Multiple Sclerosis in Childhood: Report of 15 Cases

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We report the preliminary results of an ongoing study of multiple sclerosis (MS) in childhood. The investigations include an analysis of the clinical picture and course. Multiple sclerosis in early childhood may present atypically, with a symptomatology suggesting diffuse encephalomyelitis, meningeal reaction, brain oedema, seizures, impaired consciousness and in some cases take a lethal course. Imaging studies including MRI and MR-spectroscopy, CSF-analysis, electrophysiology (VEP, BAEP, SER), and virological and immunological investigations are performed. So far 15 children have been studied. Their age at the onset of the disease ranged from 3 to 15 years. Abnormal CSF-findings with pleocytosis and oligoclonal IgG bands were present in 11 and 10 out of 15 patients respectively. MRI revealed numerous white matter lesions in the brain stem and cerebral hemispheres. VEP, BAEP and SER's were abnormal in most children. Proton magnetic resonance spectra from plaques exhibited a 50–80% decrease in N-acetyl aspartate, which is a potential marker of vital neuronal tissue, a decrease of the creatine pool and an increase of choline-containing compounds. Lactate was not increased. Our observations of MS in early childhood cast doubt on some of the previous notions concerning a latency period of several years between the exposure to a still unknown agent and the manifestation of MS. In view of atypical features in the initial phase, it would seem desirable to record cases of encephalomyelitis of undetermined origin as potential cases of MS and to register the further course for verification or exclusion. ***Key words: Multiple sclerosis in childhood, clinical findings, MRI, MR-spectroscopy.***

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The occurrence of multiple sclerosis (MS) in childhood is now well established [1-16]. Until 1980 one hundred thirty six patients with MS below the age of 18 years have been described. The disease started in 129 of those below the age of 18 years, in 20 of them before puberty. Since then the number of reported cases has steadily increased.

Over the ten year period from 1980 to 1990 a total of 235 cases has been published, 176 with onset before the age of 18, in 43 patients before puberty (Table 1). There are now a number of well documented cases where the first symptoms of MS occurred before the age of 5 years [17-22] (Table 2).

Although the diagnosis of MS is in principle a clinical one, paraclinical investigations including MR-imaging, studies of evoked responses (visual evoked potentials (VEP), brain stem acoustic evoked potentials (BAEP), somatosensory evoked responses (SER)) and of immunoglobulins of CSF have proved extremely valuable in the identification and monitoring of demyelinating disorders in childhood. Particularly the non-invasive magnetic resonance imaging (MRI) shows a high sensibility in detecting white-matter abnormalities in children with MS [23-26].

We report the results of an ongoing prospective study of childhood MS.

MATERIALS AND METHODS

Fifteen patients, 11 female and 4 male children have been studied so far. Their age at onset of the disease ranged from 3 to 15 years (Fig 1). They were further divided into a prepubertal and an adolescent group (Table 1). Cranial

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Table 1 *Multiple sclerosis in childhood*

	Age at onset	
	Prepuberty	*Adolescence*
Studies bef. 1980 (n = 136)	20/129+	109/129++
Studies since 1980 (n = 235)	43/176+	133/176++
Göttingen-study (n = 15)	12/15+	3/15+++

+: < 12 years, ++: < 18 years, +++: < 15 years.

Table 2 *Multiple sclerosis in childhood: Patients with earliest onset of MS*

		Earliest age of onset (yrs)
1990	Bauer, Hanefeld, Christen [22]	3
1984	Bejar, Ziegler [18]	2
1988	Boutin et al [14]	2
1981	Brandt et al [17]	2
1985	Bye et al [6]	3
1987	Golden, Woody [23]	3
1987	Haas et al [24]	4 1/2
1982	Hauser et al [5]	3
1984	Ishihara et al [36]	5
1989	Kesselring et al [26]	2
1989	Maeda et al [20]	1 1/2
1988	Mattyus, Veres [16]	4
1990	Miller et al [11]	2
1969	Schneider et al [46]	4
1987	Shaw, Alvord [21]	2 1/4
1988	Vergani et al [47]	2

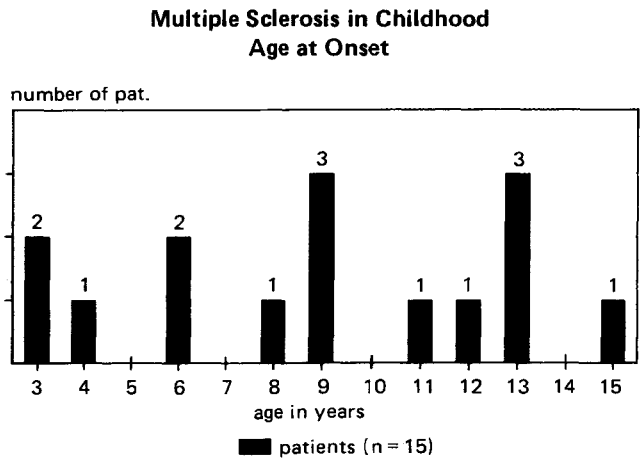

Fig 1 *Multiple sclerosis in childhood: 15 patients of Göttingen-study.*

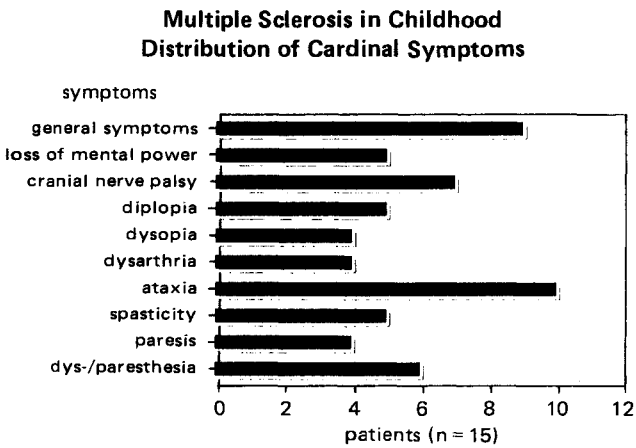

Fig 2 *Multiple sclerosis in childhood: Distribution of cardinal symptoms.*

computerized tomography (CCT), MRI, localized proton MR-spectroscopy (MRS), electrophysiological examinations (VEP, BAEP, SER) and CSF analysis were performed in all patients. Localized proton MRS was performed using a stimulated echo aquisition mode (STEAM) sequence with an echo time of 20 ms yielding spectra from 1-12 ml volumes of interest (VOI) within 5-10 min. All studies were performed at 2.0-T (Siemens Magnetom) using the regular imaging head coil for both MRI and MRS [27].

The patients were classified as definite, probable and possible cases according to the criteria of the IMAB-enquete [28-31].

RESULTS

The results of our study are shown in detail in Table 3 and summarized in Table 4. Out of the 15 children five were classified as probable and two as possible cases of MS. In eight children a definite diagnosis of MS could be established, including our youngest patient (case 6) in whom the disease started before the age of 4 years.

The age at onset ranged from 3 to 15 years, with a sex ratio (female:male) of 3:1. First symptoms occured in 12 children (9 girls, 3 boys) before puberty; in 3 children (2 girls, 1 boy) they started in adolescence. Initial symptoms ranged from school problems, paresthesias and transient visual disturbances to rather dramatic clinical presentations, suggesting diffuse encephalopathy with cerebral oedema, meningeal reactions, nerve palsies and impaired consciousness. Seizures were not observed (Fig 2).

Later on a variety of symptoms developed and persisted. 11 of the children now show persistent neurological symptoms with a Kurtzke scale (EDSS) from 1.5 to 7.0 [32]. The CSF showed a pleocytosis (5-50 cells/

Table 3 *Multiple sclerosis in childhood: Data of 15 patients of Göttingen-study*

Case number, sex	*1. F*	*2. F*	*3. F*	*4. M*	*5. M*
History	N	N VI-palsy	Nystagmus, bronchial asthma	Tonsillectomy, infect. mononucleosis	Adenoidectomy, allerg. diathesis
Vaccinations	DPT, polio	?	?	Measles, mumps, BCG, polio, DPT	Polio, tetanus, BCG, diphtheria
Age at onset (yrs)	9	11 1/2	15	13 1/2	9 1/2
Main neurol. symptoms	Charcot triad, ataxia, spastic paraplegia	N VII-palsy, encephalopathy, paresis right leg, paresthesia	Visual disturbances, head retraction	Cranial nerve palsy, motor-sensory hemiplegia	N, VI/VII-palsy, spastic paraplegia
CSF cells/mm³	15	20	17	8	30
protein (mg %)	41	59	54	24	42
IgG	autochthonous	autochthonous	autochthonous	autochthonous	autochthonous
oligoclonal bands	+	+	+	+	+
VEP	P	P	Not valuable	P	P
BAEP	P	P	P	P	P
CCT	Hypodensities	Hypodensities	N	N	N
MRI	ML	ML	ML	ML	ML
Therapy	Cortisone, azathloprine, cyclophosphamide	Cortisone	Cortisone	–	Cortisone, azathloprine
Course	Chronic progressive	Intermittent	Chronic	Intermittent	Intermittent
Diagnosis	Definite	Definite	Definite	Definite	Definite

Case number, sex	*6. M*	*7. F*	*8. F*	*9. F*	*10. F*
History	Cesarian section, hypotonia measles	Infect. mono-nucleosis	N	N	N
Vaccinations	DPT, polio, mumps	DPT, BCG, polio, measles	7	DPT, polio, measles, BCG	BCG, DPT, measles
Age at onset (yrs)	3	13 1/2	3 1/2	13	6 1/2
Main neurol. symptoms	Nystagmus, ataxia	N VII-palsy, motor-sensory hemiplegia, ataxia	Nystagmus, optic atrophy, ataxia	Diplopia, N VI-, VII-, XII-palsy, ataxia	Nausea, diplopia, dysarthria, ataxia
CSF cells/mm³	1	1	60	Pleocytosis	18
protein (mg %)	16	41	86	46	108
IgG	autochthonous	autochthonous	autochthonous	autochthonous	autochthonous
oligoclonal bands	+	+	–	+	–
VEP	P	N	N	P	N
BAEP	P	N	P	N	P
CCT	N	Hypodensities	N	Hypodensities	Hypodensities
MRI	ML	ML	N	ML	ML
Therapy	–	Cortisone azathioprine	Dexamethasone	Cortisone dexamethasone	–
Course	Intermittent	Intermittent	Intermittent	Intermittent	1 attack only
Diagnosis	Definite	Probable	Probable	Definite	Probable

F: female, M: male, ML: multiple lesions, N: normal, P: pathological.

(continued)

Case number, sex	*11. M*	*12. F*	*13. F*	*14. F*	*15. F*
History	N	N	N	Strabismus converg.	Allerg. diathesis
Vaccinations	?	DPT, rubella	?	Measles, mumps, rubella, diphtheria BCG, polio, tetanus	?
Age at onset (yrs)	4 9/12	12 1/2	6	9	8 1/2
Main neurol. symptoms	N VI-palsy, anisocoria, meningism, ataxia	Headache, 3 episodes of hemiparesthesia	Facial tic, dementia	Ataxic gait urinary urgency incontinence	Visual disturbances, ataxia, spastic paraplegia, par-/dysesthesia
CSF cells/mm³	27	16	1	1	5
protein (mg %)	42	71	17	20	
IgG	N	autochthonous		11 mg/dl	
oligoclonal bands	–	+	+	–	+
VEP	P	P	N	P	P
BAEP	P	P	N	P	Not valuable
CCT	?	N	–	–	N
MRI	ML	Small lesions (?)	ML	ML	ML
Therapy	–	–	–	–	Dexamethasone
Course	?	3 relapses compl. remission	Chronic	Chronic	Intermittent
Diagnosis	Probable	Probable	Possible	Possible	Definite

F: female, M: male, ML: multiple lesions, N: normal, P: pathological.

Table 4 *Multiple sclerosis in childhood: Summarized results of Göttingen-study*

Number of pat.:	15 (11 female, 4 male)	
Definite MS: 8,	Probable MS: 5, Possible MS: 2	
Age at onset:	3–15 yrs.	
Paraclinical results:	CSF: Pleocytosis	11 pat.
	Increased prot.	10 pat.
	Oligocl. bd.	10 pat.
	Pathol. VEP:	9 pat.
	Pathol. AEP:	11 pat.
	Pathol. CCT:	5 pat.
	Pathol. MRI:	14 pat.
	Pathol. MRS:	12 pat.

MS: Study Göttingen 05.91.

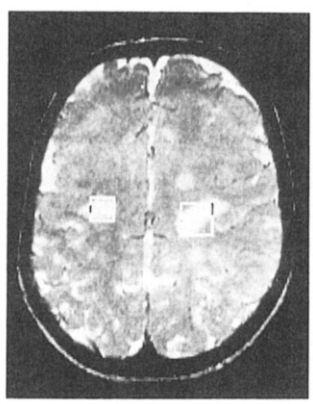

Fig 3 *Case no 6, age: 7 1/2 yrs, MRI.*

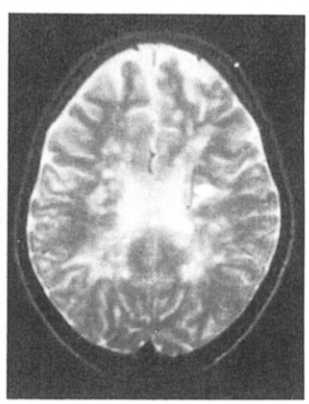

Fig 4 *Case no 1, age: 15 yrs, MRI.*

mm³), increased levels of IgG and oligoclonal bands in all definite cases.

Evoked responses (VEP and/or BAEP) were abnormal in all definite cases. MRI studies of the brain proved to be the most sensitive method in detecting cerebral white-matter abnormalities. Asymmetrical multifocal and periventricular white-matter lesions were observed in both cerebral hemispheres, the cerebellum and brain stem (Fig 3, 4). The CCT of one patient (case 2) initially showed multiple ring-like structures resembling a cerebral abscess (Fig 5). MR spectroscopy, performed in 14 patients, showed a 50–80% decrease of N-acetyl aspartate (NAA) which is a marker for vital neuronal tissue, a similar decrease of the creatine pool, an increase of choline-containing compounds, and, more discretely, an increase of the inositols in the lesions. Lactate was not increased. Adjacent white matter showed similar results as normal

controls, cortical gray matter related to neighboring multiple sclerosis lesions showed a reduction of N-acetyl-aspartate (Fig 6a, 6b).

Longitudinal studies in 3 patients revealed a consistent pattern of the plaques (detailed publication in preparation).

Most patients were treated with steroids during the acute phase, some received azathioprine, one cyclophosphamide with the same conflicting results as known from adult patients.

DISCUSSION

Our data from 15 patients confirm earlier publications on childhood multiple sclerosis: it is a rare but existent disease in childhood. Its frequency is approximately 0.3% to 2% of all cases of MS [8, 33]. There are now 24 children known in whom the disease started before the age of five years (Table 2).

The female preponderance reported by others [8] was also evident in our prepubertal (juvenile) group. Although the symptomatology of childhood MS shows no qualitative differences to adult patients, some atypical presentations have to be mentioned. Multiple sclerosis in early childhood more frequently shows acute symptoms suggesting diffuse encephalomyelitis [34, 35], or even a cerebral abscess or an acute metabolic encephalopathy [16, 36].

An analysis of 71 cases showed a lethality of 10% during the first 5 years of the disease in children compared to 0 in 800 adult patients [12]. These peculiarities of childhood MS might be due to the increased vulnerability of the developing brain and the immaturity of the immune system in children.

From our data no conclusions can be drawn with respect to early childhood infections, vaccination or inheritance [37].

A history of optic neurits was not noticed in any of our patients. This is probably due to the small number of cases, since several publications describe the development of MS in up to 10% of all children who suffered from optic neurits [38-42].

As in other publications the MRI proved to be the most sensitive method for the diagnosis as well as for follow-up studies. However it must be pointed out that its specificity is low. The introduction of gadolinium to a certain extent makes a distinction of acute and chronic lesions possible [43].

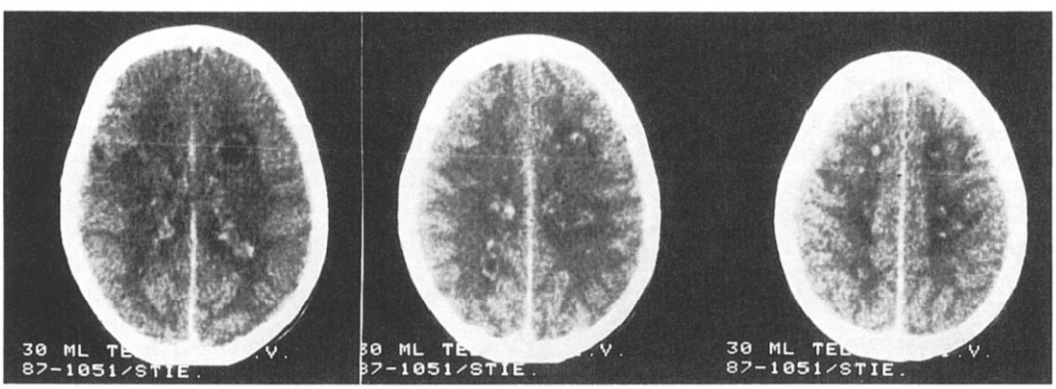

Fig 5 *Case no 2, age: 11 1/2 yrs, CCT: multiple hypodense foci, ring-like structures without marked surrounding oedema.*

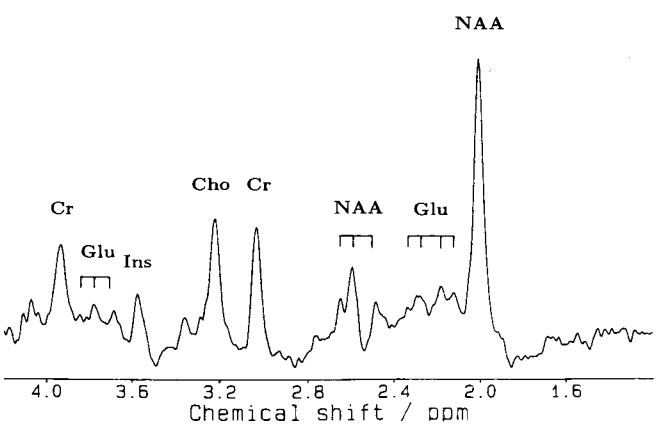

Fig 6a: *Normal control, age: 12 1/2 yrs, MRS TR 3000 AC 128 TE 20 12 ml.*

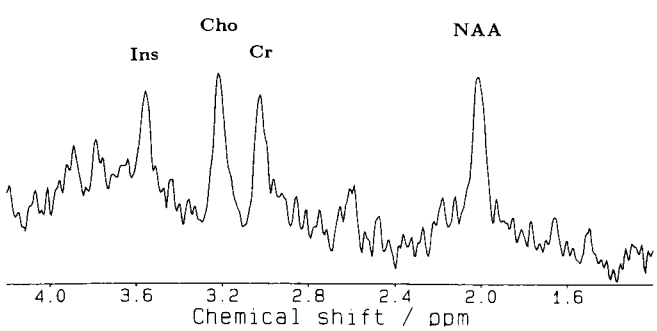

Fig 6b: *Case no 2, age: 14/12 yrs, MRS TR 3000 AC 128 TE 20 4 ml.*

Thus far MR spectroscopy has not been performed in MS in children. The findings are similar to results reported in single adult patients [44]. This method is very promising and will probably provide more insight into the metabolic events during inflammatory demyelination, about the progress of the disease and the value of treatment modalities.

The hypothesis has been widely accepted that MS is an autoimmune disease following the exposition to a transmissible agent, possibly a virus, before puberty. Presumably due to the persistence of a virus or of virus fragments, an autoimmune reaction against myelin basic protein or some other component of myelin, a latency ("incubation") period of some years is believed to elapse before the manifestation of MS later in life. Under the assumption of a "point source" epidemic in the Faroe islands an interval of 6 years or more between the exposure to a transmissible agent and the appearance of clinical symptoms was calculated [45]. The fact that MS can occur in early childhood (before the age of 3 years) casts some doubts on this hypothesis. Furthermore due to the application of rigid criteria (onset from 10 to 50 years) childhood MS has been largely neglected in research on this disease in the past. From the data available in literature and reported here it seems necessary to classify patients with early onset of the disease as infantile/juvenile form of MS. Unquestionable, strict definitions are an essential prerequisite for reliable information on childhood MS.

In view of atypical features in the initial phase, it would also seem desirable to record cases of encephalomyelitis of undetermined origin as potential cases of MS and to register the further course for verification or exclusion.

Essential features in the chain of immunopathological events leading to demyelination in MS have been demonstrated in animal models of experimental demyelination and have served as leads for directing immunological research in MS. In the variable, undulating and chronic-progressive course of MS in the adult, it is very difficult to show that the pathogenicity in the human disease is the same as in experimental models. In childhood MS an earlier and more rapid sequence of pathogenetic events pinpoint the way to some unsolved questions.

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