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Mitochondrial neurogastrointestinal encephalomyopathy in three siblings

Clinical, genetic and neuroradiological features

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Abstract Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disorder in which a nuclear mutation of the thymidine phosphorylase (TP) gene causes mitochondrial genomic dysfunction. Patients suffer from gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoparesis, myopathy and polyneuropathy. Magnetic resonance imaging (MRI) shows leukoencephalopathy. We describe clinical, genetic and neuroradiological features of three brothers affected with MNGIE. Clinical examination, laboratory analyses, MRI and magnetic resonance spectroscopy (MRS) of the brain, and genetic analysis have been performed in all six members of the family with the three patients with MNGIE. Two of them are monozygous twins. They all suffered from gastrointestinal dysmotility, cachexia, ophthalmoplegia, muscular atrophies, and polyneuropathy. Urinary thymidine was elevated in the patients related to the severity of clinical disease, and urinary thymidine (normally not detectable) was also found in a heterozygous carrier. Brain MRI showed leukoencephalopathy in all patients; however, their cognitive functioning was normal. Brain MRS demonstrated reduced N-acetylaspartate and choline in severely affected areas. MRI of heterozygous carriers was normal. A new mutation (T92N) in the TP gene was identified. Urinary thymidine is for the first time reported to be detectable in a heterozygous carrier. MRS findings indicate loss of neurons, axons, and glial cells in patients with MNGIE, but not in heterozygous carriers.

Key words mitochondrial neurogastrointestinal encephalomyopathy MNGIE · thymidine phosphorylase · magnetic resonance spectroscopy

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Introduction

Mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE; Mendelian Inheritance in Man number 603041, Genome Database accession number 9835128) is a rare autosomal recessive disorder. To date, fewer than 100 verified [1–33] patients have been published. Its cause is a mutation in the gene for thymidine phosphorylase (TP) [34, 35] on chromosome 22q13.32-qter that leads to deletions in and a depletion of mitochondrial DNA. MNGIE is thus a mitochondriopathy caused by a nuclear genomic defect. Clinical hallmarks are disturbed gastrointestinal motility with intestinal pseudoobstruction, cachexia, ptosis, external ophthalmoplegia, and polyneuropathy. The brain MRI shows leukodystrophy, and mitochondrial dysfunction can be found in laboratory tests. Life expectancy is reduced and death occurs as a result of cachexia and intestinal complications. A specific therapy is not known however, one patient has recently successfully undergone stem cell transplantation [35a].

We describe a family with 4 children, in whom three brothers are affected. Two affected brothers and the healthy sister are triplets. Moreover, the two triplet brothers are monozygous twins. The sister and the parents are healthy and have normal weight and muscles. There is no known consanguinity of the parents.

Patients and Methods

Patient reports

Patient 1

The 22 year-old male index patient was referred after several episodes of non mechanical intestinal obstruction of unknown cause. Pregnancy, birth and psychomotor development were normal. At age 3, he suffered from intestinal obstruction, and during childhood and adolescence he had recurrent abdominal pain, frequent diarrhoea and occasional vomiting. At age 22, laparoscopy performed because of acute abdominal pain showed inflamed intestines and peritonitis without obstruction. A few months later, nonmechanical ileus required resection of a part of the small intestine. Numerous diverticula were found, and the muscularis propria near the large blood vessels was lacking. Histology showed foamy cells in the intestinal wall. Gastroscopy was normal. Steatosis hepatis was noted on abdominal ultrasonography. The patient worked full time in an office after an apprenticeship in business administration. At age 22, limitations in physical activity started. At age 23, a bilateral ptosis developed. He complained of flatulence and erectile dysfunction. The clinical exam showed scoliosis and marked muscular atrophy, mainly of the shoulder and pelvic girdle. Muscle strength was mildly reduced. Body weight was 50 kg and height was 180 cm (BMI 15.4 kg/m^2). Loud borborygmi were heard. Extraocular movements were severely limited horizontally and upwards. Pupillary reaction to convergence was delayed and limited. Sensation in the hands was normal except for mildly impaired stereognosis. Perception of vibration, temperature and touch was clearly reduced in both feet. Tendon reflexes were absent except for symmetrically very weak biceps reflexes and knee jerks. Romberg's test was positive and tandem gait was not possible without correction steps.

Nerve conduction studies: Conduction velocity of the right peroneal nerve was slowed in the popliteal fossa segment (25 m/s); the compound muscle potential (CMP)of the anterior tibial muscle was normal, but no CMP of the extensor digitorum brevis muscle could be elicited. Motor nerve conduction of the right ulnar nerve was slowed (above elbow 33 m/s, elbow-wrist 31 m/s) and motor latency to the abductor digiti V muscle was prolonged (4.6 ms). The amplitudes of the CMP were normal. No conduction blocks were noted. Sensory-antidromic potentials of the right ulnar nerve, sensory-orthodromic potentials of the left sural nerve, and F-waves were absent. Qualitative and quantitative electromyographies of the right tibialis anterior and the right interosseus dorsalis I muscle were normal. In summary, electrophysiology confirmed axonal and demyelinating sensorimotor neuropathy.

MRI of the brain showed large confluent hyperintense signal changes on T2-weighted and FLAIR images indicating leukoencephalopathy, predominantely in the periventricular areas and the pons.

The electrocardiogram showed sinus rhythm and incomplete right bundle branch block.

Genetic testing of the mitochondrial genome showed no deletions of mtDNA in lymphocytes and skeletal muscle. Depletion of mtDNA was not assessed. Lactate (3.1 mmol/l, normal 0.63–2.44) and serum liver enzymes were elevated (aspartate aminotransferase 50 U/l, normal 10–41; alanine aminotransferase 86 U/l, normal 5–41; gamma-glutamyltransferase 103 U/l, normal 11–64). Extensive laboratory blood testing showed no additional abnormalities. Cerebrospinal fluid analysis showed one mononuclear cell and elevated values for lactate (4.6 mmol/l, normal 1.2–2.1) and protein (2.71 g/l, normal < 0.44). The clinical and laboratory findings suggested MNGIE. The diagnosis was confirmed by a thymidine phosphorylase (TP) assay that did not show any activity in leucocytes.

At age 24 non mechanical ileus recurred and additional parts of the small bowel were resected. Both sensory and motor signs of neuropathy progressed after initiation of total parenteral nutrition. Thorough laboratory testing did not identify a nutritive cause, but fluctuating signs suggested an inflammatory cause. However, intravenous immunoglobulins (a total of 300 g given in six cycles) did not improve neuropathic signs, as found by others [36].

Patient 2

The older twin brother was seen at age 20. He was asymptomatic and his previous medical history unremarkable. He indicated occasional moderate borborygmi when he had an empty stomach. His weight had been constant at 52 kg, his height was 174 cm (BMI 17.2 kg/m^2). He was working full time at an office and experienced no limitations in gymnastics or basketball. Muscles of the shoulders and pelvic girdle were slightly atrophic and strength mildly reduced. Tendon reflexes of the arms were absent, but Achilles tendon reflexes were normal. Sensation of both hands was normal. Pallaesthesia of both feet was slightly impaired. There was exotropia. Corrected visual acuity was 0.6 on the left and 0.9 on the right. Upward gaze was limited and there was a fluctuating ptosis on the left. Cardiac auscultation suggested mitral valve prolapse.

Patient 3

The younger twin brother weighed only 1750 g at birth. He was examined at age 20 years when his weight was 49 kg and the height 174 cm (BMI 16.2 kg/m^2). He occasionally suffered from diarrhoea and vomiting. For some months flatulence, and for years

borborygmi had been present. At age 13, surgery for strabismus was performed. He was working full time as a gardener and did not engage in any sports. There were cachexia and marked atrophies of the back, shoulder and thigh muscles and moderate proximal weakness of the arms and mild weakness of the legs. Corrected vision was 0.6 on the right and 0.8 on the left, and there was exotropia. Upward gaze was limited to less than 20° and pupillary reaction to convergence was delayed and impaired. Tendon reflexes of the arms were absent and weak in the legs. Tactile sensation was normal. Perception of vibration of the legs was slightly diminished. The patient was unsteady when standing with closed eyes. Blood pressure was 105/65 mm Hg. There were a systolic heart murmur and loud borborygmi.

Genetic testing

Genomic DNA was extracted from circulating blood white cells using a Qiagen kit (Qiagen, Valencia, California, USA) according to manufacturer's instruction and amplified by PCR using the enzyme Taq Plus from Stratagene (La Jolla, California, USA). Primers were designed to amplify the open reading frame and exon-intron boundaries into 4 fragments, which encompassed exons 2–3; 4; 5–6; and 7–10, respectively. The amplified products were purified using the QIAquick PCR purification kit protocol and cycle sequenced using the Big Dye Terminator sequencing kit (Perkin-Elmer, Foster City, California, USA) on an ABI 3100 genetic analyser (Applied Biosystems, Foster City, California, USA). The study was approved by the local ethics committee. Written informed consent was obtained from all participants.

Magnetic resonance imaging and spectroscopy

MRI was performed on a 1.5T Sonata (Siemens, Erlangen, Germany) in the four siblings and their parents. Axial T1 weighted spin echo (T1w)-, T2 (T2w)-, and proton density weighted (PDw) fast spin echo, diffusion weighted images and coronal FLAIR images were obtained. In additon, magnetic resonance spectroscopy (MRS) was performed. In the affected brothers sagittal T2w scans and axial T1w scans after intravenous (i.v.) administration of 0.1 mmol/kg body weight gadolinium-DTPA (Magnevist, Schering, Berlin, Germany) were also obtained.

MRS was performed before contrast administration using point resolved spectroscopy (PRESS) technique (TR 1500 msec, TE 135 msec, 192 averages). Two voxels, each sized $1.5 \times 1.5 \times 1.5$ cm^3, were placed in the white matter of the right hemisphere, one in the centrum semiovale and the other in the paratrigonal region. For each region a non-water suppressed signal spectrum was also recorded to perform eddy current correction. Spectroscopic data were quantified using a prior knowledge based fitting algorithm (TDFDFIT) [37]. Peak areas of water, N-acetylaspartate (NAA), choline (Cho), creatine/phosphocreatine (Cr) and lactate (Lac) were assessed and metabolite ratios of NAA/Cr and Cho/Cr calculated. For group comparison mean values of the three affected brothers were compared to that of their healthy relatives (Table 1).

Follow-up MRI scans of the index patient were compared with a MRI examination performed 11 months earlier on a 1.5 T Signa scanner (GE Medical system, Milwaukee, USA) including a coronal FLAIR sequence, axial PDw, T2w and T1w images before and after i.v. Gd-DTPA.

Urine analysis

Thymidine was assessed by liquid chromatography in spontaneous urine samples of all family members with a technique adapted from Simmonds et al. [38]. Urine samples were frozen at −20 °C after collection and later analysed by chromatography. Thymidine levels were assessed in relation to creatinine in the urine samples.

Results

Genetic testing

The three affected members of the family were homozygous for a new mutation in exon 3 at g.2182C > A (genomic). This caused a ACC to AAC codon change and a T92N aminoacid substitution. The healthy parents and sister were heterozygous C/A for the same mutation. 100 chromosomes of controls did not show this mutation (Fig. 1).

MRI and spectroscopy findings

The MR scans of the three affected brothers showed widespread and nearly symmetrical signal changes, hyperintense on T2w and hypointense on T1w images (Fig. 2). In the index patient, signal changes were

Table 1 Magnetic resonance spectroscopy

	Paratrigonal white matter						Centrum semiovale					
	Water	Cho	Cr	NAA	NAA/Cr	Cho/Cr	Water	Cho	Cr	NAA	NAA/Cr	Cho/Cr
Patient 1	6.98	16.75	11.17	21.36	1.91	1.5	5.72	13.84	10.07	23.51	2.34	1.38
Patient 2	4.84	18.63	16.36	26.72	1.63	1.14	3.45	17.49	16.22	33.67	2.08	1.08
Patient 3	4.17	14.97	11.43	23.37	2.08	1.31	3.05	16.29	12.08	29.55	2.45	1.35
Mean	5.33	16.79	12.98	23.93	1.87	1.32	4.07	15.87	12.79	28.91	2.29	1.27
SD	1.20	1.83	2.93	2.68	0.23	0.18	1.44	1.86	3.14	5.11	0.19	0.17
Sister	3.4	17.75	12.95	29.82	2.30	1.37	2.56	15.33	13.62	30.90	2.27	1.13
Mother	3.00	26.49	17.31	33.15	1.92	1.53	2.75	21.64	15.35	35.75	2.33	1.41
Father	2.88	25.40	18.55	32.72	1.76	1.37	2.68	21.52	13.29	31.41	2.36	1.38
Mean	3.09	23.31	16.27	31.89	1.99	1.42	2.66	19.50	14.09	32.69	2.32	1.31
SD	0.27	4.76	2.94	1.81	0.28	0.09	0.10	3.61	1.11	2.67	0.05	0.15

Peak intensities are given as institutional units. NAA = N-acetylaspartate, Cr = creatine and phosphocreatine, Cho = choline and choline containing compounds

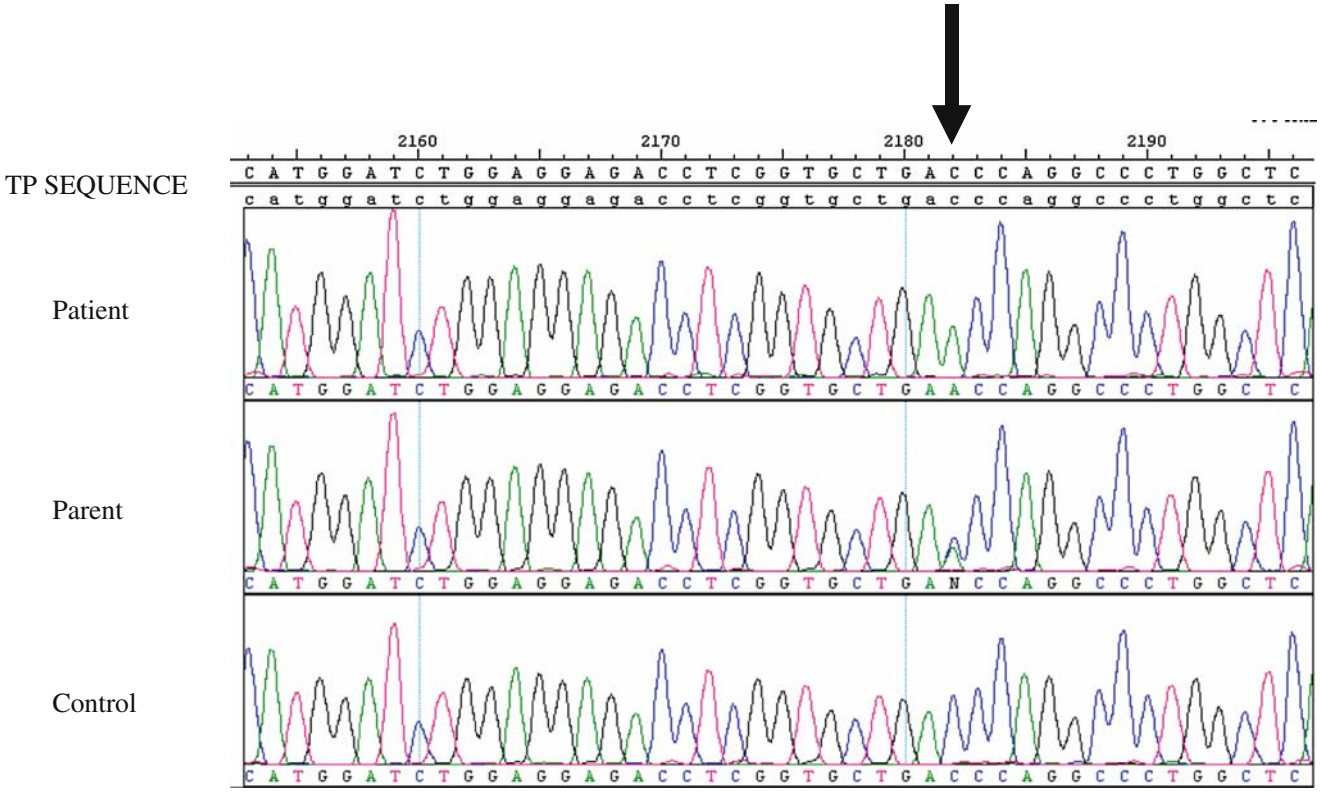

Fig. 1 Electropherograms of the DNA sequence analysis of the thymidine phosphorylase (TP) exon 3 showing the C2182A mutation (arrow) in the homozygotic (patient) and heterozygotic state (father) and a healthy control

pronounced in the periventricular white matter and also involved the corpus callosum, pons, internal capsule, thalamus and putamen. Arcuate fibres and the cerebellum were spared. There was no brain atrophy, no blood-brain-barrier breakdown, and no acute diffusion disturbance. The follow-up MRI in the index patient did not show progression of the signal changes after 11 months. MRI of the two less affected brothers showed patchy periventricular hyperintensities on T2w images, but less pronounced than in the index patient. The white matter of the temporal lobes, brain stem, arcuate fibres, corpus callosum, and internal capsules was spared. There was no atrophy and no enhancement after gadolinium administration. Diffusion weighed images were normal. Cerebral MRI of the parents and the sister were normal.

MRS (Fig. 3) did not show any lactate-peak. Areas of T2w hyperintense white matter showed increased water content that was highest in the index patient (Table 1). In the paratrigonal region group comparison of the three affected brothers with their three healthy relatives showed a reduction of NAA (mean patients 23.9 ± 2.68 vs. mean controls 31.9 ± 1.81), Cho (mean patients 16.8 ± 1.83 vs. mean controls 23.3 ± 4.76), and Cr (mean patients 13.0 ± 2.93 vs. mean controls 16.3 ± 2.94). Water signal was clearly increased in the patients (mean patients 5.33 ± 1.12 vs. mean controls 3.09 + 0.27). Owing to the few measurements, no statistical analyses have been performed.

Metabolite changes in the centrum semiovale were less pronounced. Metabolites were most reduced in the index patient, who also showed extensive T2w signal changes in this location as compared with his brothers, in whom these areas were much less affected on conventional MRI. No differences for the calculated ratios (NAA/Cr and Cho/Cr) were observed in the centrum semiovale.

Urine analysis

Thymidine was not detectable in the mother and the healthy sister. Thymidine was 86.3 µmol/mmol creatinine in the index patient and 25.5 and 20.9 µmol/mmol creatinine in his two affected brothers. Thy-

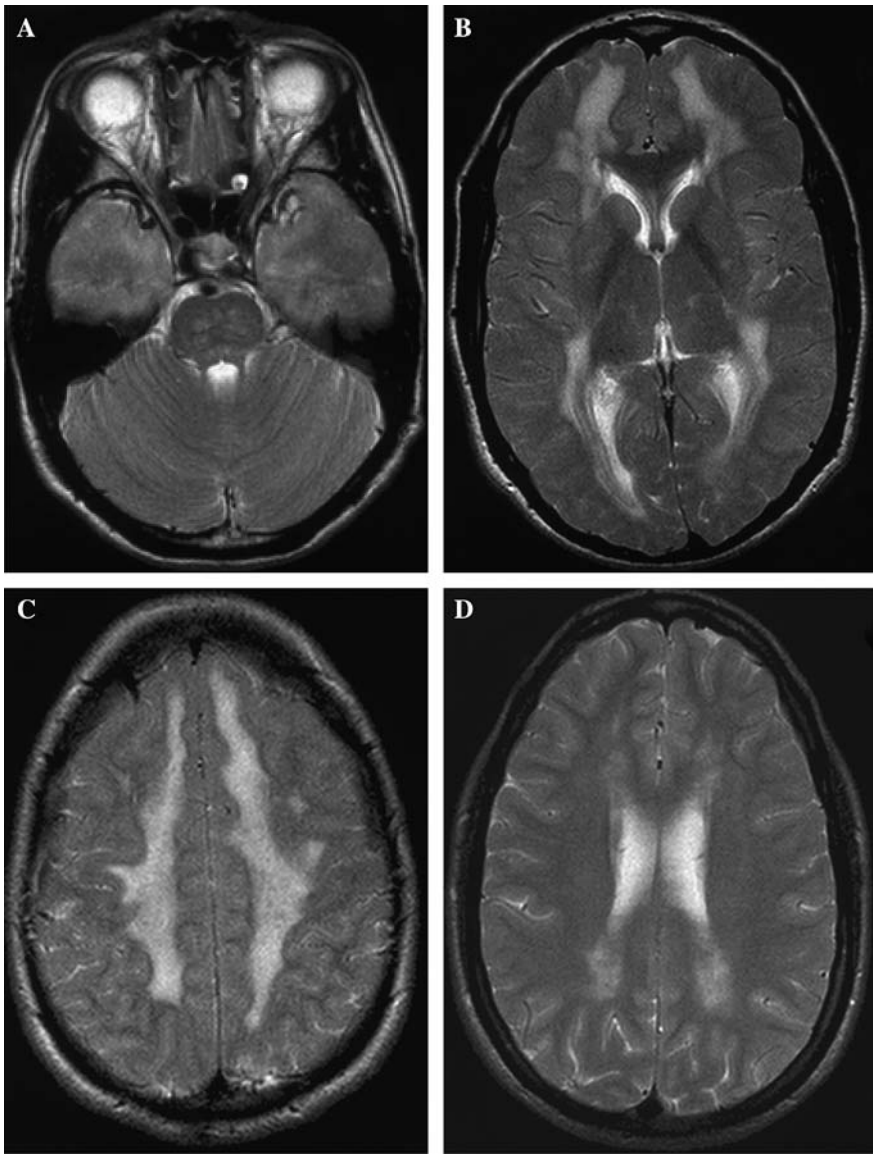

Fig. 2 Axial T2 weighted images of the index patient at the level of **A**) pons, **B**) basal ganglia and **C**) centrum semiovale showing focal hyperintensities in the brain stem and confluent hyperintensities of the cerebral white matter sparing U-fibres. Much less pronounced white matter changes are present in the paratrigonal region in the younger brother (**D**). There is no atrophy in either patient

midine was 1.97 μmol/mmol creatinine in the father. Creatinine was normal in all samples.

Discussion

The first clinical description of MNGIE dates back to 1976 [1] as "congenital oculosceletal myopathy with abnormal muscle and liver mitochondria". In 1994, Hirano et al. [14] coined the name of autosomal recessive MNGIE for this mitochondrial disorder with a nuclear genetic defect. Other previously used acronyms and names for syndromes that probably correspond to MNGIE were POLIP [5] (polyneuropathy, ophthalmoplegia, leukoencephalopathy, and intestinal pseudo-obstruction), OGMID [12] (oculogastrointestinal muscular dystrophy), and MEPOP [39] (mitochondrial encephalomyopathy with sensorimotor polyneuropathy, ophthalmoplegia, and pseudo-obstruction). MNGIE is caused by a mutation in the nuclear gene for TP, gene locus 22q13.32-qter [34, 35]. We describe a new mutation in exon 3 at g.2182C > A with a ACC to AAC codon change that leads to a T92N amino acid substitution. Synonyms for TP are platelet-derived endothelial cell growth factor (PDECGF), endothelial cell growth factor 1 (ECGF1), and gliostatin. Many reports have indicated a role of PDECGF in angiogenesis, cell trophism and tumour growth, and inhibition of glial cell proliferation and neurotrophic actions. However,

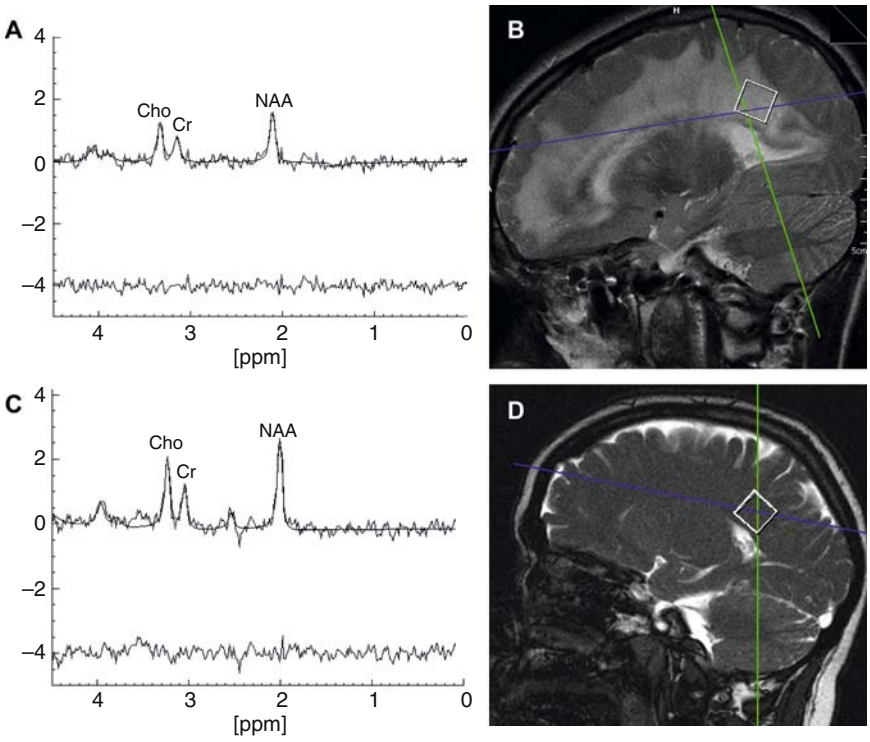

Fig. 3 Point resolved spectroscopy (PRESS) (repetition time 1500 ms, echo time 135 ms) localized in the paratrigonal white matter of the index patient (**A** and **B**) and his healthy mother (**C** and **D**). T2-weighted MRI (**B** and **D**) and corresponding MR spectra (**A** and **C**). MR spectra (**A** and **C**) and fit are shown on the upper trace, the residuum after fit is shown on the lower trace. No lactate was found at 1.33 ppm. Levels of all metabolites were diminished in the index patient. NAA = N-acetylaspartate, Cr = creatine and phosphocreatine, Cho = choline and choline containing compounds

loss of function in MNGIE is not associated with altered angiogenesis or neoplasms. TP catalyses the reversible phosphorolysis of thymidine and phosphate to thymine and 2-deoxy-D-ribose-1-phosphate. Mutations lead to loss of function of TP in patients [35] and to reduced activity in heterozygote carriers [40], resulting in more than 60-fold increased plasma levels of thymidine in MNGIE [40] and also in an increase of deoxyuridine [41]. This leads to a mitochondrial nucleotide pool imbalance with elevated levels of deoxythymidine triphosphate [42], which, in turn, may cause dysfunction of mitochondrial DNA replication, repair, or both [43] resulting in alterations of mitochondrial DNA [44].

Ten years after Hirano et al. [14] had outlined clinical diagnostic criteria for MNGIE, biochemical assays for its diagnosis were created [45] (plasma levels of thymidine and deoxyuracil, and TP activity in buffy coat). Elevated urinary thymidine [40] and deoxyuridine, thymine, and uracil [46] have been reported recently in MNGIE and may be used for diagnostic purposes. Our results indicate that urinary thymidine may be not only a diagnostic measure, but also correlate with the severity of the clinical disease. Normally, thymidine is not detected in urine. Therefore, detectable urinary thymidine in the patients' father is likely to relate to his heterozygous state. Heterozygous relatives have reduced TP activity, but undetectable thymidine serum levels (< 0.05 μM). Detectable urinary thymidine in a heterozygous person has, yet to our knowledge not been described.

The clinical manifestations of the few known MNGIE patients have been reviewed in detail [8, 20, 43]. Frequent findings in MNGIE (> 70% of all cases in the series of Hirano et al. [43]) that we observed in one or more of our patients were: cachexia, intestinal pseudo-obstruction, borborygmi, abdominal pain, diarrhoea, early satiety, abdominal cramps, nausea, vomiting, ptosis, ophthalmoparesis, polyneuropathy, and areflexia. Further findings in our index patient that have been described in MNGIE previously are: diverticulosis of the small intestine, hepatopathy, lactic acidosis, elevated CSF protein, and abnormal nerve conduction tests. Cognitive impairment is typically absent. Leukoencephalopathy was present in all of our patients. Incomplete right bundle branch block – as found in our index patient – has previously been noted [43]. Except for three recently reported patients with late-onset MNGIE [32], all previously reported patients had died by the age of 58 years, and the average life expectancy of deceased patients was 37 years. The delay until diagnosis is long, in the average over 10 years, as in our index patient. A causal therapy does not exist, and prokinetic agents are not efficient. Total parenteral nutrition may delay cachexia. One reported patient responded well to celiac plexus neurolysis [8]. Stem cell transplantation has been successful in one patient so for and may be used in further patients [35a].

Brain spectroscopy has according to our knowledge not been detailed in typical cases of MNGIE. The higher age of the heterozygous control group may have influenced metabolite concentrations. NAA decreases with age in grey matter which corresponds to volume loss of the cortex. However, there was no brain atrophy on MRI, and NAA and Cho in white matter are not age dependent [47, 48]. The changes observed in our patients are therefore probably disease related. Areas of T2w hyperintensities correlated with increased water content. Despite the lack of volume loss of brain tissue in conventional MRI, MRS revealed a reduction of NAA and choline in the severely affected areas. This might indicate loss of neurons, axons, as well as glial cells [49, 50]. The lack of a reduction in the less affected white matter indicates that MRS is not able to detect metabolite changes earlier than conventional MRI detects white matter abnormalities indicative of leukoencephalopathy. Because all three main metabolites (NAA, Cr and Cho) are reduced, ratios (NAA/Cr and Cho/Cr) do not differ between patients and controls. The reduction was strongest in the index patient suggesting a correlation of the clinical course, the extent of leukoencephalopathy and NAA and choline decrease. Therefore, these values may be useful in follow up examinations. The lack of a lactate peak corresponds to the slowly progressive course of the disease and suggests intact aerobic glycolysis.

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