Journal of the Neurological Sciences 277 (2009) 124–129

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Proton magnetic resonance spectroscopy and cognition in patients with spastin mutations

A.K. Erichsen [a,*], A. Server [b], N.I. Landrø [c], L. Sandvik [d], C.M.E. Tallaksen [a,e]

[a] Department of Neurology, Ullevål University Hospital, Oslo, Norway
[b] Department of Neuroradiology, Ullevål University Hospital, Oslo, Norway
[c] Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Norway
[d] Section of Biostatistics and Epidemiology, Ullevål University Hospital, Oslo, Norway
[e] Faculty of Medicine, University of Oslo, Norway

ARTICLE INFO

Article history:
Received 14 March 2008
Received in revised form 26 September 2008
Accepted 31 October 2008
Available online 12 December 2008

Keywords:
Hereditary spastic paraplegia
Neurodegenerative disorder
SPG4
MRS
Cognitive impairment

ABSTRACT

The hereditary spastic paraplegias (HSP) are heterogeneous neurodegenerative disorders characterized by progressive spasticity and weakness in the lower limbs. Axonal loss in the long corticospinal tracts has been shown. Supraspinal symptoms and findings in the most common dominant HSP type, SPG4, support the theory that the disease also causes cerebral neuronal damage in specific parts of the brain. To investigate whether SPG4-HSP is associated with neuronal biochemical changes detectable on MR spectroscopy (MRS), single-voxel proton MRS of the brain was performed in eight subjects from four families with genetically confirmed SPG4-type HSP and eight healthy age-matched controls. Volumes of interest (VOI) were located in the frontal white matter and motor cortex. N-acetyl-aspartate-to-creatine ratio (NAA/Cr), N-acetyl-aspartate-to-choline (NAA/Cho), cholin to creatin (Cho/Cr) and myo-inositol-to-creatine (Ins/Cr) ratios were calculated for both locations. Neuropsychological tests were performed to support the neuroradiological findings. The Cho/Cr ratio in motor cortex (MC) of SPG4-HSP subjects was significantly lower than in controls. This reduction of the Cho/Cr ratio in SPG4 subjects was significantly associated with age-related verbal learning- and memory (CVLT) reduction. Our findings support involvement of motor cortex in SPG4-HSP. Proton MRS could be a useful tool for detecting metabolite abnormalities in areas of brain that appear normal on MRI. Cho/Cr ratio may be a marker of neurodegenerative process in SPG4-HSP.

© 2008 Elsevier B.V. All rights reserved.

1. Introduction/background

The hereditary spastic paraplegias (HSP) are a group of heterogeneous neurodegenerative disorders characterized by progressive spasticity and weakness in the lower limbs for the pure forms. Additional symptoms, particularly cerebellar ataxia, neuropathy, mental retardation, cognitive impairment, visual dysfunction and epilepsy are described in complicated forms. About 40% of all dominant HSP are caused by mutations in the *SPAST* gene [1,2]. Different degrees of cognitive involvement have been reported in this genetic form [2–5] and executive functions connected with frontal and prefrontal areas appear to be the most vulnerable [2].

The *SPAST* gene product spastin is involved in axonal microtubuli dynamics [6–10], and non-functioning spastin leads to neuronal dysfunction and axonal degeneration of corticospinal tracts [8,11]. Spastin is ubiquitously expressed in human tissue and brain, with high expression in motor cortex and basal ganglia [12,13], indicating that in addition to causing axonal damage, SPG4-HSP may also affect supraspinal neuronal function. The few reports on the neuropathology of SPG4-HSP are of single cases. The main findings have been degenerative changes in the corticospinal tracts with loss of myelin and axons, most marked in thoracic and lumbar cord. Loss of pyramidal neurons, Betz cells, from the motor cortex has also been reported [4,14,15]. Neuroradiological findings include moderate spinal cord and cerebral atrophy, white matter lesions [16] and reduced cerebral blood flow in frontotemporal areas [17]. Based on this, we suspected that there could be specific "radiologically silent" changes in the motor cortex or/and the frontal white matter, and wondered if they could be visualized by more sensitive neuroradiological techniques.

Proton magnetic resonance spectroscopy (MRS) [18–21] has proved useful in investigating neurodegenerative diseases, but has so far only been performed in complicated forms of HSP [22,23]. Our hypothesis was that SPG4-HSP leads to cerebral changes reflecting a pathological process involving specific parts of the brain, among them motor cortex and frontal white matter. The main objective was to investigate whether the disease leads to neuronal biochemical changes detectable on MRS, and neuropsychological tests were

* Corresponding author. Department of Neurology, Ullevål University Hospital, 0407 Oslo, Norway. Tel.: +47 23016317/+47 92239010; fax: +47 23015949.
E-mail address: anhs@uus.no (A.K. Erichsen).

0022-510X/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2008.10.030

Table 1
Data on the study population

	Families (Id number)	Sex	Onset	Duration of disease	Disability	MRS	Neuropsyk.	SPG4-mutation
Patients	A (5,6,33)	m,f,m	2,1,3	3,1,1	3,2,1	+/+/−	+/+/+	Missense/exon13
	B (3,9)	m,m	1,4,	6,1	5, 0	+/+	+/+	Frameshift/exon 5
	C (1,2)	f,f	2,2	1,1	1,2	+/+	+/+	Frameshift/exon 5
	D (7,13)	f,m	2,4	4,1	5, 0	+/+	+/+	Missense/exon 7
	E (16,17,18,21,23,29)	m,f,m,m,f,m	3,2,1,4,3,3	1,3,3,2,2,1	3,3,3,3,2,0	−/−/−/−/−/−	+/+/+/+/+/+	Missense/exon 8
	F (24)	f	3	2	3	−	+	Missense/exon 7
	G (26,27)	f,f	2,2	1,2	2,3	− −	+/+	Missense/exon13
Controls	A (10,11,30,31,32)	m,f,f,f,f				+/+/−/−/−	+/+/+/+/+	
	B (4,8,34)	f,m,m				+/+/−	+/+/+	
	C (12)	f				−	+	
	D (14)	f				−	+	
	E (19,20,22,28)	f,f,f,m				−/−/−/−	+/+/+/+	
	F (25)	m				−	+	
	Non-fam.(35,36,37,38)	m,f,f,f				+/+/+/+	+/−/+/+	

Onset: (in years) 1=0–19, 2=20–39, 3=40–59, 4=>60, Duration of disease: (in years) 1=0–9, 2=10–19, 3=20–29, 4=30–39, 5=40–49, 6=>50.
Disability: 0=no handicap, 1=signs at examin., 2=mild, 3=moderate, limited walking, 4=severe, one stick, 5=two sticks,6=wheelchair; +=yes, −=no.

performed to support the neuroradiological findings. To our knowledge, this is the first study where MRS has been performed in patients with SPG4-HSP.

2. Materials and methods

2.1. Subjects

Eight affected subjects (carriers of an identified mutation in the *SPAST* gene) from four SPG4-confirmed families with a pure form of the disease seen at our department in the period from February 2006 to February 2007 were examined by MRS. Eight unaffected age-matched controls (four intrafamilial, four non-familial) were examined according to a similar protocol. Mean age in this MRS-group was 48.4 years (SD 7) for subjects and 46.2 years (SD 16) for controls. Cognitive examination was performed in all subjects and controls from the MRS-group with the exception of one non-familial control who went abroad. Twenty-one other individuals, three unaffected controls from the same four SPG4 families and 18 (ten affected subjects and eight age-matched unaffected controls) from other genetically confirmed SPG4 families were investigated in order to strengthen the neuropsychiatric findings. Mean age for all 36 that underwent cognitive examination was 49.4 years for subjects (SD 13) and 50.7 years (SD 10) for controls. There was no clinically significant comorbidity among subjects or controls, and particularly no thyroid and no hepatic disease. Mild chronic ischemic changes were described on MRI in two subjects and one control from the same family. Clinical details are given in Table 1.

2.2. MR spectroscopy

Single-voxel MRS of the brain was performed with a 1.5 T MRI system (Magnetom Sonata, Siemens, Germany) in all eight subjects and their matched eight controls. Fully relaxed short-echo time proton MR spectra were recorded using a point-resolved spectroscopy sequence with chemical shift-selective water suppression (TR/TE 1500/30 ms). Time of acquisition was 3.18 min. The volumes of interest (VOI) measured 2×2×2 cm and were located in areas were neuropathological and neuroradiological studies earlier have shown pathology [4,14,15,17]. There was no evident pathology detectable on MRI in the selected areas in any of the subjects or controls. One box was placed anteriorly in the left frontal normal-appearing white matter (FWM) laterally to the genus of the corpus callosum, the other box was placed anteriorly to the central sulcus in the precentral gyrus of the normal-appearing motor cortex (MC) (Fig. 1). Care was taken to avoid incorporating cerebrospinal fluid spaces and skull in VOI. Peaks of N-acetyl aspartate (NAA), creatine (Cr), choline-containing compounds (Cho) and myo-inositol (Ins) were analyzed, and NAA/Cr, NAA/Cho, Cho/Cr and Ins/Cr ratios were calculated for FWM and MC. An automated software package provided by the manufacturer (syngo MR 2004 A/V, Siemens Medical Systems) in a remote workstation was used for post-processing of spectroscopic data.

2.3. Cognitive examination

All 18 SPG4 subjects (nine men and nine women) and all 18 familial controls (six men and twelve women) were tested by a neurologist under standardized conditions. Fifteen validated tests covering seven aspects of cognitive function were chosen to investigate psychomotor speed, attention, memory, executive functions and general cognitive functions (Table 2). All subjects and controls consented to participate in the study, which was approved by the regional committee for medical research ethics. References for the tests are available on request.

2.4. Statistics

SPSS software version 15 was used for all statistical analyses. We used independent-samples *t*-test with a 5% significance level to

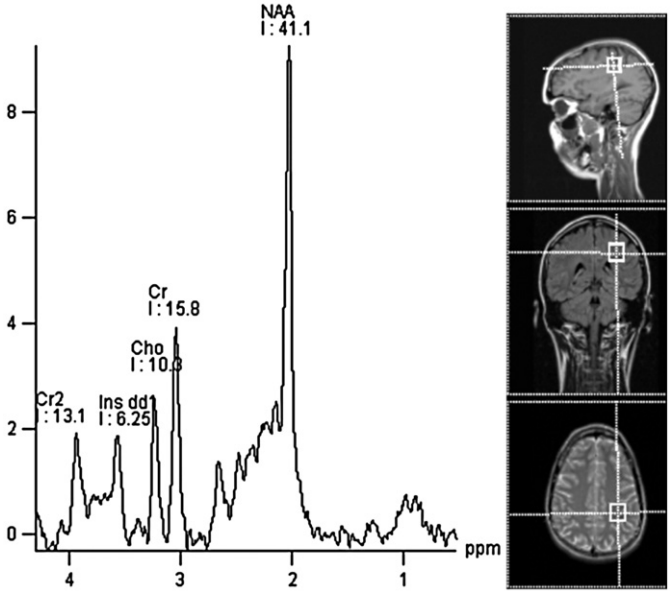

Fig. 1. T2-weigthed MRI and localized proton MRS (TE=30 ms) with illustrated volumes of interest in the left frontal white matter and the left precentral gyrus.

Download English Version:

https://daneshyari.com/en/article/8283515

Download Persian Version:

https://daneshyari.com/article/8283515

Daneshyari.com