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Neurophysiological study in chronic GM2 gangliosidosis (hexosaminidase A and B deficiency), with motor neuron disease phenotype.

Mondelli M.*, Rossi A.*, Palmeri S.*, Rizzuto N., Federico A.***

* *Istituto di Scienze Neurologiche, Centro per lo studio delle Encefalo-Neuro-Miopatie Genetiche, Università di Siena*

** *Dipartimento di Neuropatologia, Università di Verona*

We report the electrophysiological investigation of two adult cases with GM 2 gangliosidosis with hexosaminidase A and B deficiency. Superficial peroneal biopsy was obtained from one patient. The electrophysiological alterations of the peripheral nervous system were fasciculations, signs of collateral reinnervation and loss of motor units, decrease in sensory potential amplitude and increase in distal motor latency. Increase in N9-N13 interpeak latency of the somatosensory evoked potentials and an increase I-V interpeak latency of the brain-stem auditory potentials were evident in both cases. Visual evoked potentials were normal. Nerve biopsy showed a severe loss of myelinated fibers, especially of those with the largest diameter, with no signs of segmental demyelination, or remyelination. A tentative interpretation of our findings is given.

Key-Words: GM2 gangliosidosis — sensory and motor peripheral neuropathy — somatosensory evoked potentials — brain-stem auditory evoked responses — visual evoked potentials

Introduction

GM2 gangliosidosis is an inherited metabolic disorder, characterized biochemically by accumulation of GM2 and GA2 gangliosides in neural and non neural tissues subsequent to a deficiency of hexosaminidase A (Tay-Sachs form) or A and B (Sandhoff variant) or an absence of the activator protein of the enzyme. This disorder is clinically very heterogeneous and there are cases with infantile, juvenile and adult onset [11, 21, 7]. Different phenotypic manifestations of the diseases are known: cases with amyotrophic lateral sclerosis-like [14, 9, 5] or with Kugelberg-Welander syndrome [20, 10, 13, 6, 24], spinocerebellar ataxia [25, 23, 32] or Ramsay-Hunt syndrome [12] or dystonia [18, 22] or more complex phenotypes [15, 1, 2, 19] have been reported. Federico et al. [8] reported two siblings, 49 and 44 years old, with hexosaminidas A and B deficiency and slowly progressive ataxia, fasciculations, peripheral neuropathy and autonomic nervous system involvement. Lysosomal enzyme analysis showed a severe deficiency of both hexosaminidase A and B. Here we report the neurophysiological study of these two subjects (including multimodal evoked potentials

and peripheral nerve study) and peroneal nerve biopsy findings.

Patients and methods

A case study of the two patients (49 and 44 years old respectively) has already been reported by Federico et al. [8]. Briefly the main clinical features of the 2 cases were slightly ataxic gait, progressive weakness, distal atrophy of the limbs, frequent cramps, fasciculations and paresthesia of the extremities associated with autonomic symptoms (sweating, loss of libido).

Both subjects underwent neurophysiological examination including multimodal evoked potentials and peripheral nerve study. Standard needle electromyography was performed in the brachial biceps, common extensor of the fingers, first dorsal interosseus of the hand, abductor pollicis brevis, tibialis anterior, vastus medialis and gastrocnemius muscles. Motor conduction velocities and distal motor latencies of the ulnar, median, tibial and peroneal nerves were determined through surface electrodes. Sensory conduction velocities and sensory potential amplitudes of the median, ulnar superficial peroneal and sural nerves were also evaluated transcutaneously. The details of the method are reported elsewhere [26].

Brain-stem evoked responses (BAER) were elicited by monaural stimulation with 10 Hz alternate clicks at 65 dB above sensation level with 45 dB white noise masking of the other ear. Click duration was 100 ms. Responses were recorded from the vertex (CZ) referenced to the ipsilateral mastoid and filtered (band pass 3-3000 Hz). Between two and four separate trials, each consisting of 1024 responses, they were recorded for each ear.

Visual evoked potentials (VEP) were recorded from 01, OZ and 02 with FZ as reference. A check-board stimulator of 30' of the visual field with 75% contrast was used. Each eye was stimulated separately. 256 responses were avereged and filtered (band pass 1-250 Hz). Sensory evoked potentials (SEP) were recorded from Erb point (EP), 7th cervical vertebra referred to FPZ and on the hand area of the somatosensory cortex contralateral to the stimulated arm referred to earlobe. A stimulus of 0.2 ms duration was applied to the median nerve at the wrist at 2 Hz and with an intensity sufficient to produce a moderate motor twitch. The standard filter setting was 3-3000 Hz. At least 2 consecutive recordings were performed, each consisting of 1024 responses. Motor evoked potentials were evaluated according to Rossini's methods [28] in one case (patient 2).

Histochemical and electromicroscopical investigations of superficial peroneal nerve biopsy, performed in patient 1, were done according to techniques previously reported [26].

Results

1) Electromyography

There were identical electromyographic anomalies in both subjects: frequent fasciculations and sporadic denervation activity in the form of fibrillations and positive sharp waves bilaterally in the muscles of the lower limbs and the intrinsic muscles of the hand. Motor unit potentials of the lower limbs showed an increase in duration (mean 95%, range 53-165%) and amplitude (mean 143%, range 62-213%). The upper arms presented slighter anomalies: the mean increase in duration was 67% (range 13-98%) and in amplitude 47% (20-90%). Maximum effort showed a greater loss of motor unit potentials in the lower limbs.

II) nerve conduction study

Table I summarizes the motor and sensory nerve conduction velocities, distal motor latencies and sensory amplitudes of the two subjects. The anomalies consisted in a marked reduction in amplitude of the sensory potentials of the upper and lower limbs associated with normal or slightly reduced sensory conduction values. Motor conduction velocities were normal with an increase in the distal motor latencies.

III) Evoked potentials

SEP of the upper limb showed a significant increase in the bilateral N9-N13 interpeak latencies with a normal N13-N20 central conduction time in both cases and a significant reduction in amplitude of all evoked components. The BAERs showed bilateral increase in I-V interpeak latency. VEP showed a normal P 100 component. Stimulation of the motor cortex was performed in patient 2 and showed normal bilateral central conduction (motor cortex-cervical medulla). In both patients the neurophysiological parameters revealed no progression of the disease after 5 years.

IV) Nerve biopsy

Light microscope examination of plastic-embedded semithin sections showed a severe loss of myelinated fibers, especially of those with the largest diameter (Figs. 1 and 2). There were no signs of demyelination, remyelination or Schwann hyperplasia.

Occasional clusters of axonal regeneration were found.

The perineurium was thickned; the endo- and perineural vessels showed thickened and hyalinized walls. At electron microscope examination a marked reduction in unmyalinated axons and collagen pockets was evident. No deposit of amyloid was found. In teased fiber preparations the internodes did not differ significantly from controls.

TABLE I. *Motor conduction velocity (MCV), distal motor latency (DML), sensory conduction velocity (SCV) and sensory potential amplitude (S ampl.) in chronic GM2 gangliosidosis.*

Nerves		Patient n. 1	Patient n. 2
Median	MCV	55.1 m/d	59.1 m/s
	DML	*4.8 ms/7 cm	*4.2 ms/7 cm
	SCV	*35.3 m/s	*42.7 m/s
	S. Ampl	*9.2 μV	*3.9 μV
Ulnar	MCV	64.8 m/s	60.1 m/s
	DML	*3.8 ms/7 cm	3.2 ms/7 cm
	SCV	*38.8 m/s	*43.6 m/s
	S. Ampl.	*3.1 μV	* 2.3 μV
Deep peroneal	MCV	41.8 m/s	48.1 m/S
	DML	4.9 ms/9 cm	*5.6 ms/9 cm
Superficial peroneal	SCV	42.5 m/s	*40.6 m/S
	S. Ampl	*3,8 μV	*2.2 μV
Tibial	MCV	42.0 m/s	48.8 m/s
	DML	4.9 ms/10 cm	*5.3 ms/10 cm
Sural	SCV	*39.8 m/s	*35.0 m/s
	S. Ampl.	*1.8 μV	*1.5 μV

The values marked with an asterisk are 2.5 SD below or above the mean of controls.

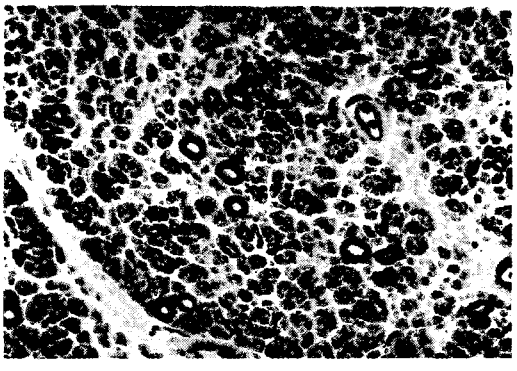
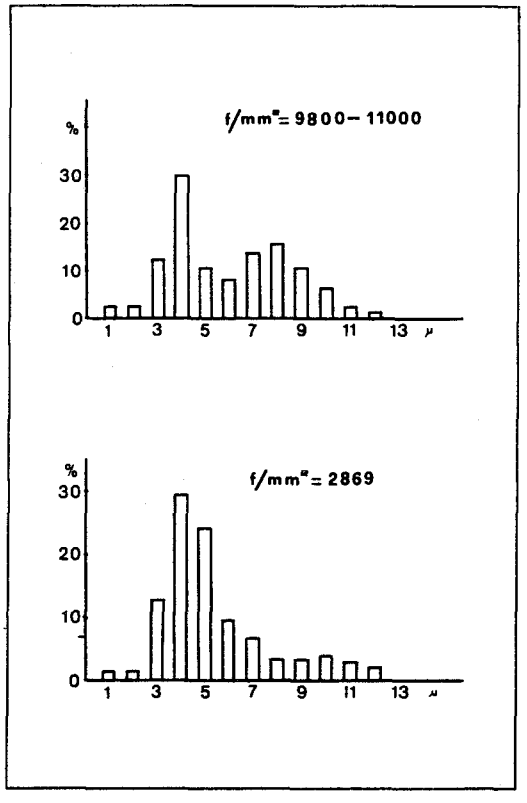


Fig. 1. *Semithin tranverse section of superficial peroneal nerve biopsy from patient 1 (X 400)*

Fig. 2. *On the right: histogram of myelinated fiber diameters from patient 1; on the left: control.*



Discussion

Electrophysiological findings in our patients suggest chronic axonal neuropathy. EMG examination showed signs of collateral reinnervation and loss of motor units in nearly all the tested muscles. These anomalies, together with normal motor conduction velocity and frequent fasciculations, indicate an axonal lesion of the motor fibers. The increase in distal motor latencies observed in both cases might be due to loss of the largest myelinated fibers, to atrophy of axons, thin regenerated axons or to secondary changes in the myelin

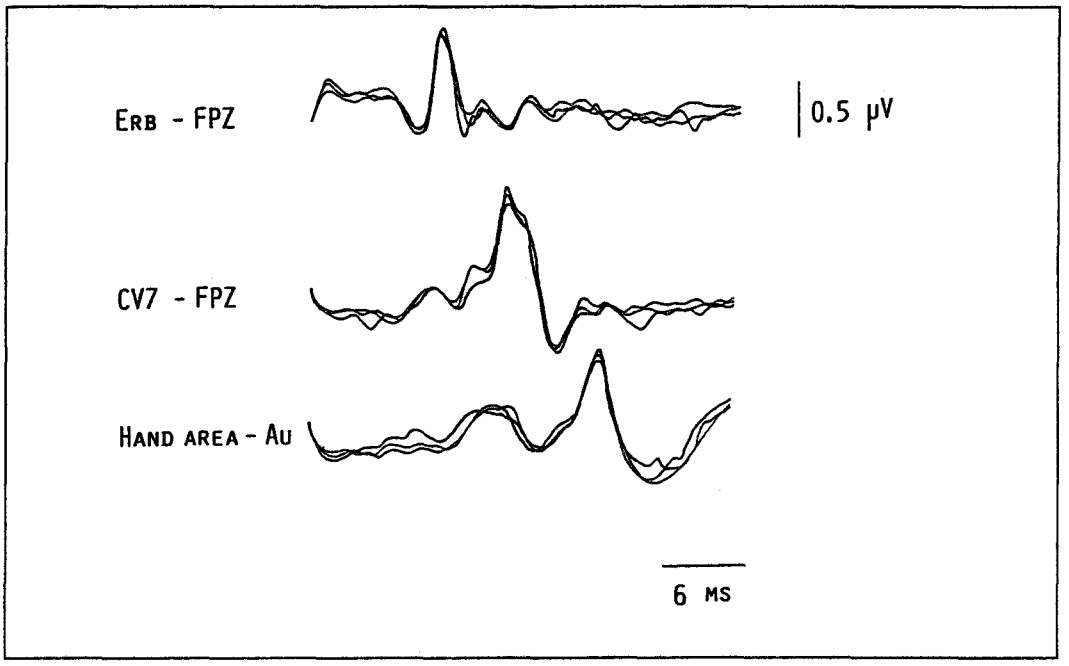
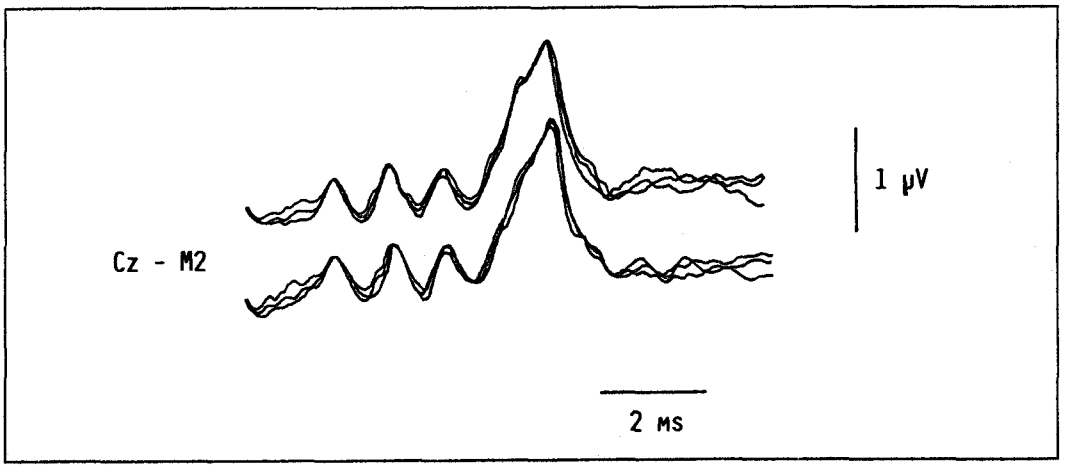


Fig. 3. *Short-latency somatosensory evoked potentials following right median nerve stimulation in patient 2. The EP and N 20 potentials are reduced in amplitude. N9-N13 interpeak is remarkably prolonged, but central conduction time (N13-N20) is normal.*

Fig. 4. *Brain-stem evoked responses from patient 2 (right ear). The interpeak I-V latency is significantly prolonged.*



sheaths which may occur in a motor neuronal degeneration [4]. The finding of motor neuron disease in our cases confirms what has previously been reported in case of GM2 gangliosidosis in adults, with hexosaminidase A deficiency [13, 1, 15, 24, 19, 10] and in the four cases reported to date of combined hexosaminidase A and B deficiency [23, 2], although it was usually the only clinical finding.

The motor lesions in our patients do not seem to involve the 1st motor neuron, as often occurs in cases of hexosaminidase A deficiency [25, 32, 19,

TABLE II. *Short-latency somatosensory evoked potentials and brain-stem auditory evoked responses in chronic GM2 gangliosidosis.*

Somatosensory evoked potentials							
	Patient n. 1			**Patient n. 2**			
	R		L	R		L	
	ms	μV		ms	μV	ms	uV
N 9	10.9*	0.57*	N.P.	9.36	0.91*	9.36	0.61*
N 11	13.1	0.63		11.1	0.87	11.2	0.73
N 13	16.6	1.46*		14.5	2.17	14.6	1.54*
N 20	22.8	1.33*		21.1	1.33*	20.5	1.78*
P 25	28.2			27.8		26.8	
N 9-N 11	2.2			1.74		1.84	
9-N 13	5.7*			5.14*		5.24*	
N 13-N 20	6.2			6.4		5.9	

Brain-stem auditory evoked responses				
	Patient n. 1		**Patient n. 2**	
	R AU	L AU	R AU	L AU
I	1.68 ms	1.60 ms	1.60 ms	1.80 ms
II	3.20	3.16	3.20	2.96
III	4.16	4.12	3.88	4.04
IV	NI	NI	5.16	5.56
V	6.32	6.24	6.16	6.20
I-III	2.48	2.52	2.28	2.24
III-V	2.16	2.12	2.28	2.16
I-V	4.64*	4.64*	4.56*	4.40*

The values marked with an asterisk are 2.5 SD below or above the mean of the controls matched for age and sex. NP = not performed. NI = not identifiable.
R AU = right ear; L AU = left ear.

1]. This is confirmed by the normal latency of conduction of the bilateral pyramidal pathways, which were studied in one subject.

In both cases the sensory potentials were significantly reduced in amplitude with normal or only slightly reduced conduction velocities, suggesting an axonal loss. These data have been confirmed by the histological findings showing a severe loss of myelinated fibers.

The changes in the peripheral fibers were associated in both cases with an increase in the N9-N13 interlatencies of the SEP but normal N9-N11 values, suggesting a conduction defect along the dorsal columns of the spinal cord (Fig. 3). This lesion does not seem to extend above the dorsal column nuclei, since the central N13-N20 conduction time was normal [16, 31]. The association of peripheral sensory fibers and dorsal column damage suggests that the lesion could primarily involve the sensory ganglion cells and then both their central and peripheral projections [30, 27].

Electrophysiological evidence of peripheral sensory alterations was reported by Mitzumoto et al. [19] in one case (hexosaminidase A deficiency) and by Maselli et al. [17] in two cases (hexosaminidase A and B deficiency). Besides, clinical sensory changes have been reported by Barbeau et al. [2] in one case and by Oonk et al. [23] in two cases with hexasaminidase A and B deficiency. The autopsy of one of these subjects, performed 8 years later, revealed a severe lesion of the posterior columns of the spinal cord [3].

In both our patients the BEAR showed an increase in I-V interpeak latency (Fig. 4). Satya-Murti et al. [29] suggested that this abnormality might reflect axon degeneration beginning from Corti's spinal ganglion and extending along the auditory nerve to its central connections. These data agree with our hypothesis of primary involvement of the ganglion cells.

In conclusion, the main electrophysiological abnormalities in the present subjects consist in a chronic axonal sensory and motor peripheral neuropathy associated with a lesion of the dorsal columns of the spinal cord.

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Sommario

Gli autori riportano lo studio neurofisiologico ed istologico di 2 soggetti adulti affetti da GM2 gangliosidosi da deficit di esosaminidasi A e B. Le alterazioni elettrofisiologiche del sistema nervoso periferico consistono in fascicolazioni, segni di reinnervazione collaterale e perdita di unità motorie, riduzione in ampiezza dei potenziali sensitivi e incremento delle latenze motorie distali. Sono presenti in ambedue i casi un incremento dell'interpicco N9-N13 dei potenziali evocati somatosensoriali e un aumento dell'interlatenza I-V di quelli uditivi. Normali sono i potenziali evocati visivi. La biopsia del nervo peroneo superficiale eseguita in un solo soggetto dimostra una severa perdita di fibre mieliniche soprattutto di più grosso calibro, senza segni di demielinizzazione segmentaria o rimielinizzazione. Viene infine proposta un'interpretazione di tutti i dati.

Address reprint requests to:
Prof. Antonio Federico
Istituto di Scienze Neurologiche
Centro per lo studio delle
Encefalo-Neuro-Miopatie Genetiche
Università di Siena
viale Bracci - 53100 Siena

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