Acta Neuropathol (Berl) (1982) 56:87–92

Acta Neuropathologica

Gerstmann-Sträussler's Disease, Atypical Multiple Sclerosis and Carcinomas in a Family of Sheepbreeders

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Summary. A new family with the Gerstmann-Sträussler type of subacute spongiform encephalopathy is described. Atactic symptoms, dysarthrias, and personality changes characterized the clinical course. The clinical pattern of a father and his two sons was very similar. They had been in contact with sheep by occupation. A rapidly progressing demyelinating disease (transitional diffuse-multiple sclerosis) occurred in the same family, as well as numerous cases of carcinoma. Morphologically, the Sträussler type can be differentiated from other subacute spongy encephalopathies by the occurrence of Kuru-Plaques and numerous multicentric floccular plaques both in the cerebral and cerebellar cortex, basal ganglia, and white matter.

Key words: Sträussler's disease – Jakob Creutzfeldt's disease – Subacute spongious encephalopathy – Multicentric floccular plaques – Slow virus disease – Multiple sclerosis

Introduction

Gerstmann-Sträussler's disease (GSD), a special type of the subacute spongy encephalopathies (SSE) of adults found a renewed interest because of its connection with slow virus infections (Masters et al. 1980), the report of new cases by Seitelberger (1981) and the observations of Boellaard and Schlote (1980) and Schlote et al. (1980). We had the opportunity of examining another family some members of which suffered from GSD, others from a demyelinating disease, and several others from carcinoma.

Case Reports

Family History and Clinical Findings

The family N. has lived in Württemberg (Southern Germany) for many generations. The genealogic tree (Table 1) is based on information from three members of the family (cases 9, 14, and 19). Our neuropathologic examination was performed on cases 8 and 35. The symptoms of cases 2, 5, 8, 10, and 35 were assembled from the medical histories, the documents of annuity proceedings, and information from relatives. Cases 1 and 2, 5 and 10 were farmers and sheepowners. The siblings of cases 5 and 10 had grown up on the paternal farm and had been in close contact with sheep during their childhood and youth.

Case 1 died in 1913 aged 63, supposedly as a result of an agricultural accident.

Case 2 had, in her old age, a peculiar staggering gait and had been somewhat confused. According to the family it could have been a disease similar to that of cases 5, 8, and 10.

Cases 3, 4 and 7 (a set of siblings) died of carcinoma as did case 12.

Case 6 like his daughter (case 15), committed suicide both supposedly due to reactive depression.

Disease of nearly an identical course was observed in case 5 and his two sons, cases 8 and 10. The wives of cases 8 and 10 were sisters, cases 9 and 11.

Case 5. Friedrich N. aged 48 was a farmer and sheepbreeder. Several years before his death (1931) he suffered from increasing disturbance of gait and 1 year later by disturbance of speech. The disease advanced relatively fast. In the beginning the patient was able to walk with two sticks, but later became unable to do so. One year before his death he had an agricultural accident which obviously did not influence his underlying disease. He spoke in a more and more unintelligible manner and ultimately showed lack of judgement. According to his wife cerebellar damage (bleeding or softening) was found at the post mortem examination the record of which is no longer available.

Case 8. Ernst N., a man of 64, noted pains in the calf and coldness of the extremities at the age of 60. Intermittent claudication was suspected. One and a half years before his death attacks of dizziness occurred, first without signs of a neurological focus (A. basilaris syndrome?). Some weeks later, he experienced an increasingly depressive mood, disturbances of sleep, inner restlessness, and anxiety and emotional instability. He appeared to be worn out. He was blind and his gait was unsteady. He had horizontal nystagmus. A diagnosis of involutional psychosis with organic traits was made.

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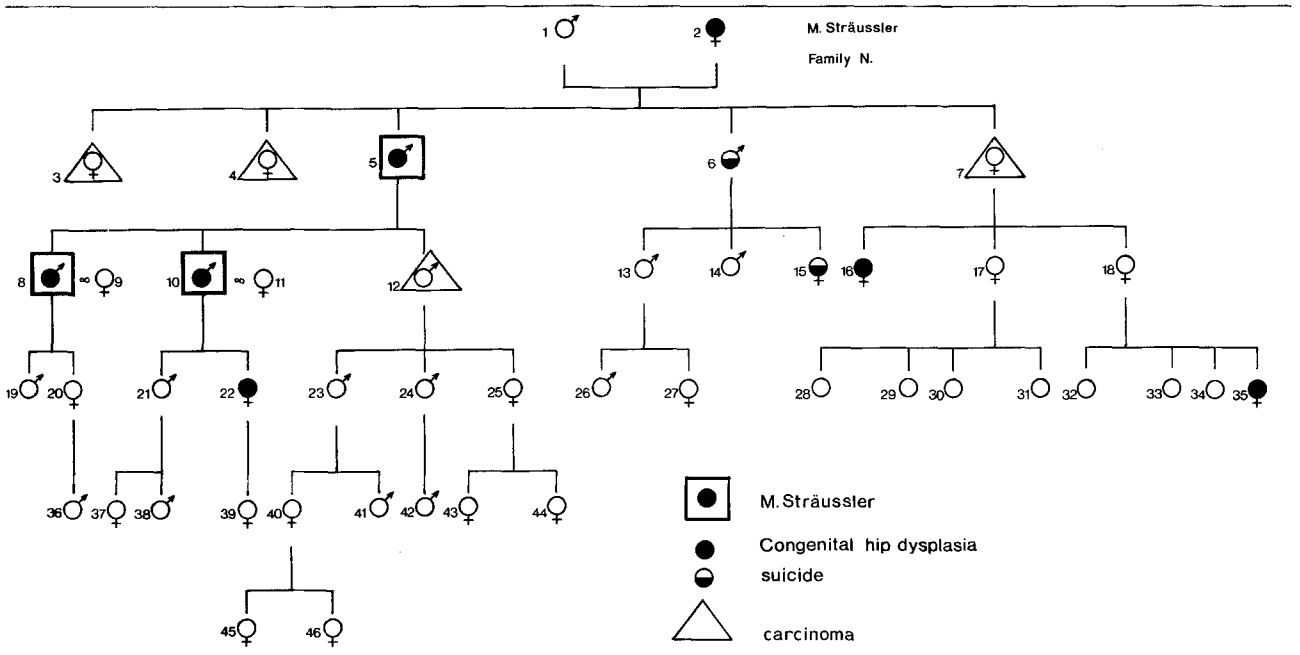
Table 1. Genealogical tree of the family observed



Ten months before his death (1980) areflexia of the legs was noted (beginning polyneuropathy). Nerve conduction velocity was normal and no fasciculations or fibrillations were observed in the EMG. Two months later he had pallhypesthesia and dysesthesia in both legs. Distal nerve conduction time was prolonged. After another 8 weeks, he showed increasing disturbance of gait and marked ataxia in the heel-knee-shin test. In the last month of his life disturbances of balance and gait became rapidly worse. He had increasing difficulties with memory and concentration. Computer tomography showed slight cortical atrophy. The EEG showed no irregularities. He displayed suicidal tendencies in the last weeks of his life.

Post Mortem Examination

Emboli of the pulmonary arteries bilaterally, acute diffuse edema of the lungs, slight non-stenosing coronary sclerosis, and general arteriosclerosis.

Case 10. Wilhelm N., a man of 47, suffered from hunger dystrophy during a period of war captivity. Five years after discharge from captivity at the age of 41, disturbances of gait occurred progressively and led do complete abasia and astasia within 2 years. In the beginning double vision was thought to be present. He experienced pains in the trunk and thoracic girdle. In the 4th and 5th year of the disease he had increasing dizziness, disturbance of balance, and sleeplessness. His speech became blurred and almost unintelligible due to dysarthria. Areflexia in the lower extremities and hyperreflexia in the arms were noted. There was disturbance or urination. One year before his death the EEG was normal. The masseter and orbicularis oculi reflexes were increased. The calf muscles were slightly atrophied. The clinical diagnosis was suspected systemic cerebellar atrophy. Further examinations in a psychiatric hospital showed increasing disturbance of memory, increasing lack of judgement, affective lability with worsening ataxia. The differential diagnosis 3 months before his death was multiple sclerosis, degenerative disease of the cerebellar system, and Lindau's tumor. In the terminal period (1959) there were increasing disorientation, motor restlessness, delusions of being poisoned and somnolence.

Post Mortem Examination

There was slight cardiac dilatation and emphysema of the upper lobes of the lungs. Some pleural adhesions on both sides and bronchopneumonia were found.

The brain weighed 1,255 g. There was moderate internal hydrocephalus. No demyelination was observed. There was generalised but not systemic atrophy of the brain with loss of nerve cells in the cerebral cortex and basal ganglia, particularly in the small nerve cells of the putamen. Abundant pseudo-calcium concretions were seen in the pallidum. Terminal brain edema with fresh ring hemorrhages was seen in the pons. Club-shaped distensions were noted in the cauda equina just beyond the exit of the nerves through the spinal dura mater. No specific neuropathologic examination of the cerebellar cortex was done to detect plaques or similar alterations by special staining techniques.

Diagnosis. Generalized but not systemic cerebral atrophy. Hypertrophic neuritis of the cauda equina.

Case 35. Regine W., a woman of 19. When aged $18^1/_2$ years she had hemihyperpathia on the left side and a mydriasis became evident for a few days. Four weeks later during a second attack a paraparesis affected especially the left side, vestibularis break down on the right side as well as dysacousis of the inner ear were observed. The CSF contained 13/3 cells, 50 mg total protein, and the electrophoresis was normal. Slight general organic personality changes were observed. There was a remission with corticotropin treatment.

Eight weeks later there was a sudden onset of a right hemiparesis with a slight spastic component. Rapidly progressive deafness was noted: at first on the left side, then bilaterally. A paresis was noted which was first spastic and later flaccid. Pallor of the optic disc was noted on both sides. Immunosuppressive therapy (Imurek) produced a short interruption of the progress. Increasing blindness, deafness, and extreme personality changes followed, and finally

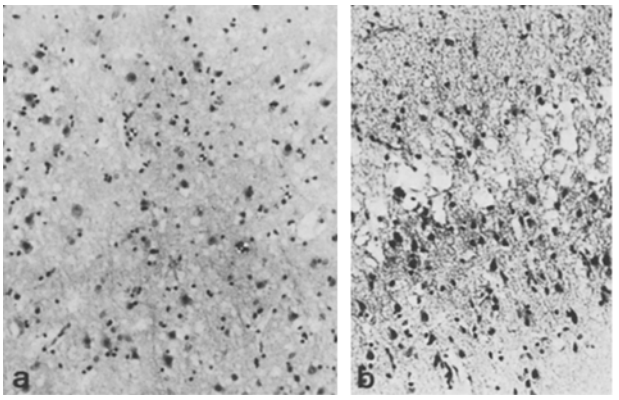


Fig. 1a, b. Spongy changes in the cerebral cortex. **a** Small spongiform changes with many birefringent plaques (half-polarization). HE, ×37. **b** Spongy state of the 2nd and 3rd cortical layers, ×148

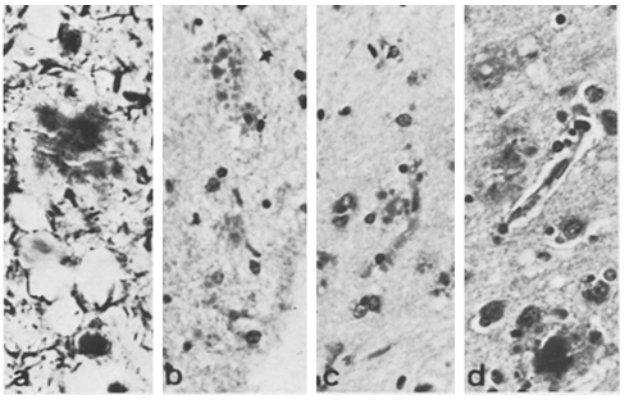


Fig. 3a–d. Case 8 (Sträussler's disease). Multicentric fluccular plaques in the cerebral cortex. **a** Bodian, ×548. **b** and **c** HE, ×134. **d** PAS, ×212

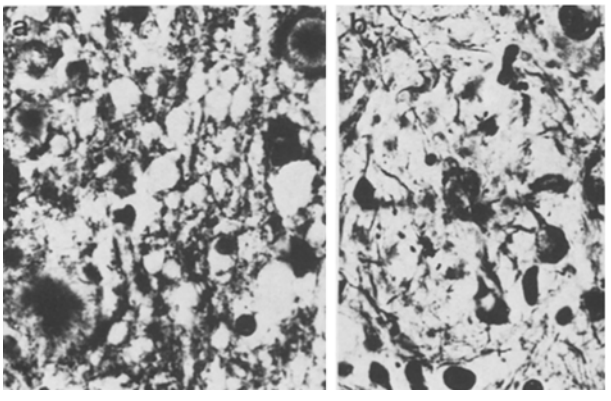


Fig. 2a, b. Case 8 (Sträussler's disease). **a** Kuru plaques. Mallory, ×192. **b** Senile plaques. Bodian, ×481

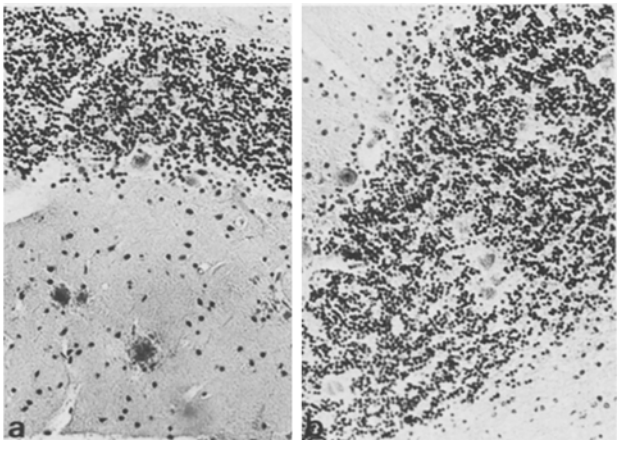


Fig. 4a, b. Case 8 (Sträussler's disease). Multicentric floccular plaques in the cerebellar cortex. **a** Molecular layer. **b** Granular layer. ×150

she was no longer responsive. There was complete apathia. No rise in the level of gamma globulins was found.

Post Mortem Examination

Left ventricular hypertrophy, bronchopneumonia, and ascending hemorrhagic urocystopyelitis.

Neuropathological Findings

Case 8 (ES84/80). Diagnosis: M. Sträussler.

Cortical atrophy affected the upper frontal and parietal regions especially. The ventricles showed slight symmetrical dilatation.

Histology: Marked spongy vacuolation occurred in the cerebral cortex especially in the frontal regions and particularly in the first and third layers. Their appearance varied between the small spongiform changes described by Masters and Richardson (1978) and more obvious spongy vacuolation (Fig. 1) which was more marked in the neocortical regions where neuronal loss was noted as well as in the deeper cortical layers. Numerous plaques were observed in the cortex in HE preparations and by polarization microscopy. This was confirmed by fluorescent microscopy in preparations stained with Thioflavin S, with PAS reaction and those impregnated with silver. Only some plaques were typical senile plaques. Kuru plaques and peculiar multicentric floccular plaques in particular were observed more frequently (Fig. 2). In comparison with senile plaques these other plaques were devoid of the corona of swollen neuritic endings and usually of any microglial reaction.

Only rarely did the plaques show a central core. More frequently several homogeneous floccular aggregations with diffuse borders were found (Fig. 3). These sometimes flowed together and were seldom surrounded by a narrow margin of radially orientated fibrils as in Kuru-plaques. Such floccular multicentric plaques were found not only in the convexity, but also in the subiculum, lamina medullaris circumvoluta of the Ammon's horn, central white matter, neostriatum and thalamus, but especially in the cerebellar cortex (Fig. 4). Here they lay between the granular cells and also in the molecular layer. The plaques were especially well seen when stained by the Mallory trichrome technique. They were dark blue sometimes with a red center. With the Klüver-Barrera staining technique they were light blue to violet, but were more faint. They were slightly congophilic. Besides plaques, there were also some small isolated congophilic plaque nuclei corresponding in size to nerve cell nuclei. By polarized light the "nuclei" of the small plaques showed a clear double refraction in the form of a Maltese cross

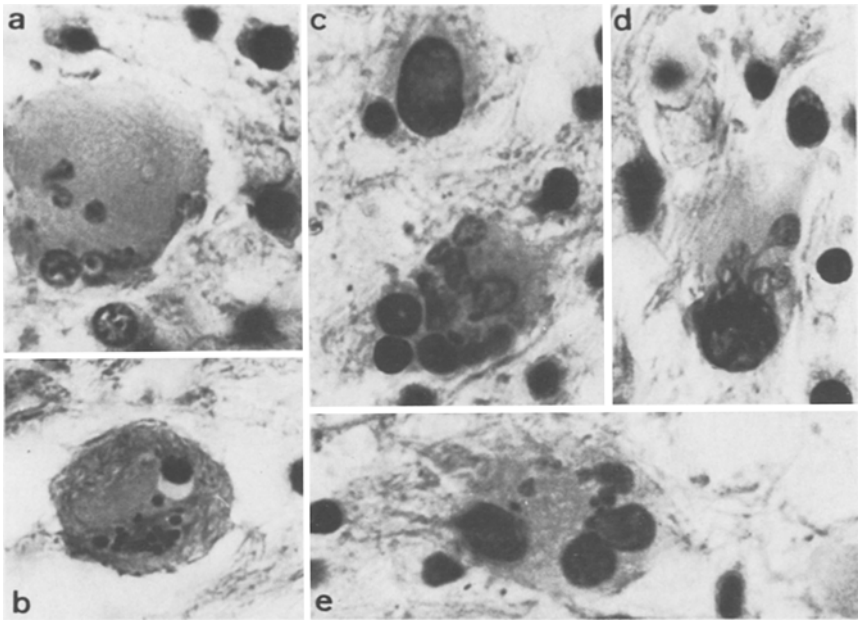


Fig. 5a–e. Giant astrocytes with atypical nuclear material and tongue-like sprouts. HE, ×825

with greenish stain in one axis and yellowish stain in the other (Fig. 1a). There were no Alzheimer tangles. The astrocytes showed moderate proliferation: they were often of the Alzheimer type II cells.

In the cerebral cortex, dentate nucleus, and mediodorsal areas of the inferior olive, the number of nerve cells was moderately reduced. There was only slight vacuolation of the granule cell layer and almot a normal content of Purkinje cells.

Torpedos were found in Bodian preparations within the granule cell layer of the cerebellum and rarely the subcortical white matter.

Case 35 (ES 10/72). Diagnosis: Transitional form of multiple and diffuse sclerosis.

All coronal sections presented patches of demyelination of different color. They were often confluent. Softer reddish patches were above all seen in the parietal and occipital white matter. There were marked foci of demyelination around the Steiner's areas and the two posterior horns of the ventricles. The optic nerves and tracts did not appear to be affected. In the spinal cord the posterior tracts were greyish white.

Histology: Numerous patches of demyelination surrounded the ventricular angles and the posterior horn and extended into the corpus callosum. Occasionally, small bridges of intact myelin tissue were seen between adjacent demyelinated plaques. Here and there small islands of intact myelin were seen in the midst of demyelinated areas. The demyelination extended into the grey matter of the cortex and basal ganglia, but was predominant in the white matter. Burnt-out foci were not present in the cerebrum nor in the demyelinated medulla oblongata and spinal cord. The age of the foci was generally rather uniform and they were filled with numerous glial macrophages. By Klüver-Barrera staining these macrophages sometimes contained material with the color of broken down myelin which, however, had lost its ability to stain in other areas. Here and there in older patches, blue green lipophages were frequent perivascularly. The inflammatory reaction was relatively moderate and lay usually at the border of the foci and consisted predominantly of plasma cells but at times with a greater number of small lymphocytes. An unusually marked reaction of astrocytes with abundant cytoplasm was noted. They often lay closely together. They presented mitotic figures which were sometimes atypically formed; the nuclei of these astrocytes often showed tongue-like sprouts (Fig. 5). Their cytoplasm contained inclusions of different sizes. These cells often corresponded to the giant cells described by Creutzfeldt in Schilder's disease. Bodian preparations demonstrate that the axons in the demyelination patches were mostly intact. Swellings of axons and little axon balls were found especially near the borders of the foci. The foci in the pons were distributed irregularly and asymmetrically with a preference for the areas near the surface. Sometimes a very small subpial layer was spared from demyelination. Starting from the crura cerebellomedullaris the central cerebellar white matter was also undergoing demyelination. Where the demyelination extended into the lobules of the cerebellar cortex, the granule layer stained more faintly than usual. Here the Purkinje cells were often shrunken and hyperchromatic. In the molecular layer diffuse PAS-positive zones were rarely found: they were somewhat reminiscent of floccular plaques but not identical because they did not show any amyloid-like reaction.

Discussion

Gerstmann-Sträussler's disease (GSD) like both JCD with its variants (incl. Heidenhain's disease) and juvenile Kuru disease of the Fore tribe belongs to the subacute spongy encephalopathy syndrome (SSE). Cases of GSD are clinically similar to the atactic type of JCD.

Neuropathologically, there are some similarities between GSD and the JCD: Spongiform changes can be found in the cortex of the cerebrum and cerebellum and often in different regions of the basal ganglia. These changes are accompanied by astrogliosis. The content of nerve cells is often markedly reduced in the cerebral cortex including the gyrus hippocampus, in the striatum, sometimes in the thalamus and regular-

ly in the cerebellar cortex, here especially in the Purkinje cell layer. Many cases show tract degeneration in the spinal cord.

The main difference between GCD and JCD consist in the presence of large numbers of special plaque types and in their distribution in GSD. The following plaque types can be differentiated:

1. Typical senile plaques with their variants (primitive plaques, core plaques, and burnt-out plaques) (Terry and Wisniewsky 1970).

2. Kuru plaques (Klatzo et al. 1959; Neumann et al. 1964).

3. Multicentric floccular plaques.

Senile plaques rarely occur in GSD. They have a typical picture with neuritic swelling and a predominantly microglial reaction around the congophilic center of the plaques. Kuru plaques can be seen more often in GSD. They show radially orientated, fibril-shaped condensations around the congophilic center.

The multicentric floccular plaques are the dominant type. Nevertheless, they are not pathognomic of GSD, because such plaques sometimes can be observed in Alzheimer's disease. However, their distribution seems specific:

In contrast to senile plaques, multicentric plaques occur not only in the cerebral cortex, but also in the white matter, in the basal ganglia, and especially in the cerebellar cortex (Fig. 4). Electron-microscopic descriptions were presented by Boellaard and Schlote (1980) and Schlote et al. (1980). Boellaard and Schlote (1981) showed that in these Sträussler plaques as well as in Kuru plaques extracellular amyloid deposits are located between interdigitating, filament-free astroglial processes, surrounded by enlarged, filament-rich astrocytes. Therefore, the authors differentiate these types as glial plaques from the neuritic plaques in Alzheimer's disease. Of significance for the differential diagnosis of Alzheimer's disease is the lack of Alzheimer tangles and the infrequency of typical senile plaques. Among the GSD it is remarkable that often endfolium and Sommer's sector of the Ammon's horn are free of Kuru plaques, whereas they can be observed more often in the lamina medullaris circumvoluta and in the subiculum, as well as in the gyrus hippocampus (van Braunmühl 1954; Boellard and Schlote 1980, own case). Yet, this distribution pattern is not a general phenomena of GSD. The same can be remarked for the paleo-cerebellar damage to which Seitelberger et al. (1962), Horoupian et al. (1972), and Krücke et al. (1973) had drawn attention. Brownell and Oppenheimer (1965) mentioned a similar distribution in the atactic form of JCD without Kuru plaques. Therefore, this is not a useful criterion for differentiation. Our case corresponds to the descriptions given by most authors.

For these SSE as for visna, scrapie, and Mink-encephalopathy the slow virus genesis has been proved by transmission of the disease (for GSD Masters et al. 1980). With regard to this, two facts concerning the family of our case are perhaps important: the father of our patient Ernst N. had been a farmer and sheep-breeder. Both sons had worked on their father's farm during their youth and had been in contact with sheep for years. It must remain an open question whether any deductions can be drawn from this observation as to the possible transmission of a slow virus disease from sheep to the family members. The possible connection between the incidence of JCD and contact with sheep has been discussed by Mitrová (1979) in an epidemiologic study in East Slovakia.

It is also worth noting that a demyelination disease confirmed neuropathologically (transitional form of diffuse multiple sclerosis) occurred in another member of the family. The disease had a very rapidly progressive course, which led to death within a few months. Intracytoplasmic inclusions were found in the nerve cells particularly at the border of the demyelinated foci. Observations on familial forms of multiple sclerosis and the HLA examinations indicate that – as for the SSE – genetic factors play a role in MS. A slow virus genesis, which has been verified in SSE, is discussed for MS. The question whether there are pathogenetic connections between GSD, multiple sclerosis, and the high carcinoma rate in the same family, may be justified. Speculations about a possible common factor in disturbed immunoreactivity, however, are not today based on hard facts. Nevertheless, our observations of the family described after new aspects worth to be considered in similar cases.

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Received February 23, 1981/Accepted November 23, 1981