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Calcification of the central nervous system in a new hereditary neurological syndrome

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Summary. A case of a new hereditary neurological condition with extensive calcifications of the central nervous system is described. The calcium deposits were especially localized to the leptomeninges, the first layer of the cerebral and cerebellar cortex, and along the ventricular wall. The neuropathological findings were in accordance with the clinic. The case was familial and the pedigree suggested an X-linked recessive inheritance.

Key words: Neural hearing loss – Optic atrophy – Dementia – X-linked recessive inheritance – Idiopathic cerebral calcification

Calcification of the brain is a well-known observation in a number of different conditions. Half of the cases have deficiency of the parathyroid hormone, while most of the remainder is idiopathic, that is without demonstrable endocrine or metabolic disorders. This group also includes a number of familial cases [4, 12, 13].

In the present report we describe an apparently new hereditary neurological condition [7, 8] showing extensive calcifications of the brain and the spinal cord forming a very unusual pattern. The neuropathological changes are consistent with the clinical findings.

Case reports

The propositus (II-4 in Fig. 1) was a 38-year-old man, who died at that age in a psychiatric hospital. He had been deaf from early infancy and an audiometric examination revealed a severe, bilateral neural hearing loss. From the age of 14 he experienced a slowly progressive visual failure because of optic atrophy and from the third decade signs of progressive disturbance of mental function became apparent. He was admitted twice to a psychiatric hospital because of behavioral disturbances suggesting organic psychosis. Unfortunately, no CT scan of the brain was performed. By the time of death he was characterized by advanced mental deterioration and severe motor disability. A thorough autopsy was performed (see below).

An older brother (II-3 in Fig. 1) experienced a very similar clinical course. He could hear well in infancy, but from about the age of 1½ years a progressive, severe bilateral sensorineural hearing loss was apparent. Except for the acoustic function psychomotor and intellectual development was normal, and he was always considered an alert child. Late in the second decade he experienced a progressive visual failure because of optic atrophy. A neurological examination at the age of 27 was normal apart from the visual and acoustic disturbances described above; however, a pneumoencephalogram revealed a low-grade cortical and central atrophy. This was followed, beginning at the age of 30 years, by a slowly progressive organic dementia of unknown cause. A few years later he was institutionalized in a nursing home because of advanced mental disturbance. He died, 41-years old, in a state of general deterioration. No autopsy was performed.

The nephew of the two brothers (III-2 in Fig. 1) had suffered from a severe, bilateral neural hearing loss since the age of 1 year. When 10 years old he underwent a thorough neurological examination with the additional finding of an incipient demyelinating optic nerve lesion. A CT scan of the brain revealed a moderate cortical atrophy but no calcifications. The clinical neurological examination was otherwise normal with no sign of dementia. However, this was also to be expected as neurological and mental disturbance was first diagnosed in the two uncles in the third decade. He had normal serum levels of calcium and phosphate. The function of the parathyroid glands was normal. His karyotype was 46, XY.

The clinical findings have been described in more detail elsewhere [7, 8].

Autopsy (II-4 in Fig. 1)

The body was thin, the skin normal, and the muscles atrophic. There were contractions of the hands and elbows. Examination of the organs revealed that they were macro- and microscopical normal apart from severe bronchopneumonia, chronic ulcerations of the oesophagus, hepatic steatosis, and slightly atrophic testes; especially no calcifications and arteriosclerosis were present. The parathyroid glands were not examined.

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Examination of the central nervous system

Macroscopic. The fixed brain weighed 1200 g. The leptomeninges, especially of the hemispheres, were significantly thickened. The vessels were normal. No atherosclerotic plaques, thrombi, and anomalies were seen. The gyri were atrophic.

Coronal sections (Fig. 2A, C) of the brain revealed slightly enlarged and symmetrical ventricular system, diffuse atrophy of the gyri and the white substance, especially of the left occipital pole, and normal basal ganglia. Grittiness of the cut surface was noted. The brain stem, cerebellum, and the spinal cord looked normal. The roots were thin.

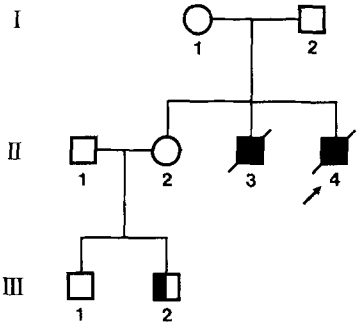

Fig. 1. Pedigree of the family. The *arrow* indicates the propositus. ■ Infantile deafness, optic atrophy, and dementia, dead. ◧ Infantile deafness, incipient optic nerve lesion and cortical atrophy

Roentgenographic. X-ray (Fig. 2B, D) of the cerebral hemispheres and the cerebellum visualized symmetrical, bilateral calcifications following the brain surface and the vessels running from the arachnoidea-pia through the cortex to centrum semiovale. In the white matter, the basal ganglia, and the dentate nucleus the calcifications were present as fine white granules. The calcification was so typical that proper interpretation can hardly be missed.

Microscopic. For microscopic examination tissue was cut from chiasma, all cortical regions, the white matter, the basal ganglia, choroid plexus, cerebellum, brain stem, spinal cord, and roots. Furthermore, peripheral nerves and muscles from the upper and lower extremities were removed for investigation. Paraffin-embedded sections were stained by haematoxylin-eosin, toluidine blue, van Gieson-Hansen, Weil, PAS, van Kossa, Perls' Berlin blue, Kongo, phosphotungstic acid hematoxylin (PTAH), Bodian, and glial fibrillary acidic protein (GFAP). Scharlach Rot was performed on frozen sections.

Chiasma

The optic nerves and chiasma were atrophic with diffuse demyelination and gliosis, and a few small calcifications. Along the third ventricular wall narrowed bands of calcium compounds were noted (Fig. 3A).

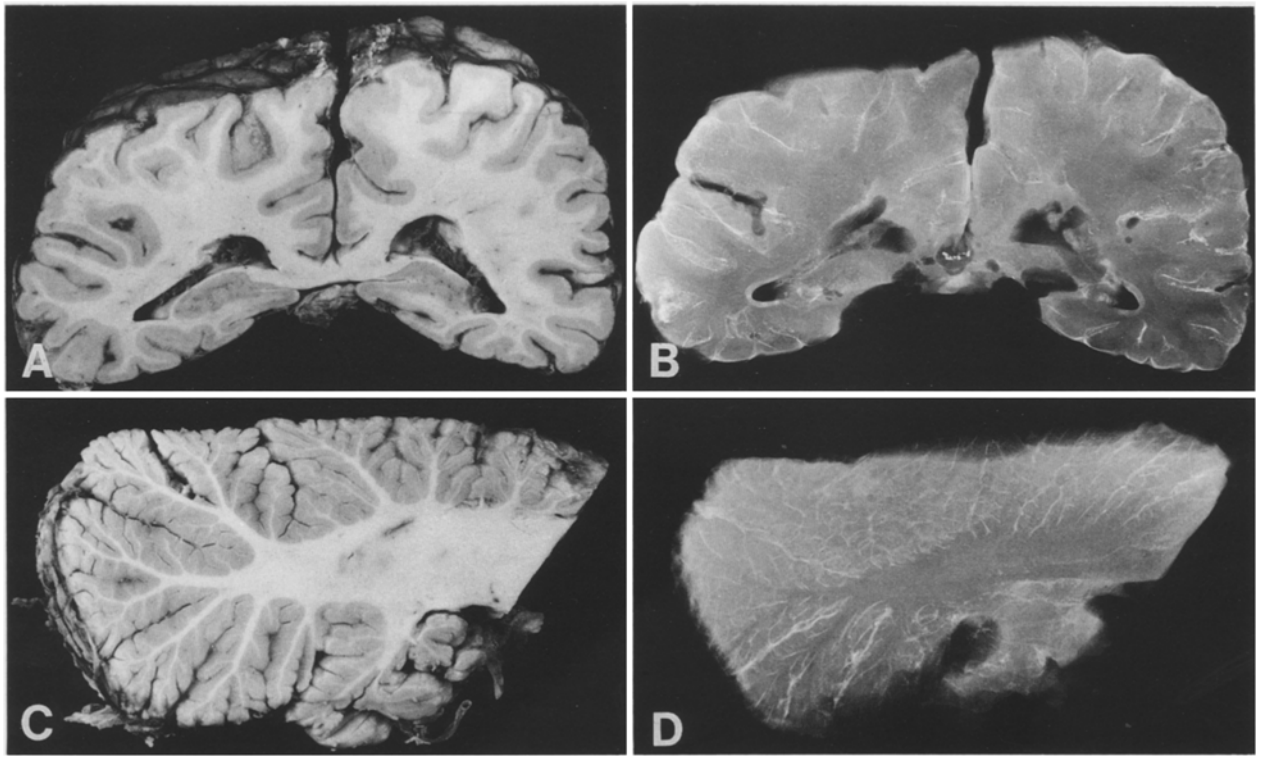

Fig. 2. **A** Coronal section through the posterior parietotemporal region of the brain. The leptomeninges are blurred, the cortex narrow, and the ventricular wall granular. **B** X-ray of same region as **A**. Calcifications are visualized as white streaks following the arachnoidea-pia and running from the leptomeninges through the cortex to centrum semiovale, as fine white dots in the white substance and as a narrow band limiting the posterior horns. **C** The left cerebellar hemisphere. Blurred leptomeninges and slightly atrophic gyri are seen. **D** X-ray of the same region as **C**. Along the surface and following the vessels fine white streaks of calcifications are noted. White dots revealing calcium compounds in the white matter

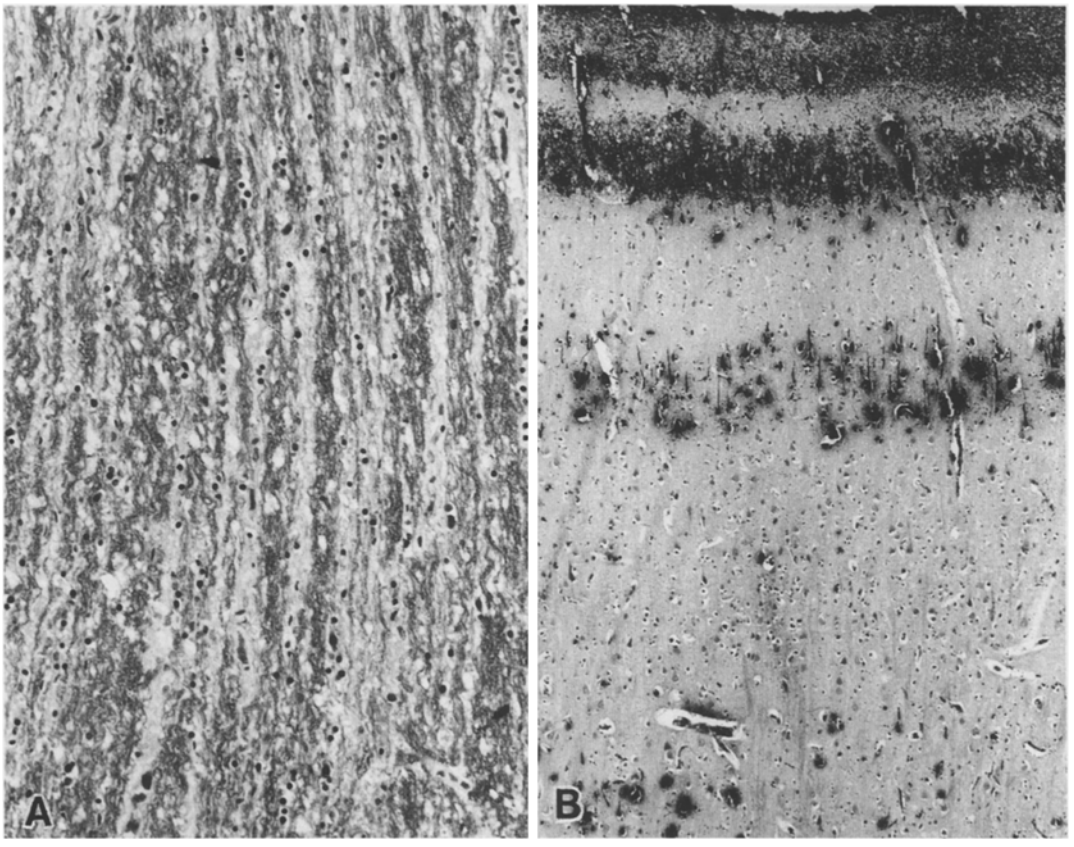

Fig. 3. A Longitudinal section of the optic nerve. Diffuse demyelination. The remaining myelin sheaths are unevenly calibrated and fragmented. **B** Cortex of the right insula. Layers of diffuse calcification and calcified nerve cells alternating with light bands. Vessels are incrustated. **A** Weil, **B** van Kossa; ×125

The cerebral hemispheres

The leptomeninges were fibrous with extensive calcifications, both as fine granules and as coralliform concretions freely lying in the subarachnoid space. Deposits of calcifications were present in the vessel walls of the medium-sized arteries and veins in a varying part of the circumference and in a varying number of the layers. Sometimes obstruction of the lumen of the vessel was caused by protruding incrustations.

In the cortical convolutions in all regions alternating parallel layers of calcareous deposits were found dispersed in the tissue. They were invariably limited to the top of a gyrus, spreading to both sides of the highest point.

The outer part of the molecular layer (layer I) consisted of closely packed dust-like and particulate deposits and this was separated from the likewise calcified external granular layer (layer II) by a narrow light band. In the deep area of the external pyramidal layer (layer III) a broad band of calcium-incrusted nerve cells were present (Fig. 3B). The following broad light band contained scattered calcified nerve cells and in the deepest part of the cortex many calcified vessel walls were seen, and between them incrusted nerve cells. Through the whole width of the cortex rows of tiny calcopherites were seen lying along capillaries, coalescing to a sheath-like investiture of the wall, which was especially seen in the hippocampus. The small- and medium-sized arteries and veins contained tubular deposits in their walls. In the white matter the calcium compounds were primarily located to the vessels forming calcareous rings in adventitia and media. In Virchow-Robin's spaces larger concretions appeared developed by coalescence of perivascular deposits (Fig. 4A), but freely lying calcium salt deposits were also seen. The staining for iron was negative both in leptomeninges, cortex and white substance.

The basal ganglia revealed calcified nerve cells and vessels and freely lying deposits in all areas. Along the ventricular walls an irregularly limited band of calcium compounds, calcified vessels, and cells were observed. Then a light band followed containing calcified astrocytes and close to the ependyma a broad layer of dust-like and granular calcium material was present. The ependymal cells, and to a lesser extent the plexus, were black in van Kossa staining and calcareous compounds walled off the ventricles. In the basal ganglia the staining for iron was positive (Fig. 4B).

In connection with the extensive calcification of the cerebral hemispheres, the nerve cells were destroyed and gliosis had developed. The changes were especially pronounced in the convolutions of occipital lobes. Status spongiosis, extensive loss of nerve cells and considerable gliosis were present. The white substance of the hemispheres was conspiciously well preserved. Leucomalacia was not observed, but some degeneration in relation to calcified areas was seen.

Cerebellum

The distribution of the calcifications were well demonstrated in van Kossa preparations (Fig. 5A). The molecular layer showed broad bands of calcium deposits on top of the gyri, and calcified

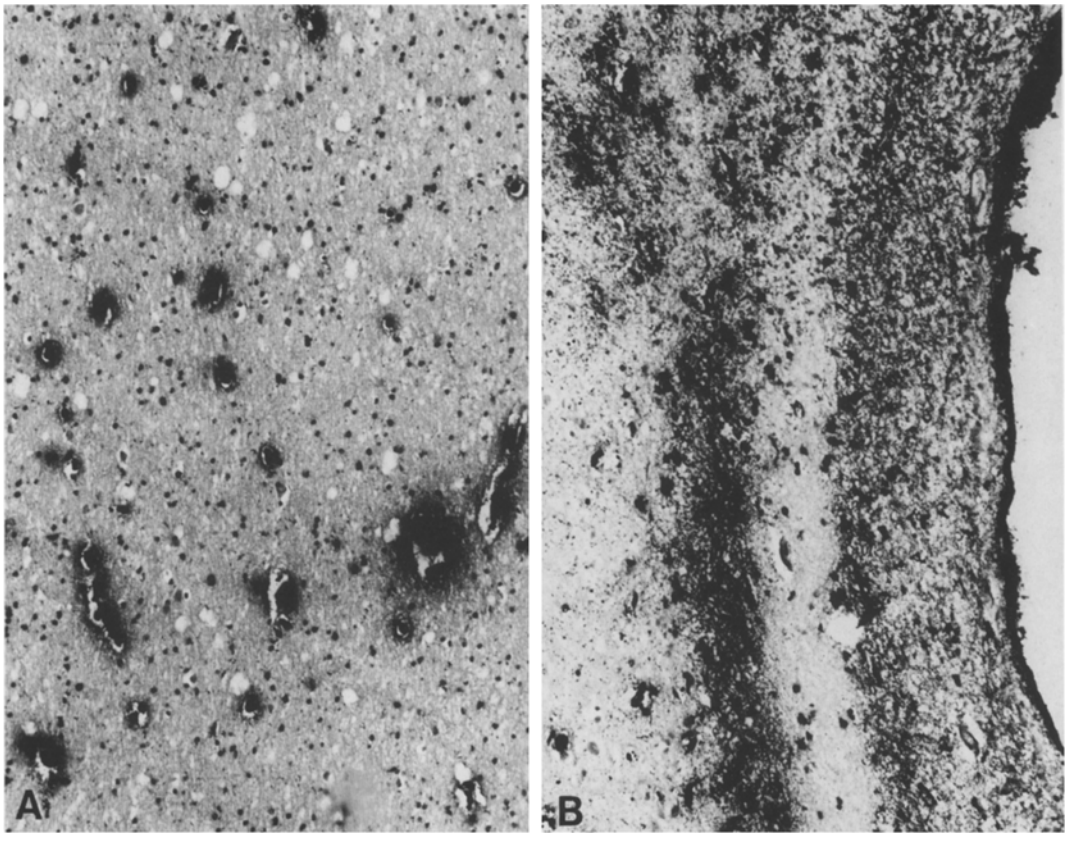

Fig. 4. **A** White matter of the right hemisphere. Numerous calcified vessels surrounded by concretions. **B** Left ventricular wall. Extensive calcifications in the nerve tissue. Note the limiting dark membrane against the lumen. **A, B** van Kossa; ×125

astrocytes were present on both sides of this layer. Purkinje cells were lost and the remaining cells calcium-incrusted both of the cell bodies and their processes. The Bergmann cells could be calcified, too. The granular layer was thinned out and contained calcium deposits. In the white matter and the dentate nucleus concretions could be seen in the neuropil, the vessels, and in the glial cells as well as in the neurons. Secondary degenerative processes and gliosis were noted. The arachnoidea-pia showed calcification.

Brain stem

The calcium compounds were localized in the leptomeninges, in the vessels, along the periphery, and around the aqueduct and fourth ventricle. Scattered calcified nerve cells were present among healthy-looking neurons. The white matter was well preserved. Both gliosis and microglial cells were seen.

Spinal cord

The deposit of calcium compounds followed the same pattern as in the brain. It was seen in the leptomeninges, the vessels, and as dust-like and particulate deposits along the periphery of the cord. The horns contained several calcium-incrusted nerve cells including the nerve cell bodies and the processes (Fig. 5B).

Loss of motor nerve cells and gliosis was present. The white matter was thinned out and bundles of glial fibrillary processes were present in the posterior columns. The roots and peripheral nerves revealed some demyelination, but no calcification. In the muscles, a secondary neurogenic atrophy was present.

Conclusion

The investigation of the central and peripheral nervous system showed heavy calcification of the leptomeninges including the vessels, curvilinear bands in the molecular layer on top of the convolutions of the cerebral and cerebellar cortex, and bands of calcified nerve cells alternating with light areas in the cerebral cortex. In the white matter and the basal ganglia coralliform or mulberry concretions were present freely dispersed in the neuropil or in relation to calcified vessels, and calcium salts walled off the ventricles. The incrustations followed the same pattern in the brain stem and spinal cord; also nerve cells were calcified. All over the CNS gliosis was present.

The central and peripheral nervous system did not reveal morphological signs of known metabolic lesions, Alzheimer's disease, atherosclerosis, amyloidosis, or inflammatory disorders.

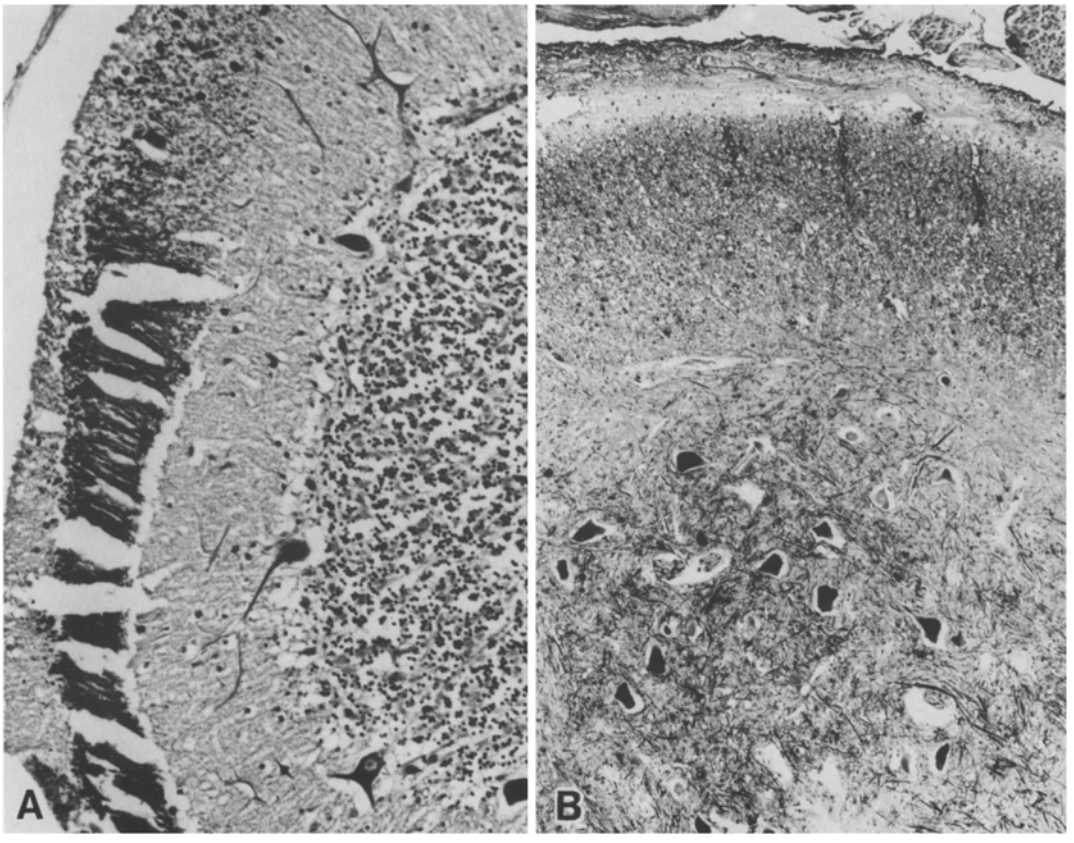

Fig. 5. **A** Right cerebellar hemisphere. A broad band of calcium compounds in the molecular layer. Note loss of Purkinje cells and calcification of the remaining cells. **B** Lumbar spinal cord. Calcium deposits in the leptomeninges, vessels, white substance, and the anterior horn. Note the incrusted nerve cells. **A, B** van Kossa; ×125

Discussion

Calcification of the brain is not an unusual observation and it may be detected as an incidental finding by computerized tomography. It is most often found in the basal ganglia without accompanying clinical features [4]. Several different conditions may, however, be associated with calcifications, such as endocrine disturbances and genetic disorders. In brains from very old persons it is a frequent finding, but also vascular lesions, anoxia, and infectious diseases such as encephalitis and parasitosis may be followed by calcification [4]. Chronic renal failure is another condition where cerebral calcium may be observed [16]. A special type of intracranial calcification of unknown nature is the so-called vascular non-arteriosclerotic bilateral calcification of the brain [11, 12]. The localization and the amount of incrustations vary from one type of disease to another. The diagnosis of calcium deposits can easily be made by CT scan of the brain; this investigation provides impressive information as to the extent and localization of the lesions, which are so typical that proper interpretation can hardly be missed [3, 4]. As mentioned, the disorder can be silent, but a variable pattern of clinical features may be observed [4, 5, 10, 14, 15]. At autopsy, brain calcification may be observed in the leptomeninges and in the parenchyma as brain stones consisting of huge, confluent masses, while smaller deposits may reflect the light and cause grittines of the cut surface. X-ray examination of the brain sections reveals only the larger deposits. The concretions of the brain are confirmed by microscopy, and in many brains the calcium deposits are only seen at the microscopic level. Histochemical techniques has shown that calcium is usually mixed with metals, as for example iron and copper, and a chemical determination on non-formalin-fixed material can give valuable information on the quantitative content of metals [11, 12].

The disorder described in the present study was familial and the pedigree suggested an X-linked recessive inheritance. The two brothers had an identical clinical course and their 10-year-old nephew had initial clinical signs of the same disorder corresponding to the age. He revealed no sign of parathyroid dysfunction or other metabolic disorders. A CT scan showed light

cerebral atrophy but no calcifications. In the propositus, calcium deposits were suspected at the autopsy and confirmed by X-ray examination of brain sections and by microscopy using advanced histological techniques. However, no biochemical analysis was performed. The autoptic finding of severe and widespread calcifications of the CNS was surprising. The distribution of calcium deposits followed a very unusual pattern in the present case. The brain and the spinal cord were encompassed by calcified leptomeninges and vessels and calcium incrustations walled off the ventricles. Between the outer and inner limits of the brain and spinal cord calcified curvilinear bands were observed in the molecular layer of the cerebral and cerebellar cortex on top of the convolutions, as a broad layer in the ventricular wall, and in the spinal cord along the periphery of the white matter. Parallel layers of incrustated nerve cells were present in the cerebrum as well as freely dispersed concretions in the white matter and basal ganglia. In all areas calcified vessels were present. The neuropathological findings were in accordance with the clinical symptoms and signs. Because of no suspicion of disturbance of calcium metabolism no investigation of calcium was performed when he was alive.

Basal ganglia calcifications can be seen in dysfunction of the parathyroid gland [2, 5], but also in patients without endocrinological symptoms [11]. In juvenile diabetes mellitus silent calcium deposits have been detected microscopically in the globus pallidus in 8 of 16 cases, and in the dentate nucleus of the cerebellum in 2 of the 16 diabetics [14]. Grotemeyer et al. [3] published two cases of juvenile diabetes combined with mitochondrial myopathy and epilepsy and he found, by CT scan, symmetrical calcifications of the basal ganglia. The striopallidodentate calcification may also be observed in patients without demonstrable endocrinological disorders [4] and without clinical features, but familial cases with ataxia and pigmentary macular degeneration have been reported [11].

Secondary cerebral calcifications may be seen in several well-defined diseases. Using CT scans, Sly et al. [15] detected scattered dense cerebral calcifications prevalent in the basal ganglia in 12 unrelated families with a deficiency of carbonic anhydrase II, and in children with renal failure Swartz et al. [16] described curvilinear calcification of the base of the cortical sulci combined with heavy basal ganglia incrustations. In the cerebro-oculo-facio-skeletal (COFS) syndrome symmetrically located intracranial calcification are observed by CT scan and by microscopy in the region of the lenticular nucleus and the white matter of the frontal and occipital lobes. The autopsied brain was small and firm. The cortex had few or no neurons [10]. Kobayashi et al. [9] stress that in idiopathic non-arteriosclerotic cases the calcium deposits are especially found in the deep cortex and not observed in the Purkinje cells and plexus and he did not mention calcifications of the leptomeninges and of the ventricular wall.

In the present study the brain thus showed a distribution of calcium deposits that is different from those described earlier. However, the distribution is not unique, as a similar pattern has been observed in two cases of arthrogryposis multiplex congenita in a family with autosomal recessive inheritance [6] and in the Prader-Willi syndrome, which is frequently associated with chromosome anomalies (Reske-Nielsen, unpublished observations). In contrast, the autosomal dominant disorder described by Boller et al. [1] showed quite a different distribution of calcifications in the CNS. The calcification of the CNS observed in the present case is suggested to be an unspecific secondary reaction to a fundamental dysfunction of the central nervous system. The particular pattern of the calcium distribution might indicate an unknown disturbance of cellular metabolism.

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References

1. Boller F, Boller M, Gilbert J (1977) Familial idiopathic cerebral calcifications. J Neurol Neurosurg Psychiatry 40:280–285
2. Friedman JH, Chiucchini MJ, Tucci JR (1987) Idiopathic hypoparathyroidism with extensive brain calcification and persistent neurologic dysfunction. Neurology 37:307–309
3. Grotemeyer KH, Lehmann HJ, Jörg J, Reinhard V, Hartjes W (1984) Familiäre Stammganglienverkalkung, mitochondriale Myopathie und Epilepsie – Folge einer einzigen Stoffwechselstörung? Nervenarzt 55:202–207
4. Harrington MG, Macpherson P, McIntosh WB, Allam BF, Bone I (1981) The significance of the incidental finding of basal ganglia calcification on computed tomography. J Neurol Neurosurg Psychiatry 44:1168–1170
5. Illum F, Dupont E (1985) Prevalence of CT-detected calcification in the basal ganglia in idiopathic hypoparathyroidism and pseudohypoparathyroidism. Neuroradiology 27:32–37
6. Illum N, Reske-Nielsen E, Skovby F, Askjær SA, Bernsen A (1988) Lethal autosomal recessive arthrogryposis multiplex congenita with whistling face and calcifications of the nervous system. (in press)
7. Jensen PKA (1981) Nerve deafness, optic nerve atrophy and dementia: a new X-linked recessive syndrome? Am J Med Genet 9:55–60
8. Jensen PKA, Reske-Nielsen E, Hein-Sørensen O, Warburg M (1987) The syndrome of opticoacoustic nerve atrophy with dementia. Am J Med Genet 28:517–518

9. Kobayashi S, Yamadori I, Miki H, Ohmori M (1987) Idiopathic nonarteriosclerotic cerebral calcification (Fahr's disease): an electron microscopic study. Acta Neuropathol (Berl) 73:62–66
10. Linna S-L, Finni K, Similä S, Kouvalainen K, Laitinen J (1982) Intracranial calcifications in cerebro-oculo-facio-skeletal (COFS) syndrome. Pediatr Radiol 12:28–30
11. Löwenthal A (1986) Striopallidodentate calcifications. In: Vinken PJ, Bruyn GW, Klawans HL (eds) Handbook of clinical neurology, vol 49. Elsevier, Amsterdam New York, pp 417–436
12. Löwenthal A, Bruyn GW (1968) Calcification of the striopallidodentate system. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology, vol 6. North Holland, Amsterdam, pp 703–725
13. Oppenheimer DR (1984) Diseases of the basal ganglia, cerebellum and motor neurons. In: Adams JH, Corsellis JAN, Duchen LW (eds) Greenfield's neuropathology, 4th edn. Arnold, London, pp 699–747
14. Reske-Nielsen E, Lundbæk K, Rafaelsen OJ (1965) Pathological changes in the central and peripheral nervous system of young long-term diabetics. I. Diabetic encephalopathy. Diabetologia 1:233–241
15. Sly WS, Whyte MP, Sundaram V, Tashian RE, Hewett-Emmett D, Guibaud P, Vainsel M, Baluarte HJ, Gruskin A, Al-Mosawi M, Sakati N, Ohlsson A (1985) Carbonic anhydrase II deficiency in 12 families with the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. N Engl J Med 313:139–145
16. Swartz JD, Faerber EN, Singh N, Polinsky MS (1983) CT demonstration of cerebral subcortical calcifications. J Comput Assist Tomogr 7:476–478

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