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Significance of MRI-Confirmed Atrophy of the Cranial Spinal Cord in Friedreich's Ataxia

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Summary. The severity of Friedreich's ataxia was graded in ten patients by clinical examination and in five by use of posturography. These data were compared with neuroradiology findings. CT-confirmed infratentorial atrophy occured only in advanced cases of Friedreich's ataxia; the correlation with the clinical score was poor. On mid-sagittal MRI planes the diameters of fourth ventricle, brain stem at the level of the inferior olive and spinal cord at the levels of the foramen magnum and C3 were measured. Patients with Friedreich's ataxia had significant MRI-confirmed atrophy of the cranial spinal cord as compared with a normal, age-matched control group. This was also observed in patients with Friedreich's ataxia in the early stages. A reliable correlation between atrophy of the cranial spinal cord and the clinical score, however, could again not be found. MRI exploration of the cranial spinal cord may be recommended as an additional diagnostic marker in Friedreich's ataxia.

Key words: Magnetic resonance imaging – Friedreich's ataxia – Spinal cord atrophy – MRI evaluation of the brain stem

Introduction

The main neuropathological finding in Friedreich's ataxia (FA) is atrophy of the medulla oblongata and the spinal cord with degeneration of dorsal root ganglion cells, dorsal columns, pyramidal and direct spinocerebellar tracts [7, 11, 12]. Additional degenerative changes have been demonstrated in the anterior horns, pons and in later stages in the cerebellar cortex, dentate nucleus and superior cerebellar peduncle; minor degeneration has been observed throughout the motor cortex, basal ganglia and in sensory cranial and peripheral nerves. Most of the necropsy reports relate to patients who had had FA for a considerable number of years; the pathology of early cases is not well documented. Computed tomography (CT) and magnetic resonance imaging (MRI) now allow us to localize and measure structural lesions and thereby to evaluate atrophic processes quantitatively during the earlier stages of the disease [1, 3–5, 16]. Patients with incipient FA have no or only minimal abnormalities on cranial CT; in particular, they do not exhibit a definite cerebellar atrophy [3]. For technical reasons, the brain stem and upper spinal cord cannot easily be measured by CT. We therefore performed MRI in these patients and focused our interest on the medulla oblongata and the cranial spinal cord. The aim of our study was to investigate whether structural lesions can be detected in living patients with FA and whether MRI can support the diagnosis of FA.

Patients and Methods

Ten patients with FA were included in this study. The diagnosis was based on one in-patient examination and on at least three follow-up assessments [14]. All patients met the clinical diagnostic criteria, including autosomal recessive inheritance; onset before age 10 years; progressive, unremitting ataxia of gait; deep tendon areflexia; progressive muscle weakness in lower extremities; dysarthria; decreased vibration and position sense in the lower limbs; and electrophysiological evidence of an axonal sensory neuropathy [6, 8]. As a parameter for the severity of the disease we used a modification of Kurtzke's

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Table 1. Neurological scale for evaluating disability [9, 10]

0 = Normal neurological examination
1 = No dysfunction but minimal signs at neurological examination, e.g. diminished sense of vibration, impaired straight line test, slight dysmetria
2 = Minimal dysfunction, e.g. instability in darkness, awkwardness, slight disturbance of speech or writing, slight visuomotor disturbance
3 = Slight dysfunction: ataxia and incoordination, broad-based gait, nystagmus, slight dysarthria, positive Romberg's test, might use a cane
4 = Moderate dysfunction: moderate ataxia and severe gait disturbance, moderate dysarthria and dysmetria
5 = Severe dysfunction: severe ataxia and dysmetria that prohibits writing; can still dress and eat without assistance; severe dysarthria, nystagmus, wheel-chair outdoors; paresis
6 = Very severe dysfunction: restricted to wheel-chair but can still use the arms; speech incomprehensible, difficulties in reading, paresis, sphincter disturbance
7 = Cannot be left alone: anarthria, severe pareses, cannot move from wheel-chair to bed
8 = Death due to spino-cerebellar ataxia

disability scale for multiple sclerosis [9, 10, 13] (Table 1). In all patients the same neurologist performed a routine neurological examination and scored the clinical signs on this scale from 0 to 8 prior to the neuroradiological evaluation.

For quantification of postural ataxia, posturography was additionally performed in five patients who were still able to stand long enough for a posturographic recording. Posturography was performed while subjects stood on a force measuring platform. Strain gauges at the four corners of the platform measured the displacements of the center of foot pressure (CFP) in anterior-posterior and lateral directions with eyes open or closed. The anterior-posterior sway was computed from the differences between the front and back strain gauges. The lateral sway was computed in an analogous manner from the two right and left force transducers respectively. Measurements were taken for a total of 25 s with a sampling interval of 25 ms. Sway path travelled by the CFP on the platform and sway area covered by the sway path within 20 s were calculated with the subject's eyes open and then closed. A sway direction histogram of the CFP was also computed. For this purpose the full circle of possible sway directions was divided into eight intervals of 45° each. The single vectors of displacements of the CFP within each sampling interval were sorted according to the directions and summed. Sway path and sway direction histograms were plotted on a digital X-Y plotter [2, 15] (Fig. 1).

CT was performed with a high-resolution Somatom DRH Scanner (512 × 512 matrix, slice thickness 0.4 cm). Evaluation of the CT scans was done independently by two experienced examiners; in cases of non-accordance a third neuroradiologist was consulted. Scores were then averaged. The neuroradiologists were unaware of the clinical status of the patients. The gradation was made according to the following criteria. A normal CT scan was designated as grade 0. Enlargement of at least one cerebellar or vermal sulcus was graded as 1. Increased vermal and/or cerebellar sulci with moderate enlargement of the cerebellar pontine or superior cerebellar cisterns were graded as 2. If more than three sulci were visible over the cerebellar hemisphere and enlargement of the cisterns was seen, grade 3 was allocated (Fig. 2).

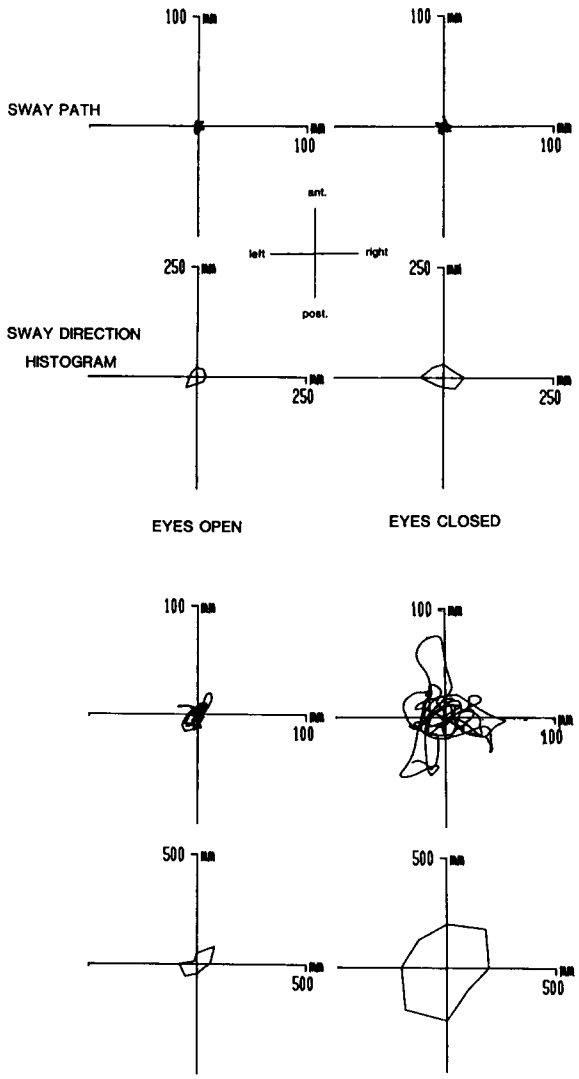

Fig. 1. Sway path and sway area from a normal subject (*upper panels*) and a patient with Friedreich's ataxia (*lower panels*). Note different scalings in the records

MRI was performed using a 1.5 T Magnetom (Siemens, Erlangen, FRG) and a special head coil with a diameter of 30 cm. Using the spin-echo technique, T1-weighted images (TR = 400 ms, TE = 30 ms) in axial, coronal and sagittal planes were obtained (Figs. 3, 4). To exclude possible intracranial lesions, such as demyelinization and focal oedema, T2-weighted multislice spin echo technique (TR = 2000 ms, TE = 60 and 120 ms) was also performed. On mid-sagittal planes the diameters of the fourth ventricle, of the medulla oblongata and of the spinal cord at the levels of the foramen magnum and C3 were measured (Fig. 3). The values were compared with a group of 15 healthy, age-matched subjects. For statistical analysis Student's *t* test was used; to measure for correlation we used point biserial correlation coefficients (r_{pbis}).

Results

The clinical, posturographic and neuroradiological features of the ten patients with FA are shown in

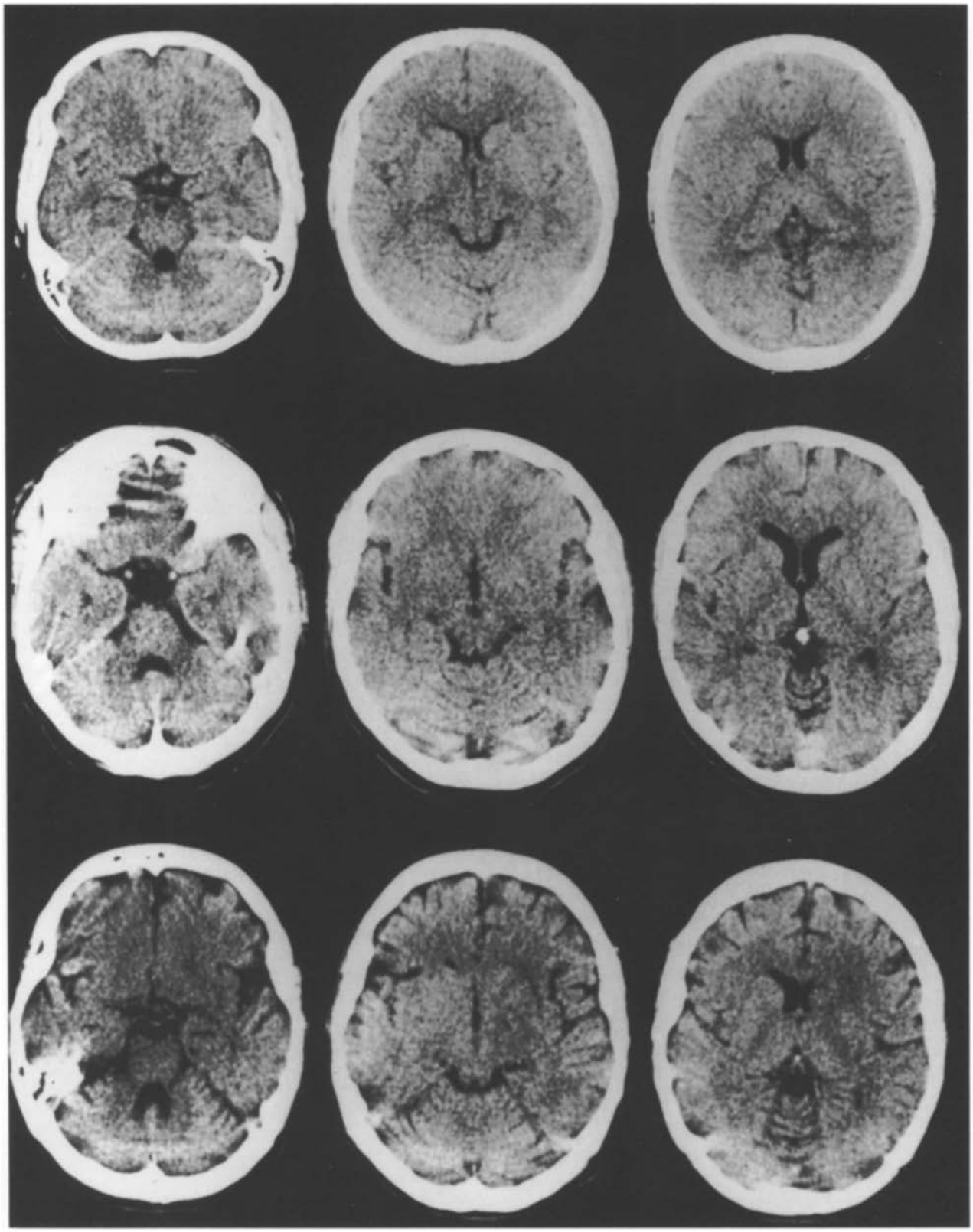

Fig. 2. CT scans of three patients with Friedreich's ataxia. Normal CT scans (*upper panels*); mild (grade 1) cerebellar atrophy (*middle*); cerebellar atrophy (grade 3) together with global cerebral atrophy (*lower panels*)

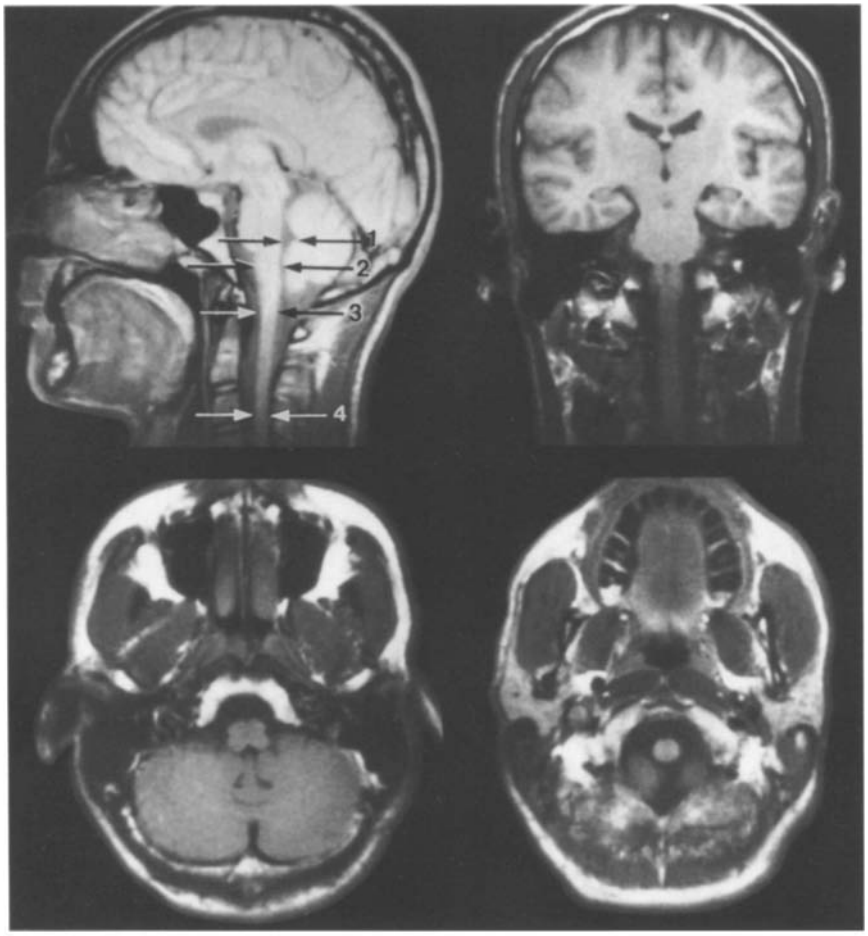

Fig. 3. T1-weighted (TR = 400 ms, TE = 20 ms) spin-echo images of a normal subject, demonstrating the normal appearance of the brain stem and the cranial spinal cord in mid-sagittal, coronal and axial planes. The levels of measured sagittal diameters on mid-sagittal planes are marked

Table 2. Clinical and neuroradiological findings in ten patients with Friedreich's ataxia. SA ec = Sway area with eyes closed

No.	Age of onset (years)	Age at examination (years)	Clinical score	Post-urography SA ec (mm^2/s)	Infratentorial atrophy (CT)	MRI diameters (mm)			
						Fourth ventricle	Inferior olive	Foramen magnum	C3
1	8	21	2	179.6	1	4.8	4.8	2.4	1.8
2	9	19	3	673.3	0	3.0	4.2	3.0	1.9
3	9	21	3	822.9	0	3.0	5.4	3.0	1.7
4	8	26	4	542.8	0	3.6	5.4	2.1	2.1
5	9	18	4	1709.6	0	3.0	4.8	2.4	2.0
6	8	27	6	–	0	5.4	4.2	2.4	1.7
7	9	20	6	–	1	4.2	4.8	2.4	1.8
8	7	30	6	–	3	6.0	3.6	2.4	1.8
9	5	20	6	–	2	2.8	4.8	2.7	1.8
10	6	24	7	–	1	4.8	5.4	2.4	1.8
AM (MRI)	7.8	22.6	4.7	785.6	0.8	4.06	4.74	2.52	1.83
S				568.76		1.15	0.6	0.30	0.13
Norm (MRI)						3.35	4.65	3.24	2.46
S						1.06	0.77	0.5	0.25
($n = 15$)						n.s.	n.s.	$P < 0.001$	$P < 0.001$
Norm (Post.)				15.7					
S				7.27					
(n = 10)									

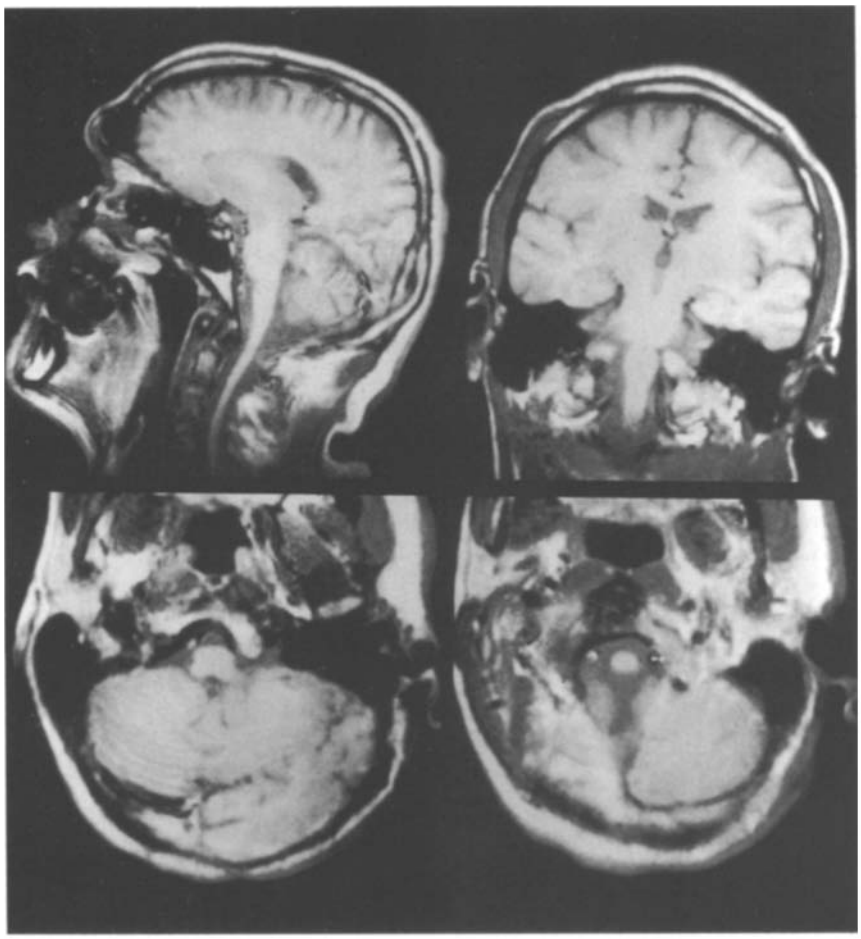

Fig. 4. In contrast to Fig. 3, T1-weighted images of a patient with Friedreich's ataxia demonstrating atrophy of the upper parts of the spinal cord

Table 2. The disability (see disability scale; Table 1) varied from mild to severe. Five patients were confined to a wheelchair. They suffered from severe dysarthria and paresis of the legs; their arms were ataxic but could still be used, except in case 10. In the other five patients there was slight or moderate dysfunction. Ataxia of stance was quantified by posturography (Fig. 1, Table 2) in five patients. The relative increase in sway area after eye closure was much higher in patients than in normals, indicating intact visual stabilization [2]. There was only a moderate correlation between the clinical score and the posturographic quantification of ataxia of stance ($r_{pbis} = 0.55$). Only patients with advanced FA showed mild cerebellar atrophy on CT scans (Fig. 2); in case 8 with cerebellar atrophy grade 3 there was also global cerebral atrophy. In accordance with a previous study [3] the correlation between the clinical score and the degree of CT-confirmed cerebellar atrophy was poor ($r_{pbis} = 0.40$). The correlation between the posturography and the degree of CT-confirmed cerebellar atrophy was very poor as well ($r_{pbis} = 0.27$). CT-confirmed cerebellar atrophy was not very well reflected in the MRI-confirmed width of the fourth ventricle ($r_{pbis} = 0.41$), and the correlation between the clinical score and the sagittal diameter of the fourth ventricle, as assessed by MRI (Figs. 3, 4), was poor also ($r_{pbis} = 0.37$).

The MRI evaluation showed no significant difference between normals and FA patients regarding the width of the fourth ventricle and the mid-sagittal diameter of the medulla oblongata. The diameter of the spinal cord at the levels of the foramen magnun and C3 ($P < 0.001$ respectively) was significantly reduced in patients with FA compared with a control group of 15 age-matched healthy subjects (Table 2; Figs. 3, 4). However, correlation between clinical score and atrophy of the cranial spinal cord (r_{pbis} for the level of foramen magnum = 0.24; for C3 = 0.18) could again not be assessed.

Discussion

In FA, the clinical findings in its terminal state correlate closely with patho-anatomical and histological lesions found at necropsy [7, 11, 12]. The degree of

morphological lesions in the cerebellum, brain stem and spinal cord in earlier cases, however, is poorly reflected in CT-confirmed atrophy (Fig. 2) [3]. This may be a consequence of the low CT resolution in the area of the brain stem and the spinal cord, which is of particular interest in FA. MRI now offers the possibility of a more precise and non-invasive evaluation of brain stem structures and spinal cord [4, 5, 16]. Our investigation indicates that significant atrophy of the cranial spinal cord can be demonstrated by this method, even in cases with moderately advanced FA (Table 2, Fig. 4). Using a special head coil (diameter 30 cm), exploration of spinal segments caudal to C3 poses methodological poblems because of the shoulders. An additional problem rises from scoliosis in FA, which complicates the focusing of the plane exactly on the middle of the spinal cord in lower segments. We therefore restricted the exploration of the spinal cord to the mid-sagittal plane at the levels of the foramen magnum and C3. Minor degrees of angulation, which result in spinal cord scan slices passing slightly obliquely out of plane, cannot be excluded. However, the marked differences in the diameters of the cranial spinal cord between FA patients and normal controls (Table 2) speak for a reliable reflection of neuropathological changes. The atrophy of the cranial spinal cord, as demonstrated by MRI, is in accordance with the maximum of structural lesions, as assessed by necropsy studies [7, 11, 12]. The lack of correlation of clinical score and posturography (Fig. 1) with atrophy of the cranial spinal cord (Table 2) may be explained by the fact that neurological deficits, in addition to visibly structural lesions, may result from synaptic disarrangement and biochemical disturbances. But the significant atrophy of the cranial spinal cord also in earlier stages of FA (Table 2) shows that neurological deficits seem to presuppose a visibly reduced volume on MRI (Fig. 4). Our results show that visible atrophy of the cranial spinal cord on MRI planes may be an early diagnostic marker in FA. These MRI findings are of importance, particularly in patients with incipient FA, where the diagnosis (8) can be difficult by clinical and electrophysiological examination.

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