetration with no aspiration neither liquid nor viscous nutrition (PEN-ASP score was 3, 3, 5, respectively).
Conclusion: There is no curative treatment for this devastating and fatal disorder and hearing impairment, balance and swallowing disorders can be seen especially late onset form of disease.

1. Introduction

Niemann–Pick disease type C (NPC) is a rare progressive neurodegenerative autosomal recessive lysosomal storage disorder. It has an estimated birth incidence of 1:150,000–1:120,000 [1]. Mutations in NPC 1or 2 genes give rise to defective intracellular lipid trafficking, with secondary accumulation of free cholesterol, sphingosine and glycosphingolipids in a number of tissues including the brain. The molecular biology underlying NPC pathophysiology: NPC is associated with mutations of genes, NPC1 and NPC2, with no primary defect in catabolic enzymes. These mutations cause severe impairment of intracellular lipid transport. When the NPC1 or the NPC2 protein is nonfunctional, the cellular trafficking of endocytosed LDL-derived cholesterol is impaired and leads to accumulation of unesterified cholesterol and other lipids in perinuclear lysosomes. The pattern of accumulating lipids is different in brain and non-neural organs. Accumulation of un-esterified cholesterol, phospholipids, and glycosphingolipids in liver and spleen may result in organomegaly and liver dysfunction [2]. On the other hand, neurons store only a minimal amount of cholesterol while levels of glycosylceramide, lactosylceramide, and GM2 and GM3 gangliosides are markedly increased in the brain [3].

Typical neurological manifestations include vertical supranuclear gaze palsy, saccadic eye movements, cerebellar ataxia, dystonia, dysmetria, dysarthtria and dysphagia. Oropharyngeal

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dysphagia can be particularly important since it can lead to food aspiration. Epidemiological data suggest that bronchopneumonia subsequent to food/fluid aspiration is a major cause of mortality in NPC [4]. There is limited literature suggesting that the auditory system is affected [4]. Our objective was to search audiovestibular and swallowing manifestations of this rare neurological disease.

2. Methods

The data of NPC patients who were diagnosed and followed in Hacettepe University Medical School Department of Pediatric Neurology and Department of Otorhinolaryngology were evaluated prospectively between 2013 and 2015. Otorhinolaryngologic examinations including peripheral vestibular system were conducted, flexible endoscopic evaluation of swallowing (FEES) test and some neurological parameters were registered. Special attention was given to the hearing, balance and swallowing states of the patients.

The *FEES* protocol, as established by Langmore et al. is a comprehensive evaluation of swallowing, including three major components: (a) structural movement, sensory status, and anatomic support for swallowing; (b) ability to swallow food and liquid; and (c) response to postural, dietary, or behavioral alterations to alter the path of the bolus or the way it is swallowed [5]. The FEES test was performed on each patient via endoscopic examination using Penetration and Aspiration (PEN-ASP) scale. PEN-ASP scale evaluates swallowing with liquid and viscous nutrition and this scale contains aspiration or penetration states and is an alternative to modified barium swallow evaluation of patients at risk for aspiration [6]. Table 1 shows the PEN-ASP scale using the FEES method.

After the ear examination, audiologic evaluation and ABR were performed on all patients. PTA and baseline ABR tests were used for evaluation of hearing.

2.1. Computerized posturography

Postural control was evaluated during 30 s standing on a force platform (400 × 400 × 75 mm) equipped with six strain-gauge sensors. The custom built force platform recorded torques and sheer forces with six degrees of freedom using force transducers with an accuracy better than 0.5 N. Data were sampled at 50 Hz by a computer equipped with a 12-bit AD converter. After information about the test procedure the subjects were instructed to stand erect but not at attention, with arms crossed over the chest and feet at an angle of about 30° open to the front and the heals approximately 3 cm apart. All tests were performed by the same examiner and thus received the same instructions prior to each test. Romberg test can be measured also in tandem stance and standing on foam, we used the above-described method since it is the most used method.

The research was conducted in compliance with the Ethic principles of the Declaration of Helsinki.

Table 1
8-Point aspiration-penetration scale.

Score	Description of Events
1	Material does not enter airway
2	Material enters airway, remains above vocal folds, and is ejected from airway
3	Material enters airway, remains above vocal folds, and is not ejected from airway
4	Material enters airway, contacts the vocal folds, and is ejected from airway
5	Material enters airway, contacts the vocal folds, and is not ejected from airway
6	Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway
7	Material enters the airway, passes below the vocal folds, and is not ejected from trachea despite effort
8	Material enters the airway, passes below the vocal folds, and no effort is made to eject

3. Results

There were 16 NPC patients from 15 different families with a median age of 6.5 years old (between 2–11 years of age). Five (31.25%) of the patients were boy and 11 (68.75%) were girls. Table 2 summarizes the diagnosis age of the patients.

Patients were evaluated in terms of swallowing functions and hearing situation. Table 3 summarizes the descriptions of the swallowing stage, penetration and aspiration scores for liquids and viscous food (PEN-ASP). Nine of sixteen patients (56.25%) had some degree of dysphagia (either penetration or aspiration). Two patients (12.5%) showed aspiration both liquid and viscous nutrition, non-oral feeding (gastrostomy) were suggested (PEN-ASP score were 7 and 7, respectively). Three patients (18.75%) showed aspiration primarily in liquids and two of them had penetration with viscous nutrition (PEN-ASP score were 5, 3, 3, respectively). Viscous nutrition intake was recommended to these patients. Three patients (18.75%) had just penetration without aspiration neither liquid nor viscous nutrition (PEN-ASP score was 2, 3, 3, respectively).

The data of PTA and ABR were collected. PTA findings were summarized at Table 3. Two of the patients had no reliable thresholds and two patients showed no answers to sound stimulus. Rest of the patients had normal audiogram. Table 4 shows the number of ears with normal and abnormal ABR findings. The most common ABR abnormalities were absent waves I and III (%75 absent I waves, %43.75 absent III waves). Three patients (18.75%) had normal wave 1, 4 patients (25%) had normal wave 3 and five patients (31.25%) had normal wave 5. Twelve of sixteen patients (%75) had an ABR abnormality in at least one ear, of these, four patients had normal hearing.

Twelve patients (75%) had postural imbalance. Patient's balance states were detected via posturography that evaluates objective impairment of the vestibular system. Peripheral postural imbalance was the most common finding. 11 patients (69%) had some

Table 2
Age of diagnosis onset.

Age of diagnosis					
		Frequency	Percent	Valid percent	Cumulative percent
Valid	<3 months	1	6.3	6.3	6.3
	3–24 months	2	12.5	12.5	18.8
	25–72 months	7	43.8	43.8	62.5
	73–120 months	5	31.3	31.3	93.8
	>121 months	1	6.3	6.3	100.0
	Total	16	100.0	100.0	