A new familial infantile form of diffuse brain-sclerosis. By Knud Krabbe, MD Copenhagen. From Queen Louise's Hospital for Sick Children (Professor Monrad), and from the Children's Department of the University Hospital, Copenhagen (Professor Bloch). Brain 1916; 39: 74–114

Knud Krabbe (1885–1961) has already described a child, aged 1 year, with ‘perivascular necrosis of the medullary substance’, which he considers to be the preliminary stage of ‘diffuse sclerosis of the brain’. Now he has access to the details of five others cases observed at the Dronning Louise's Bernes hospitaal (Queen Louise's Hospital for Sick Children) and in the private practice of Professor (Carl Edward) Bloch (1872–1952). Two families have affected sibling pairs, and one is isolated. Although not previously reported, these cases have been discussed at meetings of the Paediatric and Biological Societies of Copenhagen by Professor (Sven) Monrad (1867–1945), Dr Poulsen (nk) who has held back from reporting the cases himself, Dr Joergen Bech (nk) and Professor Bloch. Dr Krabbe has been helped by Professor (Carl) Friedenreich (nk) from the Psychiatrical Laboratory of the University of Copenhagen, whereas most of his own work has been carried out in the Children’s Department of the Rigshospitalet.

Kai Bn starts to regress at 5 months with frequent crying and gasping; extensor spasms of the neck, trunk and limbs; and inability to sit (Fig. 1). He is periodically pyrexial and loses weight. Eventually Dr Poulsen summarizes the case as showing intense stiffness of the extremities with tonic spasms, gasping and cyanosis induced by noise or physical examination, and with optic atrophy, after which the child gradually becomes stuporose dying on 29 December 1913 aged 13 months. The diagnosis is ‘sclerosis cerebri diffusa’. At post-mortem, the brain is small and hard in consistency. Histologically, the most obvious feature in the cerebral hemispheres is extensive destruction of medullary sheaths in the white matter with a preserved rim under the cortex, the destruction increasing towards the centre of the cerebrum and especially, around the larger blood vessels. Whereas cortical neurones are intact, there is extensive loss of axis cylinders corresponding to changes in their medullary sheaths. These abnormal areas are characterized by intense overgrowth of glial cells and their fibres (Fig. 2); a few cells contain fatty granules but no accumulation of plasma cells, lymphocytes or polymophonuclear leucocytes (Figs 3 and 4); and the blood vessels are normal. By comparison, the cortex is relatively unaffected (Fig. 5). Appearances in the anterior visual pathway and cerebellum are just as marked, whereas they are slightly less conspicuous in the mid-brain, and reduce towards the pons. The medulla and spinal cord show extensive loss of axis cylinders and their medullary sheaths especially affecting the pyramidal tracts, and proliferation of glia.

Kai’s older sister, Bodil Bn, is stiff at birth and starts to regress mentally from 4 months with an increase in episodes of stiffness of the neck and limbs, which have been present intermittently from birth, with crying and cyanosis (Fig. 6). When first seen she appears stupid, has optic atrophy, nystagmus, and lies in a posture of opisthotonos with rigid extended legs and tetanic hands further accentuated by periodic violent spams provoked by light or touch that leave her in an arc en cercle. Bodil is intermittently pyrexial and gradually lapses into coma dying on 6 February 1912, shortly before her first birthday. At post-mortem, the brain is hard due to diffuse sclerosis and the cut appearance shows normal appearing cortex with an intact rim of white matter fading into obviously abnormal tissue more centrally. Histologically, the meninges are oedematous; the cortex is normal apart from some loss of pyramidal cells and an abundance of blood vessels, without inflammatory cells, that shades into the abnormal white matter. This shows extensive loss of the myelin sheaths and axis cylinders with widespread proliferation of glia and more obvious fat laden scavenger cells than Case 1 (Kai Bn). There is relative sparing of the occipital lobes but the cerebellum, and optic and facial nerves, are involved. The spinal cord also shows vascular proliferation, extensive loss of myelin sheaths and selective tract degeneration, with extensive gliosis.

Apart from a convergent squint at birth, Agnes AB is normal until aged 5 months when she develops episodes of stiffness with screaming during which she has opisthotonos, extended legs and flexed arms. These attacks continue as she gradually becomes drowsy and persistently rigid with nystagmus, dying on 8 June 1905 aged 9 months. Post-mortem examination shows oedematous meninges with marked atrophy of the brain. Histological examination is not reported. Her younger sister, Gudrun Marie AB, is never admitted to hospital but Professor Bloch reports a more or less similar presentation and evolution of her illness with death in February 1907, aged 1 year. ‘The parents taking an interest in whether or not the child had suffered from the same affection as her sister, Dr Bloch was permitted to perform the autopsy at the home’. The brain is hard but with no outwardly abnormal appearance. The cut surface shows a normal cortex and underlying rim of white matter but with a ‘reddish, somewhat
marbled, grey colour’ more centrally. Histologically, the white matter of the cerebrum, apart from the subcortical rim, is almost completely destroyed with an enormous increase in protoplasmic glia and infiltration of fatty granule laden scavenger cells. Frederick Ernst Ed develops episodes of screaming with tetanic rigidity of the arms in flexion, the legs extended, and kyphosis after which he starts to regress mentally and drifts into coma dying on 28 September 1906 aged 11 months. At autopsy, the meninges are oedematous and the glial tissue ‘appeared to be increased’ but no further details are reported.

With some minor variations, and despite the limited histological evidence in three cases, it is reasonable to consider that these five children all suffered from the same condition. Now Dr Krabbe summarizes the situation: ‘the clinical picture...is very characteristic, but I should not dare to use it as the only point of support for the diagnosis’; acute onset at 4–5 months in children who previously were healthy; a prodrome of episodic screaming and crying; rigidity with opisthotonos, flexion of the arms and extension of the legs but sparing the face—the tonic spasms often being induced by noise, light or touch; no further development of mental faculties after onset of the spasms; optic atrophy and persistent nystagmus but sparing of special and somatic sensation; intermittent pyrexia in the absence of infection with vomiting and diarrhoea, perhaps reflecting involvement of temperature-regulating systems in the brain; and the condition gradually passing into an agonal relaxed paralytic state.
What remains unclear is whether this progressive process is 'a variety of tumour-growth...a repaired inflammatory process...or a simple degeneration of the nerve processes'. In view of the distribution of tissue damage confined to deep white matter and with selective loss of some descending tracts but sparing others, tumour can be discounted. The same argument applies to inflammation even if one allows that the infiltration with plasma cells, lymphocytes and polymorphonuclear leucocytes may have 'passed away'. In all these respects, Dr Krabbe is struck by similarity with the case he has previously described as having 'perivascular destruction...and heaping up of glia-cells is not the primary but the secondary factor and the natural consequence of the diffuse destruction of the medullary sheaths and axis-cylinders...I have now come to the...possibility, which is in my view the most probable...that the affection is a...degenerative process, analogous to such degenerations as are frequently found in certain hereditary or familial nervous affections...for instance Friedreich's disease...with glia proliferation and infiltration of the medullary sheaths with gliogenous fatty granule-cells and other scavenger cells...a secondary process.'

So where should this disorder be placed within the general nosology of neurological disease? Did the cases suffer from congenital syphilis? The CSF was examined in some of the five cases but always normal. (Paul Ferdinand) Schilder (1886–1940) has reviewed published cases of diffuse sclerosis in children classifying four as having 'encephalitis periaxialis diffusa', a variant of disseminated sclerosis 'due to reparative inflammation'—a designation and mechanistic interpretation that Dr Krabbe does not dispute even though he considers it not relevant to his own cases on the basis that they begin in infancy, are familial and show no evidence for active inflammation. 'Disseminated sclerosis is very rarely of familial occurrence; in fact, authors such as Müller will not acknowledge cases of familial appearance as disseminated sclerosis...and this disease is very seldom found in children'. Rather, Dr Krabbe's cases belong to the familial nervous affections: 'there is just as deep a separation between my cases and Schilder's encephalitis periaxialis diffusa as between Friedreich's disease and disseminated sclerosis'. But to which of these groups do they belong—Pelizaeus-Merzbacher disease, also known as 'aplasia axialis extra-corticalis congenital', or Tay-Sachs type of familial amaurotic idiocy? There are elements of both: the early onset with extensive destruction of white matter favours the former; whereas the inexorable progression favours the latter. Taken together,

'my cases...show pictures so distinct from all other cases...that I am entitled to regard them as a special group within the familial nervous diseases...to which the name of familial early infantile brain sclerosis may rightly be given.'

Perhaps only one case previously described matches this description. Benecke (nk) has reported a boy, dying before his second birthday, in whom the characteristic extensive white matter destruction, 'progressive in the brain and finished in the spinal cord', with preservation of a sub-cortical rim and glial proliferation is present especially around blood vessels. Indeed, Dr Krabbe is dismissive of the statement by (Julius) Zappert (1867–1941) in Pflaudler Schlossmann's Text-book that the disease is of frequent occurrence in small children. As for Brain, we have published only five further papers on the disease first described in 1916 by Dr Krabbe including that by Marco Presta and colleagues in the current issue (page 2859).

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