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Speech-Language and Swallowing Manifestations in Children with Mitochondrial Disorders: Report on Two Patients

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Abstract

There are only limited reports on the voice and swallowing manifestations in children with mitochondrial disorders. This report describes the same in two children with mitochondrial disorders. The first patient with mitochondrial encephalopathy ragged red fiber syndrome had baseline speech-language delay, cognitive dysfunction, and dysarthria. The second patient with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome had prominent swallowing dysfunction and dysarthria. Recognition of otolaryngological manifestations in children with mitochondrial disorders is important to enable better care of these patients.

Keywords: MERRF, MELAS, Speech-language, swallowing

1. Introduction

Mitochondrial dysfunction is associated with a wide range of clinical presentations. Some of these include mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS syndrome), and myoclonic epilepsy with ragged red fibers (MERRF syndrome). Mitochondrial disease in children usually presents a plethora of findings, including lethargy, hypotonia, failure to thrive, seizures, hearing loss, blindness, and movement disorders [1]. There are only anecdotal reports on the speech-language and swallowing manifestations in children with mitochondrial disorders. Reading et al.[2] assessed the prevalence and severity of voice and swallowing problems in a large cohort of patients with mitochondrial disease and illustrated that voice and swallowing difficulties are frequently seen in patients with single large-scale mtDNA deletions. However, these symptoms were relatively mild in severity. Difficulties with voice production were highest in patients with m.8344A > G mutation, whereas patients with m.3243A > G had the lowest incidence and mildest difficulties in voice and swallowing. Understanding the clinical characteristics in this population is essential for making a correct diagnosis, formulating intervention goals, and improving the patient's quality of life. In this study, we sought to analyze the speech-language and swallowing manifestations in two children with genetically proven mitochondrial disorders

2. Methods

Two patients with genetically proven mitochondrial disorders were included in the study. The clinical features were analyzed with special reference to speech, language, and swallowing manifestations.

2.1. Speech-Language and Swallowing evaluation

The Receptive Expressive Emergent Language Scales[3] was used for assessing the receptive and expressive language status of the patients. The Frenchay Dysarthria Assessment (FDA)[4] was administered to assess the patients' speech and nonspeech oro-motor abilities. The FDA assesses a range of behaviors related to speech, oromotor, and swallowing function and assesses (a) reflexes, (b) respiration, (c) lips (d) palate, (e) laryngeal (f) tongue, and (g) speech intelligibility. The rating scale (a-e) is on

the horizontal axis and seven subsections on the vertical axis. The audiological screening was done using a test battery consisting of puretone audiometry, tympanometry, otoacoustic emissions, reflectometry, and brainstem evoked response audiometry (BERA).

3. Patients

3.1.Patient 1

An eight-year-old boy born of consanguineous parentage with normal antenatal and birth history presented with regression in acquired milestones and seizures. Developmental milestones were delayed, and he had hyperactivity. Speech-language development was delayed, and he presented with drooling, oromotor weakness, and slurred speech since nine years of age.

On examination, he had short stature, facial dysmorphism, hypotonia, ataxia, myoclonic jerks, and intellectual developmental disorder. The evaluation showed elevated lactate levels. Magnetic resonance imaging revealed normal findings. Complete sequencing of the mitochondrial genome revealed m.8334 A>G mutation suggesting Mitochondrial encephalopathy ragged red fiber syndrome. Family history was positive, with his elder sibling (11yr/F) having MERRF syndrome. She had the same phenotype as the proband, which included progressive myoclonic epilepsy syndrome and histopathological evidence of ragged red fibers on muscle biopsy and m.8344A>G mutation on complete mitochondrial genome sequencing.

The Frenchay Dysarthria Assessment (FDA) revealed the patient had mild oromotor weakness with evident difficulty in lip seal and lip movements during speech. Elevation of the tongue within and outside the oral cavity was also affected, and he had slurred speech quality and occasionally had to repeat what he said (Table 1).

Table 1: FDA done at 9 years of age for patient (Pt.1) with MERRF syndrome

Abnormal ←----------→Normal											
Section	Subsection	FDA rating	e		d		c		b		a
		■									
Reflex	Cough	a									■
	Swallow	b							■	■	■
	Dribble/Drool	b							■	■	■
Respiration	At Rest	b							■	■	■
	At Speech	b							■	■	■
Lips	At Rest	a									■
	Spread	a									■
	Seal	c					■	■	■	■	■
	Alternate	b							■	■	■
	In Speech	b						■	■	■	■
Palate	Fluids	b							■	■	■
	Maintenance	a								■	■
	In Speech	b							■	■	■
Laryngeal	Time	b							■	■	■
	Pitch	b							■	■	■
	Volume	b							■	■	■
	In Speech	b							■	■	■
Tongue	At Rest	b							■	■	■
	Protrusion	b							■	■	■
	Elevation	c					■	■	■	■	■
	Lateral	b							■	■	■
	Alternate	b							■	■	■
	In Speech	b						■	■	■	■
Intelligibility	Words	b						■	■	■	■
	Sentences	b						■	■	■	■
	Conversation	b						■	■	■	■

In the Receptive Expressive Emergent Language Scales[3], the child's receptive and expressive language was 4 to 4.6 years. He attended a regular school, and his academic performance was poor. The child was diagnosed as having inadequate speech and language with an intellectual developmental disorder. Recommendations included oromotor exercises, classroom strategies for learning, speech and language stimulation. Puretone evaluation revealed the hearing sensitivity of the child to be within normal limits. Both cochlear and retrocochlear function were normal, as revealed by the presence of otoacoustic emission (OAE) and brainstem evoked responses (BERA).

3.2.Patient 2

This five-year-old girl born to healthy nonconsanguineous parentage presented with recurrent episodes of neurological dysfunction starting from the age of two years. She had a normal birth and perinatal history, and her developmental milestones were normal till three years of age. At three years, she presented with encephalopathy and recurrent left-sided focal seizures precipitated by febrile illness. While recovering from encephalopathy, she had left homonymous hemianopia and left hemiparesis. Magnetic resonance imaging at the encephalopathy time revealed bilateral symmetrical signal changes in basal ganglia along with a parieto-occipital lesion on the right side. Thereafter she continued to have recurrent episodes of neuroregression especially following febrile illnesses. She was diagnosed to have mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome based on the persistently elevated lactate levels and stroke-like lesion on MRI and a m.3243 A>G mutation on complete mitochondrial genome sequencing.

The speech-Language evaluation was done at the age of five years. Reportedly receptive and expressive language was age adequate prior to the onset of seizures. In the Receptive Expressive Emergent Language Scales, the child's receptive and expressive language was three years. In the Frenchay Dysarthria Assessment (FDA), the child had significant difficulty in all the subsections, particularly swallowing, reduced bilateral palatal reflexes, weak volitional cough, respiration at speech, lip seal, etc., pitch and loudness of voice. Tongue elevation was affected, and words were decipherable only occasionally at the conversational level (Table 2).

Table 2: FDA done at 5 years of age for patient (Pt.2) with MELAS syndrome

Abnormal ←----------→Normal											
Section	Subsection	FDA rating	e		d		c		b		a
		■									
Reflex	Cough	c				■	■	■	■	■	■
	Swallow	d			■	■	■	■	■	■	■
	Dribble/Drool	c				■	■	■	■	■	■
Respiration	At Rest	b						■	■	■	■
	At Speech	d			■	■	■	■	■	■	■
Lips	At Rest	a								■	■
	Spread	b							■	■	■
	Seal	d			■	■	■	■	■	■	■
	Alternate	d			■	■	■	■	■	■	■
	In Speech	c				■	■	■	■	■	■
Palate	Fluids	c					■	■	■	■	■
	Maintenance	b						■	■	■	■
	In Speech	b						■	■	■	■
Laryngeal	Time	d			■	■	■	■	■	■	■
	Pitch	d			■	■	■	■	■	■	■
	Volume	d			■	■	■	■	■	■	■
	In Speech	d			■	■	■	■	■	■	■
Tongue	At Rest	b						■	■	■	■
	Protrusion	c				■	■	■	■	■	■
	Elevation	d			■	■	■	■	■	■	■
	Lateral	c				■	■	■	■	■	■
	Alternate	c				■	■	■	■	■	■
	In Speech	c				■	■	■	■	■	■
Intelligibility	Words	b						■	■	■	■
	Sentences	c				■	■	■	■	■	■
	Conversation	c				■	■	■	■	■	■

The child had moderate oropharyngeal neurogenic dysphagia. There was the pooling of saliva with the inability to swallow the same towards evening and night. On examination, the child could not drink from a cup, and lip closure around the spoon was not adequate. The child took around 30 minutes for the intake of a quarter glass of water/semisolid. The child was otherwise playful and able to understand simple instructions but was lethargic. The child was not cooperative for audiological evaluation. OAE and BERA were not done as sedation was contraindicatory, and the child had noisy breathing. The informal hearing screening revealed hearing within normal limits.

Discussion

The primary manifestations of mitochondrial disease are usually seen in tissues with high metabolic demand, such as muscles, brains, and nerves. Both patients presented with speech-language manifestations characterized by baseline developmental and cognitive delay in Pt.1 with MERRF syndrome and regression of acquired milestones in Pt.2 with MELAS syndrome. Dysphagia was seen in patients with MELAS syndrome alone. The severity of speech-language and swallowing issues were more in a child with MELAS syndrome.

Speech-language and swallowing issues

Children with MELAS syndrome had reduced vocal loudness, monotonous voice, reduced respiratory support for speech, and moderate oropharyngeal neurogenic dysphagia and dysarthria. On the other hand, patients with MERRF syndrome did not have a significant voice and swallowing difficulties. However, the patient had oromotor weakness characterized by inadequate lip seal, inadequate tongue elevation, and mild dysarthria. The findings in both patients are in accordance with literature findings that report that mitochondrial diseases tend to be a multi-system disorder with a wide and varying range of clinical features[5,6].

Voice production requires adequate breath support and a steady supply of air from the lungs. Anecdotal evidence suggests that dysphonia and dysphagia are recognized features of mitochondrial disease and may present in various stages of the disease.[2,7-8] Bulbar dysfunction in mitochondrial disease is usually attributed to an upper motor problem or myopathy and may manifest immediately or slowly progressive and may not be obvious on clinical assessment. [8]Studies have reported that both voice and swallowing difficulties are common in patients with single large-scale mtDNA deletions; however, clinical manifestations may differ according to the extent of gene mutation.[2,9-10] Peripheral neuropathy, smooth and skeletal muscle weakness is speculated about the possible causes for voice and swallowing dysfunction in patients with m.3243A > G point mutation and other mtDNA point mutations[2].

As reported, speech intelligibility was good in patients with MELAS syndrome prior to the onset of seizures. Postseizures, the child had moderate dysarthria. Dysarthria in MELAS is not unlikely considering the multisystem involvement in the syndrome reported in the literature[11]. A gradual decline in pragmatic skills and naming, word-finding abilities, and episodic aphasia has been reported as a characteristic feature of MELAS syndrome[12]. Our patient with MELAS also hada regression in language skills post seizures, with mild improvement over a period of time.

Patients with MERRF syndrome had oromotor weakness and mild dysarthria. The likely pathophysiological mechanism for this is cerebellar ataxia[2]. The patient had baseline delay in cognitive-linguistic skills. Literature reports of the presence of muscle weakness, myopathy, neuropathy, sensorineural hearing loss, and cognitive and functional decline in MERRF syndrome at a very young age[13]. Dysphagia was absent in our patient. This is akin to the literature findings that report the infrequent association of dysphagia in MERRF syndrome[2].

Hearing loss is common in patients with mitochondrial disorders, affecting over half of all cases at some time in the course of the disease[14]. A3243G mutation is one of the most common mitochondrial DNA mutations associated with hearing loss[15]. Both the patients' audiological profile indicates that hearing loss may not be associated with all patients with MERRF and MELAS syndrome. This may be indicative of the differential involvement of various subsystems in mitochondrial disease. Eventhough hearing is normal at this stage for our patients, clinicians

should be aware of potential deterioration in hearing at a later stage of the disease. Physicians should also be aware that individuals with A3243G mutation are at high risk of developing severe cochlear hearing deficits[16]. Hence they should exercise caution while prescribing ototoxic medications, which may further compromise cochlear function and aggravate subclinical hearing loss. Carers and professionals should be aware of the potential fordeterioration in hearing and the need for prompt assessment, use of hearing conservation strategies, and appropriate aural rehabilitation methods.

It is noticeable that the rate of disease progression and multisystem involvement was more significant in MELAS compared to MERRF syndrome. However, single case reports and the progression of disease need to be monitored more closely, and further studies with a large cohort are needed to understand these symptoms' pathophysiology. The implications of this study include early intervention in patients with voice and swallowing problems to avoid complications such as malnutrition and aspiration pneumonia. Depending on the severity of the communication problem, the use of low and high-technology communication aids may be required in the middle and later stages of the disease. The clinical scenario may be further complicated by visual and motor impairment. It is also essential that the child and caretakers are trained in using these aids. Involvement of a multidisciplinary team of neurologists, medical geneticists, speech-language pathologists, and audiologists is essential for understanding the varied clinical profile in children with mitochondrial disease and starting appropriate multidisciplinary management based on the evolving symptom profile.

Conflict of interest: The authors have no conflicts of interest

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