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Diffuse metabolic changes in the brain of patients with familial amyloid polyneuropathy. A proton MRSI study

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Abstract

Objectives: To assess brain metabolic abnormalities in patients with familial amyloid polyneuropathy (FAP) due to the transthyretin (TTR) gene mutations.
Background: The TTR-FAP has variable phenotypic expression, which includes abnormalities of the central nervous system (CNS). Several conventional MRI studies have shown brain abnormalities, probably secondary to amyloid accumulation in leptomeningeal and subarachnoid vessels. However, TTR-related amyloid deposits do not seem to significantly affect the brain parenchyma and a prominent CNS impairment is considered to be rare in TTR amyloidosis.
Methods: We performed proton MR spectroscopic imaging (^{1}H-MRSI) in the central brain of four unrelated TTR-FAP patients with either minimal or no signs of neurological involvement and eight age- and sex-matched normal controls (NC). Metabolic changes were assessed in the entire volume of interest (VOI) and in the frontal, periventricular and posterior white matter (WM).
Results: Conventional MRI was normal in 2 patients and showed minimal WM lesions in the remaining 2 patients. ^{1}H-MRSI showed *N*-acetylaspartate to creatine ratio (NAA/Cr) decreases in the central brain VOI in all TTR-FAP patients ($p < 0.005$). These NAA/Cr decreases were homogeneous in all WM regions ($p < 0.05$ for all).
Conclusions: ^{1}H-MRSI findings suggest that diffuse metabolic changes, probably related to axonal damage, are present in brains of TTR-FAP patients even when they have no or minimal clinical and MRI signs of CNS involvement. The mechanism leading to sub-clinical metabolic brain changes needs to be identified.

Keywords: Familial amyloid polyneuropathy; Magnetic resonance spectroscopy; Brain; Axonal damage

1. Introduction

Familial amyloid polyneuropathy (FAP) is an autosomal dominant inherited form of amyloidosis, mostly associated with mutations of the transthyretin (TTR) gene [1]. Most of the 80 TTR point mutations are associated with peripheral neuropathy, autonomic abnormalities, cardiomyopathy, carpal tunnel syndrome, and vitreous opacities [1]. The variable phenotypic expression of the disease may include abnormalities of the central nervous system (CNS), reported in several patients as progressive motor deficits, seizures, headache and dementia [2–9]. However, a prominent CNS impairment is considered to be rare in TTR amyloidosis [10].

A number of recent studies have evaluated the relevance of brain involvement in TTR-FAP by means of conventional magnetic resonance (MR) imaging (MRI). In most cases, conventional MRI showed diffuse leptomeningeal enhancement after contrast administration [3] often accompanied by brain ischemia/haemorrhage [5,7,11], atrophy, obstructive hydrocephalous or even superficial siderosis [8,9]. Post-mortem studies have shown that the brain abnormalities

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observed on conventional MRI are probably all secondary to the accumulation of amyloid and inflammatory cells in leptomeningeal and subarachnoid vessels [5,6]. However, whereas leptomeningeal vessels and pia-arachnoid membranes appear as the principal sites of TTR-related amyloid deposition, this does not seem to significantly affect the brain parenchyma [12].

In the last decade, new MR techniques have been used in clinical neurology to complement conventional MRI. Subtle metabolic abnormalities, for example, can be evaluated with great sensitivity by means of proton MR spectroscopic imaging (^{1}H-MRSI), as demonstrated in a number of clinical studies of patients with various neurological disorders [13]. Thus, with the aim of assessing the relative sub-clinical brain involvement of TTR-related amyloidosis, we performed ^{1}H-MRSI examination in four unrelated patients with this disease who had either minimal or no symptoms related to CNS involvement.

2. Material and methods

2.1. Patient population

Four unrelated patients (two males and two females) with TTR-FAP were studied. Their demographic, clinical and genetic features are summarized in Table 1. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Siena and informed consent was obtained from all participating subjects before performing the MR scan.

2.2. ^{1}HMRSI examination

All patients were examined using the same MR protocol, which included combined proton MRI and MRSI examinations of the brain. Acquisitions of brain were obtained in a single session of 50 min for each examination using a Philips Gyroscan operating at 1.5 T (Philips Medical Systems, Best, The Netherlands). A sagittal survey image was used to identify the anterior commissure (AC) and posterior commissure (PC). A dual-echo, turbo spin-echo sequence (TR/TE1/TE2 = 2075/30/90 ms, 256 × 256 matrix, 1 signal average, 250 mm field of view, 50 contiguous 3 mm slices) yielding proton density (PD) weighted and T_2-weighted (T_2W) images was acquired in the transverse plane parallel to the line connecting the AC and PC. Fluid-attenuated inversion recovery (FLAIR) images (TR = 9000 ms; TE = 150 ms; 50 contiguous 3 mm slices) were acquired in the same direction. These MR images were used to select an intracranial volume of interest (VOI) for spectroscopy measuring approximately 100 mm anteroposterior × 20 mm craniocaudal × 90 mm left–right. This was centred on the corpus callosum to include mostly cerebral white matter (WM) of both hemispheres (Fig. 1). Two-dimensional spectroscopic images were obtained using a PRESS sequence for volume selection (TR = 2000 ms, TE = 272 ms, 250 × 250 mm field of view, 32 × 32 phase encoding steps, 1 signal average per step) as previously described [14]. Magnetic field homogeneity was optimized to a linewidth of about 5 Hz over the VOI using the proton signal from water. Water suppression was achieved by placing frequency-selective excitation pulses at the beginning of the MRSI sequence. Prior to the water-suppressed acquisition, another MRSI was acquired without water suppression (TR 850, TE 272, 250 mm field of view, and 16 × 16 phase-encoding steps) to allow for B_0 homogeneity correction. In addition to the four TTR-FAP patients, within a time period of 3 months, eight age- (mean = 51 years, range 41–60 years) and sex- (four females and four males) matched normal controls (NC) were scanned for comparison using the identical protocol used for the TTR-FAP patients.

2.3. ^{1}HMRSI data analysis

In both TTR-FAP patients and NC, post-processing of the raw ^{1}H-MRSI data was performed as previously described [14]. The nominal voxel size of raw ^{1}H-MRSI data was 8 × 8 × 20 mm, giving a resolution of about 12 × 12 × 20 mm after *k*-space filtering. In these cerebral volumes, resonance intensity values of *N*-acetyl groups (mainly *N*-acetylaspartate [NAA], a metabolite contained almost exclusively in neurons and neuronal processes in mature brains and therefore used as marker of axonal integrity and density [15,16]), choline (Cho, arising mainly from tetramethylamines, especially choline-containing compounds [13]) and creatine and phosphocreatine (Cr) were determined automatically from peak areas relative to a spline-corrected baseline. For the purpose of this study, we selected voxels located in the frontal WM (Fr-WM),

Table 1
Demographic, clinical and genetic features of TTR-FAP patients

Patient/sex/age(years)	Onset (years)	Clinical findings	Clinical signs of CNS involvement	TTR gene mutation
1/F/63	54	Dysphonia, dysphagia, sensorimotor neuropathy, autonomic dysfunction	Bilateral Babinski sign	Glu89Gln
2/M/46	42	Sensorimotor neuropathy, autonomic dysfunction with recurrent syncope	–	Thr49Ala
3/F/42	38	Sensorimotor neuropathy, autonomic dysfunction	Brisk tendon reflexes, absent abdominal reflexes	Thr49Ala
4/M/67	60	Sensorimotor neuropathy, autonomic dysfunction	–	Phe64Leu