Syndrome of the month

Nasu-Hakola syndrome: polycystic lipomembranous osteodysplasia with sclerosing leucoencephalopathy and presenile dementia

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Presenile dementia of genetic origin is often attributed to Alzheimer's disease. This disorder remains by far the commonest cause of early dementia. Pick disease and prion protein disorders are usually discussed in the differential diagnosis. We review here Nasu-Hakola syndrome (OMIM 221770), another unusual cause of presenile intellectual deterioration, in which neurological impairment occurs together with impressive destructive changes of the skeleton.
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Historical aspects

The first reports of Nasu-Hakola syndrome (NHS) are attributed to Terayama[1] in 1961 and Järvi *et al*[2] in 1964, but the eponym recognises the major contributions to the delineation of the phenotype of Hakola,[3] who described nine patients from seven Finnish families in 1972, and Nasu *et al*,[4] who almost simultaneously reported one Japanese patient (and indeed diagnosed the patient reported by Terayama[1]). The disorder is often (but cumbersomely) termed polycystic lipomembranous osteodysplasia with sclerosing leucoencephalopathy in Finnish publications and membranous lipodystrophy by Japanese authors.

Illustrative case report

The patient is the only male child of a Belgian mother (father unknown), born in 1948, without known ancestry from northern Europe. The first stage of the disease was characterised by multiple quasi-spontaneous fractures of the extremities beginning at the age of 26, initially affecting the carpal and tarsal bones and later the tibiae and femora. Steatorrhoea appeared at the age of 41. Disturbances of mood appeared in his late thirties, followed by a rapid deterioration first noted at 40 years; there were loss of social skills, aberrant or manic behaviour, incontinence, aggressiveness, loss of memory, and confabulations. Within one year, dementia became obvious and he became bedridden and unconscious. Right focal, secondarily generalised seizures appeared. Death occurred at the age of 45 years. Permission for necropsy was refused.

Neurological assessment at the age of 42 was basically normal; there were no pyramidal or cerebellar signs, but mild apraxia, dyscalculia, and spatial disorientation. Psychiatric assessment suggested frontal dysfunction (decreased verbal fluency, perseveration, poor memory, loss of social inhibitions, and confabulation). Folstein's mini mental score was clearly in the dementia range. IQ was 54 (WAIS). EEG showed a persistent basal rhythm with posterior theta and slow waves (7-8 Hz). CT scan showed slight hemispheric atrophy. PET scan with [^{18}F] fluorodeoxyribose showed a normal global glucose metabolic rate (4.69 ± 0.65 mg/100 g/min). Regionally, the highest levels were in the occipital lobes, whereas they were lower in the frontal, temporal, and parietal regions and in the thalamic nuclei, and markedly decreased in the medial frontal area and basal ganglia.[5] Major steatosis of the liver was observed.

Epidemiology and genetics

The disorder has been observed in fewer than 150 cases (because of multiple reports of some patients, and of unpublished, but quoted cases, precise counting is difficult). Most cases come from two widely separated groups, the Japanese and the Finnish population of northern Scandinavia. At least 84 cases have been identified in Japan,[4 6–27] 30 cases in central-eastern Finland,[2 28 29] 11 in northern Sweden,[30] three in Norway,[31] four in a North American sibship of Czechoslovakian origin,[32] one in Austria,[33] two in Italy,[34–36] one in the USA,[37] one (of Afrikaner descent) in South Africa,[38] and one in Turkey.[39] Our illustrative patient appears to be the first case of this uncommon disease from western Europe.

NHS is clearly recessive and affects both sexes equally. Consanguinity has been observed in several instances.[3 10 11 13 21] There is no genetic mapping information at present.

Clinical features

NHS is a fatal disorder. No specific treatment is known. Hakola[3] divided the natural history of the disorder into four stages.

(1) *Latent stage.* This (probably) asymptomatic period extends to early adulthood.

(2) *Osseous stage.* Pain and swelling of the wrist and ankle following strain usually appear between the ages of 20 and 30 years, although some cases may already be symptomatic at the age of 10.[17] Fractures may occur after minor accidents. Radiographs show cystic rarefaction in the epiphyseal regions of the phalanges, metacarpal/tarsal, carpal, tarsal, and long bones. Metaphyseal cysts replace cancellous bone. They are filled with a jelly-like, partially necrotic lipidic material. Skeletal symptoms are often mild and in most cases the diagnosis is made after the onset of neuropsychiatric symptoms. In some cases, skeletal symptoms are delayed after the onset of stage 3.[12]

(3) *Neuropsychiatric stage.* Symptoms begin in the third or fourth decade and consist of progressive dementia with a predominant prefrontal syndrome. Agnosia, apraxia and motor aphasia, impairment of memory, euphoria, and loss of social inhibitions are conspicuous features,[40 41] leading to major psychosocial and family problems.[42] Spastic paraparesis is commonly observed, and extrapyramidal symptoms, myoclonus, or epileptic seizures occur frequently. Primitive reflexes may reappear.[41] The EEG is often typical, showing synchronous, episodic, and diffuse 6-8 Hz activity, the alpha rhythm being replaced by amorphous theta and delta activities.[43] Rarer manifestations include paralytic ileus,[32] megacolon,[32] incontinence resulting from inhibition of detrusor activity,[15 25] and impotence. Peripheral nerve conduction velocity is normal[38] or altered in a way compatible with a diagnosis of motor-sensory neuropathy.[44 45] In the only patient with published evoked potentials,[38] central conduction was surprisingly normal. Fundi may show nerve fibre layer defects or optic atrophy or both.[46] Fanconi tubulopathy[19] and chronic myeloid leukaemia[32] were observed in one case each and may be coincidental.

(4) *Dementia stage.* The patients die between the ages of 35 and 45, with cachexia and frequently with epileptic seizures. The mean duration of the clinical course after onset of neuropsychiatric symptoms is 10 years. Death usually results from chest infection. Acute renal failure was reported in one case.[21]

Radiology (fig 1)

SKELETON

The lesions involve all areas of cancellous bone. Multiple, symmetrical, non-expansile cysts lined by thin, non-sclerotic margins are located in the epiphyseal and metaphyseal areas of the long bones, patellae, and all bones of the hands and feet. Remaining trabeculae tend to have a longitudinal alignment.[47] Involved areas show increased 99Tc-methylene diphosphonate uptake.[48] The mineral density of the cortical bone is decreased.[49]

CENTRAL NERVOUS SYSTEM

Typically, CT neuroimaging shows cortical and central atrophy, accentuated in the frontal lobes, and occasionally cerebellar atrophy. The signs are sometimes visible before the onset of neuropsychiatric symptoms.[41 50 51] Hyperdensity or calcification of the basal ganglia are often observed.[7] In T2 weighted mode, MRI usually shows a low density of basal nuclei[24 26] (putamen, globus pallidus, caudate nucleus, thalamus) and a low intensity of periventricular white matter.[51]

Pathology

ADIPOSE TISSUE AND BONE MARROW (FIG 2)

Membranous lipodystrophy is a peculiar form of fat tissue necrosis. Histologically, the anomalies are referred to as membranocystic lesions. They have two components: cystic spaces filled with triglycerides and 1-2 μm thick

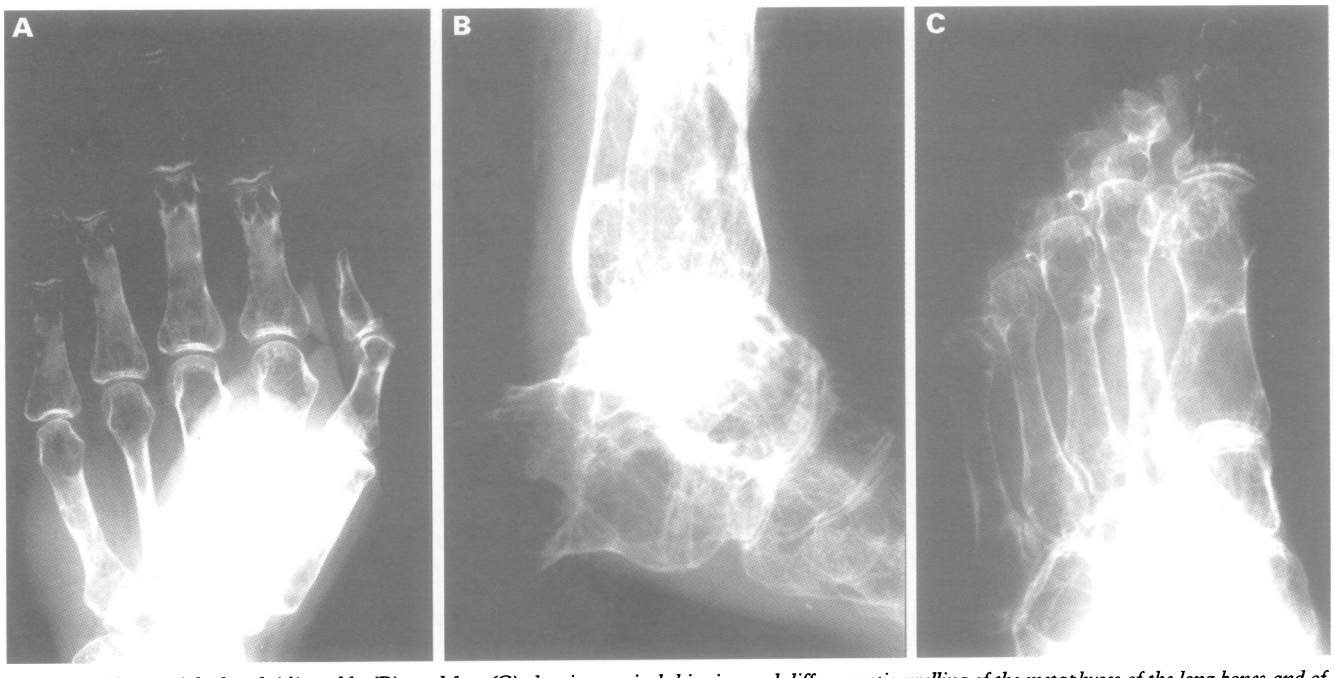

Figure 1 X rays of the hand (A), ankle (B), and foot (C) showing cortical thinning and diffuse, cystic swelling of the metaphyses of the long bones and of the small bones of the extremities.

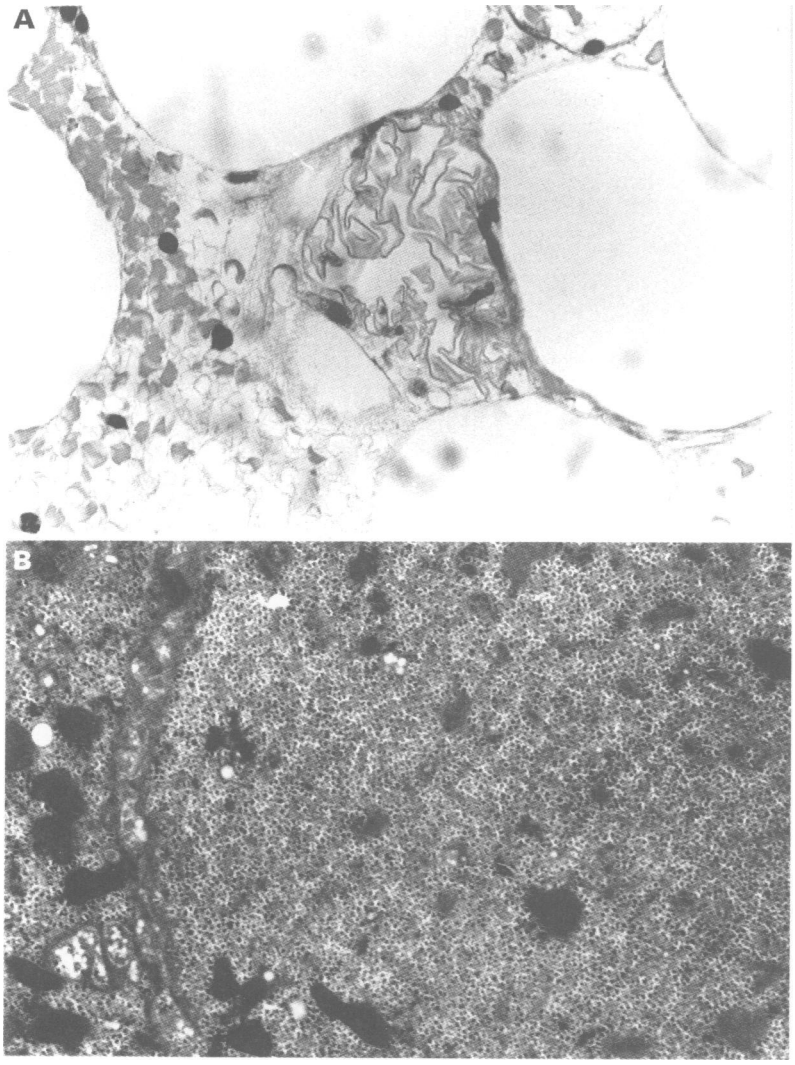

Figure 2 (A) Bone biopsy: erosion of the cortical bone and medullary hypoplasia. The bone and the haematopoietic tissue are partially replaced by a pathological tissue formed by large cysts originating from adipocytes. They are limited by irregular membranes made of a granulofibrillary material (haematoxylin-eosin, GB4 embedded, 2 μm, × 250). (B) On EM, these membranes compose a network with invaginations and vesicular or tubular structures lined by amorphous deposition (× 40 000).

membranes. The latter are autofluorescent, convoluted, eosinophilic, PAS positive, membranous and lamellar structures made of carbohydrate, lipids, and phospholipids,[52] embedding fatty acid crystals, hydroxyapatite crystals,[34] and collagenous connective tissue. Both membranes and the content of the cysts are Sudan III positive in frozen sections. On electron microscopy, the membranes are bilayered. The inner layer is made of thin, dense, phospholipidic material. This dense layer is described as the gathering of tortuous microtubular or saccular structures arranged perpendicularly to the surface[16 22 53] enclosing triglycerides, possibly representing terminal breakdown products of adipocyte membranes. The outer layer consists of amorphous material supposed to derive from degenerating cytoplasm of fat or stromal cells, or both. This initially appears at the lipid-cytoplasmic interface of adipocytes. Accumulation of this amorphous material in the interstitium leads to the degeneration and disappearance of adjacent adipocytes. The lumen of small arteries is often occluded; its muscularis layer is almost completely destroyed, the inner elastic layer is thickened, and there may be intimal proliferation. *Maclura pomifera* agglutinin (MPA lectin), which specifically binds α-D-galactose, is strongly fixed on membranocystic lesions, and especially on the microtubular structures, and *Helix pomatia* agglutinin (HPA lectin), which recognises N-acetyl-D-galactosamine, is fixed by the membranes of degenerated adipocytes, indicating that carbohydrate residues are modified during membrane formation.[18 22]

CENTRAL NERVOUS SYSTEM

Whereas the end stage histology is well known from necropsy cases, fewer data are available on the early stages of the disease. Macroscopic anomalies comprise atrophic sclerosis of the white matter predominating in the frontal region, atrophy of the corpus callosum, and enlarged ventricles. The cortex appears minimally affected. Microscopic anomalies are described as sudanophilic leucodystrophy[10] or more frequently as sclerosing leucoencephalopathy with loss of both myelin and nerve fibres, massive gliosis, and demyelination predominating in the subcortical white matter.[4 6-8 10-12 17 44 54] Senile plaques and neurofibrillary tangles have been reported.[32] Degeneration of basal ganglia[21] and calcospherite deposition may be observed, especially in the putamen and globus pallidus.[21] Neuroaxonal dystrophy (axonal swelling and spheroids with Hirano bodies) is present in hemispheric, cerebellar, and brainstem white matter.[15 55] In some patients, sural nerve biopsy showed similar anomalies, with both axonal degeneration and segmental demyelination.[20 45] Lipomembranous structures are not observed in the brain. The walls of the small vessels are altered and surrounded by areas of spongy degeneration. The endothelial cells appear larger than normal and their basement membranes are thickened and multilayered. These lesions predominate in white matter,[29] in which extravased plasma constituents are shown by immunostaining in the perivascular area.

OTHER SITES

Although lipomembranous dystrophy predominates in spongy bone areas, cutaneous and perivisceral fat tissue,[4] it may be observed in rectal mucosa, hepatic sinusoids, and alveolar septa of the lungs.[56] The typical histiocytic infiltrate of the rectal mucosa may be used for diagnosis.

Histopathological diagnosis is routinely possible from bone marrow or synovial biopsy.

Biochemistry

Triglycerides and free fatty acids represent 95-98% of the accumulated lipids.[4 20 57] In older reports, no abnormal substance has been found in lipids from the brain, bone marrow, liver, kidney, or adipose tissue. The proportion of essential and unsaturated fatty acids is remarkably low.[4 9 57] In the brain, the total lipid content is reduced to about half the normal value. Free fatty acids account for 15% of neutral fats[4] (a 5.5 fold increase). An abnormally high percentage of C16:0 and C18:0 fatty acid sulphatides, cerebrosides, and gangliosides was

shown in the cortex and white matter of some cases.[58] No lysosomal enzyme defect has ever been found and there is no abnormal saccharide excretion. Increased plasma nervonic acid and low plasma glutamine have been shown in a recent case.[26] Superoxide dismutase and erythrocyte glutathione peroxidase activities were normal in one case.[59]

Heterozygote detection

Apart from the monograph of Hakola,[3] little attention has been paid in published reports to possible minor manifestations in obligate heterozygotes. They may, in some cases, present with microcystic anomalies of the carpal and tarsal bones, focal epilepsy, or EEG disturbances similar to those of affected persons,[3] but the specificity of these manifestations and their relevance for genetic counselling remain to be investigated.

Pathophysiology

The cause of the lipomembranous lesions and leucoencephalopathy is still unknown. Two pathophysiological mechanisms have been invoked: the vascular theory (proposed by the Finnish team) and the dysmetabolic theory, favoured by Japanese workers.

Hakola and colleagues[3 43 60] suggested that membranocystic lesions result from vascular hypoplasia. Hypovascularisation would lead to slowly progressive fat necrosis (in the bone) and to demyelination and gliosis in the CNS. Cerebral hypovascularisation was confirmed by isotopic studies.[61] Based on the presence of altered basement membranes, on the observation that chronic brain oedema may cause extensive myelin loss, and on their own immunohistochemical experiments, Kalimo *et al*[29] proposed that the main pathogenetic mechanism for the leucoencephalopathy is a primary anomaly in endothelial metabolism. It results in vessel wall damage, causing the breakdown of the blood-brain barrier and leading to severe vasogenic brain oedema. Nevertheless, the possibility that these alterations and the oedema are secondary to the epileptic fits rather than the primary defect has still to be proven.

Kitajima *et al*[18] rejected this model. They stated that secondary membranous lipodystrophy occurs in areas showing granulomatous, neoplastic, or arteriosclerotic changes, whereas similar lesions occur usually without any remarkable ischaemic lesions in NHS. For Nasu,[52] the primary defect is an as yet undetected anomaly of lipid metabolism or a disorder of lipid metabolising cells. Because of anomalies in carbohydrate residues in membranes, a primary disturbance in membrane glycolipid or glycoprotein metabolism has also been discussed.[44] Kitajima *et al*[20] found histiocytes filled with membrane bound vacuoles in a rectal biopsy. The membranes showed histochemical reactivity similar to the lipomembranous lesions of fat tissue. Machinami[62] suggested that macrophages produce membranocystic lesions while processing free lipid droplets released from degenerated adipocytes. Matsushita *et al*[55] stressed the importance of axonal degeneration, but gave no explanation for bone and fat tissue changes.

Differential diagnosis

When neuropsychiatric and skeletal anomalies are taken into account, there is no differential diagnosis for NHS. Clinically, the dementia has much in common with Alzheimer's disease or Pick disease, which were the most frequent erroneous diagnoses. Skeletal anomalies have been confused with lipomatosis and hyperparathyroidism. Axonal dystrophy observed in NHS resembles neuroaxonal leucoencephalopathy.[55] Every case of unexplained, presenile dementia should be routinely screened for polycystic bone lesions in typical sites (wrist, ankle, knee). Contrasting with the pathology of NHS, similar membranocystic lesions are observed in the brain in cerebrotendinous xanthomatosis.[63]

Secondary membranolipodystrophic changes are observed as a non-generalised process in a small proportion of inflammatory lesions of adipose tissue. It has been described in association in thromboangeitis obliterans, lupus erythematosus,[64] dermatomyositis,[65] morphea profunda,[66] Behçet disease,[67] sclerosing panniculitis,[68] fat granuloma, diabetes mellitus,[69] and arteriosclerotic obstruction.[70] Very rare cases of idiopathic (non-inflammatory) membranolipodystrophic changes without neurological symptoms have been reported.[71]

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