Brain & Development 37 (2015) 101–106

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Correlation of augmented startle reflex with brainstem electrophysiological responses in Tay–Sachs disease

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Received 6 November 2013; received in revised form 16 January 2014; accepted 19 January 2014

Abstract

Aim: To clarify the evolution of an augmented startle reflex in Tay–Sachs disease and compare the temporal relationship between this reflex and brainstem evoked potentials. *Subjects and methods:* Clinical and electrophysiological data from 3 patients with Tay–Sachs disease were retrospectively collected. *Results:* The augmented startle reflex appeared between the age of 3 and 17 months and disappeared between the age of 4 and 6 years. Analysis of brainstem auditory evoked potentials revealed that poor segregation of peak I, but not peak III, coincided with the disappearance of the augmented startle reflex. A blink reflex with markedly high amplitude was observed in a patient with an augmented startle reflex. *Conclusion:* The correlation between the augmented startle reflex and the preservation of peak I but not peak III supports the theory that the superior olivary nucleus is dispensable for this reflex. The blink reflex with high amplitudes may represent augmented excitability of reticular formation at the pontine tegmentum in Tay–Sachs disease, where the pattern generators for the augmented startle and blink reflexes may functionally overlap.

Keywords: Startle reflex; Tay–Sachs disease; Brainstem electrophysiological responses; Brainstem auditory evoked potentials; Blink reflex

1. Introduction

Tay–Sachs disease or early infantile GM2 gangliosidosis is caused by a deficiency in β-hexosaminidase A. Tay–Sachs disease is characterized by psychomotor retardation and deterioration during infancy, hypotonia, exaggerated extension response to sound, and emergence of macrocephaly after the age of 2 years [1]. The augmented startle reflex is considered to be one of the earliest clinical signs of Tay–Sachs disease. This sign should prompt further examination leading to proper diagnosis [1]. However, the pathophysiology of this reflex has not been fully elucidated; therefore, the diagnosis of Tay–Sachs disease is still difficult. The accumulation of gangliosides in neurons is ubiquitous throughout the central nervous system. However, the intensity and distribution of neuronal degeneration is not uniform. Involvement of specific structures in the brainstem may result in the augmented startle reflex, although any differential neurophysiological and neuropathological involvement of specific brainstem structures in Tay–Sachs disease has not been determined till date.

The reflex pathway for the acoustic startle reflex involves the cochlear nuclear complex, a brainstem relay in the pontomedullary reticular formation, and a

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http://dx.doi.org/10.1016/j.braindev.2014.01.011

reticulospinal pathway through the medial longitudinal fasciculus that innervates the spinal and brainstem motoneurons [2,3]. In this study, we examined the function of the acoustic pathway and reticular formation in Tay–Sachs disease using electrophysiological responses. We identified auditory structures that are critical in inducing an augmented startle reflex. Furthermore, we found evidence for augmented excitability of pontine reticular formation in this disease. These outcomes facilitate our understanding of the physiological mechanisms responsible for the augmented startle reflex in Tay–Sachs disease. In addition, these outcomes may reflect differential severity in biochemical degenerative processes among different neuronal populations in Tay–Sachs disease.

2. Subjects and methods

We retrospectively examined 3 male patients (age at latest follow-up: 2 years 2 months, 6 years 7 months, and 4 years) who had visited our department between 1994 and 2013. These patients had been diagnosed with Tay–Sachs disease on the basis of β-hexosaminidase A deficiency noted in the white blood cells. Clinical data were collected from medical charts, including the age at the onset of neurological symptoms, age at the onset of the augmented startle reflex, and age at the disappearance of the reflex. Some clinical information regarding the third patient has been reported previously [4].

Brainstem auditory evoked potentials (BAEPs) were examined 2–4 times. The blink reflex (BR) was examined once in patients 1 and 2 during the follow-up periods of 4 months and 5 years, respectively. Patients were sedated with 30–50 mg/kg chloral hydrate and examined in the supine position in a dark and quiet room. BAEPs were evoked by applying click sounds to one side of the ear at a frequency of 10 Hz and white mask noise of 40 dB to the opposite ear through headphones. The intensity of the click sound ranged from 30 to 130 dB sound pressure levels (SPL) for threshold analyses. Recording electrodes were placed on each ear lobe. BRs were generated by electrically stimulating the unilateral supraorbital nerve at an intensity of 20–30 mA and duration of 0.2 ms. The surface electrodes were placed on the lateral orbicularis oculi muscles during the stimulation. Reference electrodes

Table 1
Clinical evolution of startle responses in Tay–Sachs disease.

	Age at onset	Emergence of startle responses	Age at diagnosis	Disappearance of startle responses	β-hexosaminidase activity
Patient 1	10m	1y2m	1y5m	–	4.5 nmol/mg[a]
Patient 2	6m	1y5m	1y6m	6y4m	Decreased[b]
Patient 3	6m	3m	1y6m	4y0m	Decreased[b]

[a] Normal control 317.2 nmol/mg; heterozygous intronic missence mutations of c.571-1, $G > G/T$ (previously identified in Tay–Sachs disease and published in Tanaka et al. (1993). Biochem Biophys Res Commun 1993;192:539) and c.1073 + 5, $G > G/C$ (novel mutation) were identified in this patient.
[b] Exact value of enzymatic activity not available; –: startle persisted until the age of last follow-up at 2y2m.

Table 2
Changes in brain auditory evoked potentials with age in Tay–Sachs disease.

			Latencies of evoked potentials			Threshold (dB)	Augmented acoustic startle reflex
			Peak I (msec)	Peak III (msec)	Peak V (msec)		
Patient 1	1y5m	L	2.11 (+2.9 SD)	4.76 (+3.9 SD)	6.54 (+3.9 SD)	30	+
		R	1.87 (+1.2 SD)	4.71 (+3.7 SD)	6.76 (+2.6 SD)	50	+
Patient 2	3y1m	L	1.52 (−1.2 SD)	4.62 (+3.2 SD)	6.17 (+0.5 SD)	130	+
		R	1.74 (+0.3 SD)	4.51 (+2.6 SD)	5.91 (−0.4 SD)	130	+
	4y10m	L	1.79 (+0.6 SD)	–	–		+
		R	1.93 (+1.6 SD)	4.96 (+5.0 SD)	6.80 (+2.8 SD)	130	+
	5y5m	L	3.10 (+16.7 SD)	–	–		+
		R	2.10 (+4.3 SD)	4.50 (+3.7 SD)	8.10 (+11.0 SD)	130	+
	6y10m	L	–	–	–		−
		R	–	–	–		−
Patient 3	2y	L	2.02 (+2.3 SD)	5.20 (+6.3 SD)	7.36 (+4.8 SD)	90	+
		R	1.96 (+1.9 SD)	5.17 (+6.1 SD)	7.33 (+4.7 SD)	90	+
	3y	L	2.02 (+2.3 SD)	–	–		+
		R	2.13 (+3.1 SD)	–	–		+
	4y	L	–	–	–		−
		R	–	–	–		−

–: Peaks not identified, −: augmented startles not present.