Acta Paediatrica Hungarica, 26 (3), pp. 193—204 (1985)

Multiple sclerosis in childhood: long term katamnestic investigations

A MÁTTYUS, Eva VERES

Neurological Department, Heim Pál Children's Hospital Budapest, Hungary

Sixteen children with multiple sclerosis, 14 with remitting and 2 with progressive course, and their follow up for 4—16 (mean, 9 years) are reported. The disease manifested in eight children at the age of 1.5—9 years, while in the other eight at the age of 12—14 years. The cases were acute, but had a stronger inclination to remission than in adulthood. In addition to the "classical" symptoms known in adult, multiple sclerosis, papilloedema and acute increased intracranial pressure were observed in nine children. Dehydrating treatment was life saving in these cases. Opsoclonus occurred in two patients, and two children had convulsions, one of whom later developed chronic epilepsy. The CSF was pathological in all the cases. Oligoclonal gamma-globulin subfraction was found in three out of the five patients tested. Three patients died. Histological examination was carried out in two of them; it revealed severe perivenous demyelinisation due to inflammation.

Cortisone treatment occasionally with azathioprine reduced the duration of exacerbations, but could not prevent renewed ones and caused severe side-effects.

Multiple sclerosis is a rare but not exceptional condition in children. The differences between cases in children and adults are age-dependent.

Leukoencephalomyelitis (LEM) is one of the most frequent diseases of the nervous system in adulthood. It is on the other hand still being disputed, how often it begins in childhood, to what extent do childhood cases tend to relapse, and whether or not they can directly progress into multiple sclerosis (MS). Most examinations are retrospective[1], trying to find out if parainfectious complications in the nervous system following an infection or vaccination, transient amblyopia, double vision, etc., had occurred in childhood, perhaps even decades before onset of the MS-process. So MS developed in 1/3 of the cases within 10—15 years [25] after manifestation of optic neuritis of unknown origin. Cohen et al [11] observed that 17 out of 60 cases of optic neuritis turned later into MS. Observations beginning actually in childhood are less frequent.

[1]Papers with retrospective data have not been taken into consideration in this study

Materials and Methods

Clarification of the questions mentioned above required prospective studies, so of the 4900 inpatients of our department in the 15 years 1964—1978 we followed up 16 children in whom recurring or progressive leukoencephalomyelitis had been diagnosed. The follow up lasted for 4—16 years. Our classification was carried out using the modified criteria of Bauer [1]. Cases diagnosed since the beginning of 1979 were excluded from the present study on account of the short catamnestic period. Symptoms and laboratory data are summarized in Tables I and II. Three patients died at the age of 8, 16 and 19 years, respectively. Onset of symptoms occurred between 1 1/2 years and 14 years of age in the present material (14 years is the upper age limit for admission to our hospital). Our patients have been classified into two groups on basis of their age at the first appearence of their symptoms. In Group I consisting of 8 cases, the symptoms started between 1 1/2 and 9 years of age, in Group II (also 8 cases) between 12 and 14 years. Fourteen children were observed during the appearance of their first symptoms or soon thereafter, while in two cases the first examination took place several years after the initial period.

The maternal grandmother of Case 4 died of MS at the age of 38 years. The first appearence of symptoms as well as later exacerbations were often associated with febrile upper respiratory disease (5 cases). The Paul-Bunnel reaction was positive in 3 children. Case 3 received phenytoin following febrile convulsions.

Damage of the diverse tract systems could be diagnosed on the basis of focal signs (visual, pyramidal, spinocerebellar system, sensory pathways). Psychic symptoms occurred in most cases.

Results

The characteristics of the two groups will be discussed separately.

A stormy onset was characteristic of almost every member of the younger age group. Acute paraplegia, tetraplegia, or hemiplegia were the most frequent initial symptoms, and paraplegia associated with paradoxical ischuria in Case 4. The disease of four children (Cases 2, 5, 7 and 8) started with papilloedema and headaches. In Case 6, papilloedema appeared later. With the exception of this case, no defective vision occurred simultaneously with swelling of the optic disk. Altogether three children (Cases 1, 3 and 6) developed transient amblyopia or amaurosis with decoloration of the optic disk. Rough, irregular, conjugated twitchings (opsoclonus) of the bulbs, independent of the eyes' position, were observed in two children (Cases 2 and 8), which recurred during exacerbations. Epileptic complication was observed in Case 1. Moderate mental retardation was observed in three children (Cases 1, 2 and 7).

Seven cases showed a fluctuating course, and the same symptoms returned repeatedly in four of them. Only Case 7 became chronic following the second exacerbation having had also acute initial symptoms. Three patients (Cases 4, 5 and 8) were in remission for 7—9 years. The symptoms of Cases 1 and 2 returned in short intervals. The number of exacerbations ranged from 2 to 10. Seven patients have already reached adolescence. Case 3 died at the age of 8 years after a 4-year course of remissions and exacerbations.

Case No 1. T. E., a girl born in August, 1965, after normal pre- and perinatal events had developed well up to the age of 1 1/2 years. She had been admitted in February, 1967, on account of weakness of the left limb and paralysis of the right side of the face. The most important laboratory findings in the CSF had been 298/3 cells (70% lymphocytes, 30% lymphoreticular cells), 29% protein, mastix: 22210—0.

Her next attack took place in 1968. In the following 15 years we observed a total of 9 exacerbations including the one in 1968. They showed a great variety of neurological symptoms: ataxia, transient amaurosis, hemianopsia, scotomas, pareses. She had again to be admitted in February, 1978, on account of pollakisuria, ischuria paradoxa, while in March on account of severe headaches and vomiting (signs of increased intracranial pressure).

Recurrence of the complaints was always followed by remission lasting from a few months to 2 years. Steroids were administered permanently, cytostatica temporarily. In 1972, 5 years after onset of LEM, generalised convulsions appeared, which were associated a year later with myoclonic absences.

At the last admission (4—13th October, 1978) she was a well developed girl with Cushingoid appearance. Decolorated optic disks with nystagmus of medium amplitude and frequency could be observed on either side. The speech was scanning, the gait paretico-atactic. Psychically she was aggressive and practically demented.

In the EEG a right temporal spike focus with a mirror focus on the left side appeared in July, 1974, two years after onset of the attacks. Secondary generalised convulsive activity with a temporal start could be found in later records. The CSF was tested on 11 occasions. The cell count varied between 12/3 and 82/3, while the protein content ranged from 11 to 40 mg/dl. The mastix curve was always normal (with the exception of the first puncture). CSF IgG was 3.2 mg/dl (February, 1978), while the gamma subfraction was characteristic of oligoclonal gammopathy. Electrophoresis of serum was normal (Dr. Kerényi).

All other laboratory results were normal. LE-cell, anti-H and latex were repeatedly negative. Immunoelectrophoresis showed a strong IgM precipitation line (1974).

In the last years, periodical deterioration of her condition made repeated treatment in an adult neurological ward necessary.

From the 8 patients of Group II, 7 showed remissions, and 1 was gradually progressive (Case 16). Only one of them was in durable remission in the last five years, exacerbations of the others returned frequently, and approached symptomatically the cases beginning in adulthood (age 20—27 years in December, 1982). Papilloedema was observed in a single patient (Case 15) as opposed to 5 cases in the younger group. Scotoma, transient amblyopia or amaurosis were observed in four adolescents, and decoloration of the optic disk in the same four patients (Cases 9, 10, 14 and 15).

Lesion of the pyramidal tract as well as of the spinocerebellar system was observed in every patient, except three in Group I (see Table I). It was probably due to the higher age of these patients, that five of them complained of paresthesia, as opposed to just one patient in Group I. Organic psychosyndrome developed in all but two (Cases 10 and 16) of the adolescents. Two patients died from Group II. The history of one of them was as follows.

TABLE I

Clinical data

No.	Name	Sex	Date of birth	Triggering cause	Age at onset yrs	Duration yrs	No of relapses	Papill-oedema	Sco-toma
1	E. T.	F	08. 1965	None	1 1/2	15 1/2	9	—	+
2	S. B.	F	05. 1969	Infectious mono-nucleosis	4	9	6	+	—
3	Cs. B.	M	07. 1960	Phenytoin	4	4✠	5	—	+
4	R. F.	F	12. 1968	Grippe	4	9 1/2	2	—	—
5	S. D.	M	10. 1960	None	6	16	2	+	—
6	A. B.	F	07. 1972	Grippe	6	4	3	+	+
7	C. D.	F	06. 1965	Grippe	8	9	2	+	—
8	I. K.	F	06. 1962	Infectious mono-nucleosis	9	11	2	+	—
9	G. M.	M	06. 1960	Grippe	12	4✠	12	—	+
10	J. K.	M	05. 1958	None	12	12	4	—	—
11	J. L.	M	06. 1955	None	12	15	9	—	+
12	P. B.	M	09. 1962	Grippe	12	8	8	—	—
13	Z. B.	M	06. 1962	Infectious mono-nucleosis	13	7	7	—	—
14	E. S.	F	02. 1953	None	13	6✠	8	—	+
15	I. N.	F	05. 1962	None	13	7	5	+	+
16	M. S.	F	10. 1961	None	14	7	1	—	—

Urinary retention occurred in Cases 1 and 4, opsoclonus in 2 and 8, and apraxia on the right side in Case 7

Case 9, G. M. a male patient born in August, 1960 had had temporary impairment of vision and pareses in April, 1972. Four further exacerbations had appeared in the same year (transient amblyopia, decoloration of papillas, pareses, ataxia), each one following a mild upper respiratory tract infection. Signs of brain stem herniation: anisocoria, tetraparesis, adversive convulsive attacks, coma could be observed; consciousness had returned after dehydration and i.v. administration of cortisone. After one month only minimal residual symptoms could be detected. The patient received continuously dexamethasone in large doses; upon every attempt to decrease the dose, the LEM process exacerberated. He was treated with cytostatics from January, 1974, without success. In May, 1975, we were forced to stop steroids and cytostatics on account of thrombocytopenic bleedings. He was admitted with severe tetraparesis and respiratory failure to the intensive ward in November, 1975. There, he developed amaurosis. After temporary improvement he died in May, 1976.

The ESR was regularly high (33—73 mm/h). The number of thrombocytes dropped to 22 000 during skin bleedings. The CSF was analysed 6 times. The cell count was 42—174 (lymphocytes and

Clinical symptoms						Course			Treatment	
Amaurosis	Decolor. pap.	Paresis of eye muscles	Pyramidal signs	Paraesthesia	Cerebellar symptoms	"Organic" psychic symptoms	Remitting	Chronic	Cortisone	Cytostatics
+	+	—	++	+	+++	+	+	—	+	+
—	—	++	+	—	+++	+	+	—	+	—
+	+	—	+++	—	—	+	+	—	—	—
—	—	—	+++	—	+	+	+	—	+	—
—	—	—	+	—	—	—	+	—	+	—
+	+	+	++	—	+	temp. disturbed	+	—	+	—
—	—	—	++	—	—	+	—	+	+	+
—	—	++	+	—	+++	—	+	—	+	—
+	+	—	++	+	+	+	+	—	+	+
—	—	+	++	+	+	—	+	—	+	—
+	+	—	++	—	+	+	+	—	+	—
—	—	—	+	+	+	+	+	—	—	—
—	—	+	+	—	+	+	+	—	+	—
ambl.	+	+	+++	+	+++	+	+	—	+	—
ambl.	+	—	++	—	+	+	+	—	+	—
—	—	—	+++	+	+++	—	—	+	+	+

M — male
F — female

lymphoreticular cells) in the first two years. In October, 1974, there was 148 mg/dl protein without leukocytosis. The lymphocyte migration index (LMI) was 0.69 and 0.70 in May, 1974, and May, 1975, respectively (normal value, 0.8—1.0). In the brain there was a severe inflammatory loss of perivenous white substance in the lower brain stem. Neither fresh, nor old plaques could be found.

Group I and II showed similar laboratory findings. The CSF during exacerbations was pathological (Table II). The cell count remained under 20/3 only in two patients, it exceeded 100/3 in 9 cases and 1000/3 in 1 patient; lymphocytes, lymphoreticular cells, a few plasma cells, and in some cases a few granulocytes were found.

Total protein values exceeding 30 mg/dl were considered pathological. The values of two patients (Cases 8 and 14) were below this limit, but the other data (cell count and/or colloid-curve) were pathological in these patients, too. Mild or pro-

nounced precipitation on the left side of the colloid-curve was missing in three patients only (Cases 8, 11 and 16). Since January, 1978, the CSF of five patients was analysed for oligoclonal gamma globulin. Three were pathological (Cases 1, 2 and 12), while two (Cases 6 and 7) were normal (see Table II). The lymphocyte migration index was pathological in seven patients (Cases 2, 4, 5, 6, 7, 9 and 10). It was normal in two patients and not investigated in the other 7 ones. LE-cell was positive in three out of ten analyses. Pneumoencephalography was carried out in 8 children, angiography in 5, with negative results.

The EEG was pathological in 11 children. Convulsive signs were recorded in Cases 1, 2 and 6. One patient (Case 1), receives continuous anticonvulsive treatment. The EEG was normal in three patients, and no EEG records were taken in two.

Discussion

On the basis of their clinical course and laboratory data at the first exacerbation, in most patients acute LEM had been diagnosed but the following attacks were considered signs of multiple sclerosis.

Among the causes inducing LEM, the role of common infections of the respiratory tract is widely known; we found this in the history of five of our cases. Infectious mononucleosis occurred in the history of three out of 16 children, which was a considerably higher proportion than the 1—3%, found in the literature [37, 47]. The triggering effect of diphenylhydantoin in autoimmune processes (Case 3) is well-known.

Most exacerbations, whether with early or late onset, showed a stormy course corresponding to the clinical picture of an acute inflammatory process accompanied by inflammatory changes of the CSF, differently from most cases of adult MS. The symptoms of our Case 9 resembled those of Devic's syndrome (optic neuromyelitis) six months before death due to acute amaurosis and tetraparesis [42].

The symptoms of the early group were to some extent monotonous, the same symptoms repeated themselves during the exacerbations in four cases. Most of the remissions were pronounced, even in Case 3, whose severe exacerbations had improved considerably. MS proceeds in young patients in acute or subacute series followed by more or less complete remissions. This might be explained by the nature of the histological alterations: in both cases in which a histological examination was carried out, we only found an inflammatory process [34].

Mild papilloedema was observed in five early and one adolescent cases, i.e. in more than 1/3 of the patients. The swelling was probably due to the greater water content of the brain tissue. The same may be the explanation for the repeated headaches accompanied by vomiting in Case 1, the upper brain stem herniation of Case 9, as well as for the oblongata herniation in Cases 3 and 9. It is

known that acute LEM may run its course in the form of a pseudotumour cerebri. It is less accepted, that this may also occur as a complication of later exacerbations [21]. Recognition of this complication is important, because elimination of the oedematous component by osmo- and oncotherapy may actually be life-saving. We have solved in this way the upper brain stem herniation of Case 9 three years prior to death. Even dehydration could not stop the terminal caudal brain stem symptoms in Cases 3 and 9 on account of the extremely severe oedema [34].

Opsoclonus, which occurred in Cases 2 and 8, is considered a disturbance of cerebellar function [5, 14]. This symptom is rare in childhood MS, and hardly occurs in adults. Other symptoms of our patients are regularly found in adult MS, so we shall refrain from their detailed analysis.

Out of the laboratory data, an increased ESR and a higher serum gamma globulin simultaneously with the appearance of neurological symptoms indicated an aspecific infection and proved the reaction of the humoral immune system. The positive LE-cell phenomenon found in three patients pointed towards a cellular immunopathological process [36], and so did the pathological LMI observed in seven patients [39].

The CSF showed inflammatory changes in every patient. A cell count lower than 10/3 was only encountered in Case 12, but this patient was admitted 4 years after onset of the disease, in remission 6 weeks after the end of an exacerbation. His other records were, however, pathological (Table II).

The pathological nature of the mastix reaction indicates an increase In the gamma fraction of the CSF. intracerebral IgG synthesis was first demonstrated in 1958 [17]; it can be observed regularly in prolonged viral infections and chronic inflammations of the central nervous system, such as MS.

The subfractions characteristic of the disease can be shown by electrophoresis [23, 26, 27, 29]; they may, moreover, be found also in the plaques of autopsied brains [35]. We found them in the CSF of three out of the five patients so examined (Cases 1, 2 and 12). One of them (Case 12) was the patient observed during remission, whose CSF cell-count was not increased.

Thus the clinical symptoms and laboratory data seemed to prove the presence of MS and in the majority this was confirmed by the remissions and exacerbations. Thus, contrary to general opinion, MS may start in childhood. Out of the 19 acute cases of childhood LEM observed by van Bogaert [3], 5 turned into MS during the following 18 years.

The eight cases in our Group I had all begun before adolescence. The disease is "an extreme rarity" in children below the age of 9 [33]. Those cases of Ford [16] which progressed to MS, were all older than 9 years. Out of the 8 patients below the age of 15 years of Gall et al [19], two were 7 and 8 years old, respec-

TABLE II

Laboratory Results

No.	Name	ESR mm/h	Cell/3	CSF prot. mg/dl	Mastix	Oligocl. γ glob.	LE cell	LMI	Paul-Bunnell	PEG	Angiography	E E G	Histology
1	E. T.	23	52	40	111110—0	+	neg.	n.d.	neg.	n.d.	n.d.	Temporal focus sec. gener.	
2	S. B.	75	320	30	21110—0	+	neg.	0.62	1:46	n.d.	n.d.	Right frontal spikes	
3	Cs. B.	10	30	55	21110—0	n.d.	n.d.	n.d.	n.d.	Normal	Normal	Diffuse, slowing	Perivenous encephalitis
4	R. F.	6	170	35	11110—0	n.d.	neg.	0.66	neg.	n.d.	n.d.	Diffuse, slowing	
5	S. D.	5	1168	128	23454220—0	n.d.	+	0.70	neg.	n.d.	n.d.	Normal	
6	A. B.	15	59	36	22210—0	neg.	neg.	n.d.	1:12	Normal	n.d.	Left tempero-basal slowing and spikes	
7	C. D.	15	20	31	110—0	neg.	+	0.74	neg.	Normal	n.d.	Irregular	
8	I. K.	25	130	24	10—0	n.d.	neg.	0.80	1:96	n.d.	n.d.	Slowing	
9	G. M.	33	174	154	211110—0	n.d.	neg.	0.69	neg.	Normal	Normal	Slowing	Perivenous encephalitis
10	J. K.	8	280	68	34554432100	n.d.	neg.	0.68	neg.	n.d.	Normal	n.d.	
11	J. L.	8	13	31	10—0	n.d.	n.d.	n.d.	n.d.	Normal	n.d.	Normal	
12	P. B.	4	8	43	1222110—0	+	n.d.	n.d.	n.d.	Normal	n.d.	n.d.	
13	Z. B.	33	48	40	1222210—0	n.d.	neg.	n.d.	1:48	n.d.	n.d.	Irregular	
14	E. S.	8	28	18	12210—0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	Normal	
15	I. N.	9	90	90	233210—0	n.d.	n.d.	0.90	n.d.	Normal	Normal	Left sharp waves	
16	M. S.	5	200	46	10—0	n.d.	+	0.84	neg.	Normal	Normal	Mild anomaly	

n.d. — not done
neg. — negative

tively, the rest was older. From the 711 MS cases of Carter [9], 9 were 10—15 years old. Out of the 7 childhood cases of Low and Carter [30] four had at least two exacerbations, the youngest one of these being 4 years old (and not two as Schneider et al [42] have written) while the others were 6, 7 and 8 years old. The 6-year-old girl patient of Kamio et al [24] resembled very closely our acutely remitting cases, with her 6 exacerbations within 2 years. The case of Brandt et al [8] started at the age of 2 years, and that of Bejar and Zeiger [2] also at that time but they failed to describe whether they first saw the patient then or only at the age of 16 years and whether the first 2 episodes they took from the history or they followed the case during 14 years.

The laboratory data are not characteristic of MS. Concerning the patient of Nobel [38] who died at the age of 2 1/2, we must point out that in their very short report nothing is said about the beginning of the gradually progressing case. Histologically, demyelinisation centres (Weigert preparation) appeared in the cortex and the white substance of the brain. Infiltration of the blood vessels was minimal, granular cells could only be found along the blood vessels. The histological examination was carried out by Marburg. In his opinion: "The former (i.e. multiple sclerosis) starts mostly in childhood... it appears that mostly in close connection with childhood infections". He mentioned the remitting course and even the occurrence of Charcot's triad in childhood. The published case cannot, however, be evaluated with any certainty because of the inadequate description and the lack of figures.

Our first patient, with onset at 1 1/2 years of age, was the youngest case ever reported. She is now 17 years old and has approached the adult type, despite the fact that her illness earlier was characterized by an acute course and great inclination to remissions, like all the patients in Group I.

In connection with our first patient, we must deal with the relationship between MS and epilepsy. According to some authors [20, 25] epilepsy is rare in MS; one must consider a mere coincidence in view of the frequency of the two diseases [16]. Isler [22] however thinks that epilepsy is not exceptional in adult MS. Different workers reported the frequency of occurrence of convulsions in patients with MS to be from 10.8% [18] to 1.1% [32]. The smallest and highest number of patients with MS examined from this aspect was 74 and 2400, respectively. The convulsions manifest themselves in several cases together with acute MS exacerbations, exceptionally in the form of status epilepticus [7]. When the patients died due to the basic disorder or epilepsy, fresh cortico-subcortical plaques were found, corresponding to the convulsive focus [4, 6, 7, 10]. The proportion of epileptic convulsions was 2—3% in the MS material of these workers.

Pathological EEG records were

reported by Boudin et al [4] in 33.6% and Czopf et al [12] in 64% of their cases. The corresponding number in another study [28] was 34% or 47.8% depending on the duration of the disease. Higher percentages such as 75% [18] have also been published. A pathological EEG does not, of course, necessarily mean convulsive activity in the brain.

Due to the small number of our patients, calculation of percentages would be pointless. EEG was recorded in 13 patients, taking 2—17 records in each case. It was pathological in 10 patients, convulsive activity was found in three (see Table II). Clinical epilepsy developed in one patient only (Case 1), in this case it has continued to be an important factor of the clinical events for nearly one and a half decades.

On the basis of our data, MS cannot be considered epileptogenic. Pathological EEG or even a spike focus may develop upon the basis of an organic lesion; an epileptic process is, however, rare. Occasional attacks are more frequent (Case 9).

The history of our 16 patients proves that onset of MS in childhood does not mean an unequivocally better prognosis compared with cases starting in adulthood. While inclination to remission is greater, malignant processes are not a rarity in children. Immediate life danger is great in acute exacerbations on account of the increased disposition to oedemas and to severe inflammatory reactions. In some chronic cases, the exacerbations become more and more frequent and permanent residual symptoms may develop [45].

In the two cases examined histologically, we failed to find any sign of earlier attacks and in particular of any plaque formation; we rather observed acute perivenous encephalitis. This observation corresponds to our clinical experience: acute exacerbations indicated acute inflammatory processes according to the findings in the CSF. A detailed analysis of the pathological findings lies outside the scope of the present work. We would only point out that it had been stated more than 30 years ago that perivenous encephalitis may permanently retain its histological independence [3].

As far as the therapy is concerned, most of our patients were given steroids, some of them also azathioprine. The acute symptoms disappeared quickly on cortisone. This fact is important on account of the acute course the disease takes in children. The mechanism of the quick remission has not been clarified [43, 46]. The role of remyelinisation — also proven in human subjects [41] — is insignificant in MS [44]. The maintenance cortisone dosage failed, however, to prevent recurrences, as emphasized also by Ellison and Myers [15]. They experienced the most lasting results by permanently administering azathioprine, but this entails numerous risks. We also met severe complications arising from steroid-azathioprine treatment in our Case 9. Plasmapheresis [13] has not been carried out in our cases.

On the basis of the above data it may be stated that some cases of LEM proceed with exacerbations and remissions already in childhood. Most of the individual relapses resemble single acute EM but they approach the clinical picture of chronic MS, or "progress" into it in many cases after a longer course. The clinical picture of MS is rare but not exceptional in children. It may start soon after infancy as shown by our Case 1. If the possibility of its occurrence is kept in mind, correct diagnosis is ensured by careful analysis of the symptoms complemented by laboratory tests. This may spare children the unnecessary contrast examinations, which were carried out in nearly 2/3 of our cases. The spread of computer tomography has solved this problem.

Acknowledgements

We should like to express our indebtedness to Professor L. Nyerges (László Hospital, and Heim Pál Hospital, Budapest) and Dr. L. Kerényi, scientific research fellow (Department of Neurology and Psychiatry, Pécs) for LMI and CFS gamma-globulin subfraction tests.

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Received 11 July 1984

A MÁTTYUS MD
Üllői út 86
1086 Budapest, Hungary