Nasu-Hakola disease: a rare entity in Italy. Critical review of the literature

Lorenza Montalbetti
Debora Soragna
Maria Teresa Ratti
Paola Bini
Simona Buscone
Arrigo Moglia

a Department of Neuroscience, University of Pavia, IRCCS “C. Mondino Institute of Neurology” Pavia, Italy
b Department of General Biology and Medical Genetics, University of Pavia, Italy
c IRCCS “C. Mondino Institute of Neurology”, Pavia, Italy

Reprint requests to: Prof. Lorenza Montalbetti
Department of Neuroscience, University of Pavia
IRCCS C. Mondino Institute of Neurology
Via Mondino, 2 - 27100 Pavia - Italy
E-mail: lmontalb@unipv.it

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Summary

Nasu-Hakola disease (NHD, polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, PLOSL) is a rare, recessively inherited disorder characterized by an early-onset progressive dementia with bone cysts. Most of the patients have been reported in Japan and in Finland (1); the Finnish estimated population prevalence is 2.0 x 10^-6 (2). The disease is considered to belong to the so-called Finnish disease heritage (3-5), having its origins in an isolated population with a small number of original founders. Sporadic patients have been diagnosed worldwide, most of them in Europe. In Italy there are 9 reports of NHD (6-14). The aetiology and pathogenesis of NHD are poorly understood. Recently, mutations have been associated with NHD in two genes: TYROBP (tyro protein tyrosine kinase-binding protein [MIM 604412; GenBank accession number AA481924]) on chromosome 19q13.1, and TREM2 (triggering receptor expressed on myeloid cells 2 [MIM 605082; GenBank accession number BF343916]) on chromosome 6p21.2 (15,16). We here propose a review of the literature, conducted in order better to define the diagnostic criteria of the disease, and to draw the attention of neurologists and orthopaedic specialists to this – in Italy – poorly known and misdiagnosed disease.

KEY WORDS: Italy, Nasu-Hakola disease, review.

Introduction

Nasu-Hakola disease (NHD; polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, PLOSL) is a rare, recessively inherited disorder characterized by an early-onset progressive dementia with bone cysts. Most of the patients have been reported in Japan and in Finland (1); the Finnish estimated population prevalence is 2.0 x 10^-6 (2). The disease is considered to belong to the so-called Finnish disease heritage (3-5), having its origins in an isolated population with a small number of original founders. Sporadic patients have been diagnosed worldwide, most of them in Europe. In Italy there are 9 reports of NHD (6-14). The aetiology and pathogenesis of NHD are poorly understood. Recently, mutations have been associated with NHD in two genes: TYROBP (tyro protein tyrosine kinase-binding protein [MIM 604412; GenBank accession number AA481924]) on chromosome 19q13.1, and TREM2 (triggering receptor expressed on myeloid cells 2 [MIM 605082; GenBank accession number BF343916]) on chromosome 6p21.2 (15,16). We here propose a review of the literature, conducted in order better to define the diagnostic criteria of the disease, and to draw the attention of neurologists and orthopaedic specialists to this – in Italy – poorly known and misdiagnosed disease.

Historical background

The first report of NHD was by Terayama in 1961 (17). Then, Jarvi et al. in 1964 (18) reported two patients with polycystic angionecrotic osteodysplasia with cavities in the areas of ossification in the extremities. Nasu et al. in 1970 (19) reported the autoptic findings underlying membranous lipodystrophic alterations in the bone tissue and leukodystrophic alterations of the brain in a Japanese patient and, at the same time, Hakola in Finland (20) described multiple cases, focusing on the neuropsychiatric and hereditary findings and dealing with the differential diagnostic problems. Finally, Jarvi (21) combined these skeletal and brain alterations in a single entity known as NHD.

Literature review

We searched the MEDLINE database for articles, running the queries "Nasu-Hakola disease" and "polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL)". To find any article we might have missed, we then ran the highly sensitive but less specific queries "presenile dementia, bone cysts, brain-bone-fat disease, and prefrontal dementia". All abstracts were carefully studied, and full articles containing the data we were looking for were retrieved. Moreover, reference sections of the examined articles
were checked for further leads. We selected full papers, written in English, that reported different studies of PLOSs and had been published between 1961 and mid-2003. Up to 1999 we found broad clinical or anatomopathological descriptions, Finnish authors emphasizing psychiatric and orthopaedic features, and Japanese ones illustrating, in particular, anatomopathological findings. After 1999, we found a prevalence of genetic studies and the emergence of new pathogenetic hypotheses.

It is difficult to establish the exact number of NHD cases, since there exist multiple reports of the same cases, and also unpublished but quoted cases. Approximately 160 cases have been reported (22), mainly in Japan (23-35) and Finland (20,36-39). There are anecdotal reports worldwide, particularly in Sweden (40,41), Norway (42,43), the USA (44,45), South Africa (46), Austria (47), Turkey (48), Belgium (49,50), Tunisia (51), and Bolivia (52).

Up to the end of 2001, we found 7 reports of PLOS cases in Italy, with accurate clinical and instrumental descriptions (6-12). Subsequently Paloneva et al. (16) reported a genetic study in two sibs of an Italian family, later described clinically by Salmaggi et al. (14). We have recently described a new Italian family with a novel mutation in the TREM 2 gene, different from those reported to date (13).

Clinical features

Nasu-Hakola disease is characterized by a typical clinical course with a unique combination of neuropsychiatric and skeletal symptoms that lead to death before the age of 50 years. Hakola (20) divided the natural history of the disease into four stages.

i) The latent phase: generally, psychomotor development is normal and childhood is mostly symptomless. In just three cases (one Italian patient and two Tunisian siblings) (10,51), the disease began in early infancy and developed very seriously and rapidly. In the first two cases the onset, at 14-15 months, was characterized by an atypical feature, i.e., a bilateral progressive loss of vision, leading to blindness at the age of 3 years. In the third case, onset was characterized by delayed psychomotor development and the patient began to suffer from epileptic seizures at the age of 7 years. No prominent osseous features or skeletal symptoms were reported. Otherwise, all three cases presented cystic lesions on bone radiograms. Also, very marked anomalies were detected on cerebral MRI. In all cases, mental and neurological deterioration was rapid and the patients died prematurely.

ii) The osseous stage: around the age of 20 years the patient complains of wrist and ankle pains and swelling, and later, of pathological fractures of bone extremities associated with radiological evidence of cysts. Some patients, however, do not have clinically manifest osseous problems, despite radiological evidence of cystic bone lesions (13,14,22,53,54).

iii) The neuropsychiatric stage: symptoms appear insidiously during the third or fourth decade of life and consist of marked behavioural alterations and changes of personality that lead to severe social and family problems (55): divorce and unemployment. Patients present alterations of character and social conduct in the context of a relative conservation of perception, spatial skills, praxis and memory on appropriate tests. They appear disinhibited, fatuous, aimless, and swing between euphoria and apathy, over-activity and inertia. Suicidal ideation frequently recurs. Impotence, lack of libido or hypersexuality, and urinary incontinence frequently occur in the early period of this stage. In this period, there arise problems of differential diagnosis versus addiction, frontal expansive lesions and hydrocephalus. Frontal lobe dysfunction is suggested by the presence of emotional blunting and impaired insight, associated with dietary changes, and preservative and stereotyped speech and behaviours. Patients show attentional deficits and poor abstraction and, although the primary tools of perception, spatial function and memory are spared, performances on tests may be impaired by poor attention and lack of concern for accuracy (55,56). In this period of the neuropsychiatric stage neurological signs are usually absent. With advancing disease, memory disturbances appear. These are initially slight and the patient is able to retain his most important personal data until the last stage of the disease. Then, disturbances of higher cortical functions such as aphasia, agraphia, acalculia, and apraxia appear associated with progressive signs of upper motor neuron involvement, primitive reflexes, extrapyramidal signs, myoclonic twitches, and epileptic seizures.

iv) The dementia stage: the patient loses the ability to walk and lies in a cachectic state, frequently presenting epileptic seizures, and dies from incidental infections. Dementia features are similar to those observed in Alzheimer’s disease or Pick’s disease, with which it may be confused. The mean duration of the clinical course after the onset of the neuropsychiatric symptoms is 10 years (50).

Uncommon clinical manifestations

Other systemic features are anecdotally described. It is difficult to establish whether they are linked to the disease or are coincidental. They include paralytic ileus (53), megacolon (45), Fanconi’s syndrome (57), and chronic myeloid leukaemia (45,58). Unusual features with auditory hallucinations and central hypothermia have been described in a Japanese patient presenting an atypical neuropathological picture with marked temporal atrophy, thalamus degeneration and hypothalamic haemorrhage (59). Abnormal ocular findings described by Hakola et al. in 1989 (60) consist of optic atrophy and nerve fibre layer defect at the fundus oculi. Loss of vision (51) was the first manifestation of the disease in two cases with infantile onset, associated with marked damage of the optic pathways on MRI. Additional findings of palatal myoclonus are described by Malandrini et al. (10) in a young Italian patient with radiological evidence of dentate nucleus mineralization probably triggering changes in the dentato-rubro-olivary pathways, which are involved in this paroxysmal manifestation. A doubtful and unusual case, owing to its benign course, was recently described by Haruta et al. (61): a
56-year-old woman who presented only osseous lesions without typical neuropsychiatric symptoms and neuroradiological signs.

**Instrumental findings**

**Biochemistry**

No pathognomonic biochemical anomalies have been observed in NHD. In particular, no lysosomal enzyme defects (62) or abnormal activities of superoxide dismutase and erythrocyte glutathione peroxidase have ever been found (63). In only one case have increased plasma nervonic acid and low plasma glutamine levels been reported (64), and in one patient, we demonstrated a significant increase of aspartate in the cerebrospinal fluid (11), but these findings remain isolated.

**Skeletal radiographs**

Skeletal radiological pictures are diagnostic. Multiple, symmetrical cysts with poorly defined margins and without peripheral sclerotic reactions localized in the epiphyseal and metaphyseal regions of carpal and tarsal bones and in the metacarpals, metatarsals and phalanges are pathognomonic (6,20,65) (Fig. 1). Cystic lesions and trabecular loss are most conspicuous in the fingers and in the carpal and tarsal bones (66). Functional studies have shown that mineral density of the cortical bone is decreased (67) and $^{99}$Tc methylene diphosphonate uptake is increased in the involved area (68).

**Neuroimaging**

Brain CT and MRI have revealed different degrees of cerebral atrophy according to the stage of the disease, with a marked involvement of the frontal regions and occasionally cerebellar atrophy (15,69). Sometimes these alterations are visible before the onset of the neuropsychiatric symptoms (39,70,71). The basal nuclei (putamen in particular, globus pallidus, caudate nucleus and thalamus) showed very low signal intensity on T2-weighted MR images, which may be related to intracranial calcification (34,72). The caudate nuclei heads are very small on MRI with a high bicaudate ratio (22). Moreover, T2-weighted MRI shows increased signal intensity of the cerebral white matter: it is diffuse and more prominent on the frontal lobes. Atypical radiological features are present in the cases of Chaabane et al. (51), who described high signal intensity in the lateral geniculate body, optic radiations and cerebral peduncles, linked to the presence of blindness. Malandrini et al. (10) described hypodensity of the dentate nucleus in a case with palatal myoclonus.

To date, few functional neuroimaging studies (PET and SPECT) are available (73). Maquet et al. (74) reported a PET study using $^{18}$F fluorodeoxyribose, which disclosed that regional cerebral glucose metabolism was low in the frontal, temporal and parietal regions and in the thalamic nuclei, and markedly decreased in the medial frontal area and in the basal ganglia. Another PET study (75) using $^{18}$F-2-fluoro-2-deoxy-D-glucose, showed a reduction in cerebral glucose metabolism in the bilateral frontal white matter with mild hypometabolism in the thalamus and basal ganglia, all predominantly on the right. In our patients (12), a $^{99}$mTc-HMPAO SPECT study showed bilateral frontal and right basal ganglia hypoperfusion. Impairment of frontal structures and frontal lobe dysfunction might produce the unique neuropsychiatric picture observed in these patients. The basal ganglia dysfunction correlates with extrapyramidal signs in the last stage of the disease. Neuroimaging and neurofunctional findings, although not pathognomonic, are quite typical and these studies can help in the early diagnosis of this disease.

**Neurophysiology**

EEG is characterized by synchronous and diffuse 6-8 Hz activity and replacement of the alpha rhythm by amorphous theta and delta activity and the appearance of paroxysmal activity with multifocal, or generalized spike and wave activity reflecting epileptogenic foci. The paroxysmal activity is related to the epileptic seizures that can occur in the late stage of the disease (20,76).

EMGraphic and ENGraphic findings are conflicting: normal findings (46,77), or alterations of peripheral nerve conduction compatible with the presence of a motor-sensory neuropathy (8,54,75) have been described. There have been few observations on somatosensory evoked potentials. Stubgen et al. (46) reported normal
findings in one case, while Hakola and Partanen (77) observed that the latencies of the cortical responses, normal in the early stage of the disease, can be delayed in the advanced stages, suggesting an involvement of the upper brainstem and thalamo-cortical projections. Late cortical evoked responses were also observed by Malandrinii et al. (10).

Neurphysiological findings are aspecific and do not contribute significantly to the definition of the diagnosis even though they are suggestive of a systemic involvement of the nervous system. However, patients usually die before this involvement becomes clinically apparent.

Anatomopathological features

The cystic lesions of the affected bone marrow are characterized by the presence of convoluted membranous structures lying among the fat cells (78). These membranes are mainly eosinophilic and partly basophilic and histochemical studies show them to have the characteristics of complex glycolipid or glycoprotein (78-81). Ultrastructurally the membranes consist of complex microtubular substructures filled with amorphous substances. Electron microscopic immunostaining with horseradish peroxidase-labelled lectins (maclura pomifera agglutinin) shows that they bind specifically with alpha-D-galactose residue (81). Moreover triglycerides, free fatty acids and carbohydrates are present (79,82,83).

Similar membranocystic lesions have also been described in systemic adipose tissue (79), in the lungs (31,84), and in the periadrenal region and renal pelvis (85), however these manifestations have not been adequately characterized.

On the other hand, the membranocystic lesions can be secondary, induced by inflammatory or traumatic lesions of the adipose tissue (86-92).

Macroscopically, brain weight is reduced. Diffuse atrophy of the white matter, more prominent in the frontal lobes, with atrophy of the corpus callosum and enlarged ventricles, is always present. Basal ganglia and thalamic nuclei are smaller than usual, and the bilateral globi pallidi frequently show brownish discoloration with deposits of sandy material (93-96).

Microscopically, brain pathology has been described as sudanophilic leukodystrophy (79,94,95,97) or more frequently as sclerosing leukoencephalopathy (31,85,98-100). Characterized by loss of myelin and nerve fibres, microcystic areas with atrophy of the corpus callosum and enlarged ventricles, is always present. Basal ganglia and thalamic nuclei are smaller than usual, and the bilateral globi pallidi frequently show brownish discoloration with deposits of sandy material (93-96).

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Microscopically, brain pathology has been described as sudanophilic leukodystrophy (79,94,95,97) or more frequently as sclerosing leukoencephalopathy (31,85,98-100), characterized by loss of myelin and nerve fibres, and by gliosis more prominent in the frontal and temporal lobes. Degeneration of the basal ganglia with caspohosphate deposition may be observed especially in the globus pallidus (101,102). Occasionally axonal degeneration (103) can be observed in the white matter in the cerebral hemispheres, cerebellum, basal ganglia and brainstem (104). Lipomembranous anomalies are not observed in the brain. Vascular changes are present in the white matter and involve the basement membranes of the endothelium, which appear thickened and multilayered (105). These anomalies are similar to those observed in the bones. Senile plaques and neurofibrillary (45) tangles have been reported. Peripheral nerves may also be affected and axonal degeneration is also reported in cases with peripheral neuropathy (8,106).

Generally, no intraneurial or glial pathological inclusions, immunoreactive for phosphorylated tau, alpha-synuclein, or ubiquitin are observed (22).

Lipid analyses on brain show that total lipid, cholesterol and cerebroside content is reduced in the white matter (78,107). In some cases an abnormal high percentage of Cer6.0 and Cer18.0 fatty acid sulphatides, cerebrosides and gangliosides was shown in the cortex and in the white matter, whereas in other cases the free and sphingolipid fatty acid composition did not differ from that of normal brains (78).

Unusual anatomopathological findings, such as combination with thalamic degeneration (101), and absence of fibrillary gliosis (108), have been reported. Kobayashi et al. (59) describe fibrillary gliosis and atrophy more prominent in the temporal lobe infarcts in frontal white matter and in the caudate nucleus and hypothalamic haemorrhages in a patient with auditory hallucinations and central hypothermia.

Genetics

The disease is inherited in an autosomal recessive manner. Pekkarinen et al. (5,109) carried out a genetic linkage analysis, showing significant evidence of linkage to 19q13.1 in Finnish NHD families. In 2000, Paloneva (15) characterized the molecular defect in NHD by identifying a large homozygous deletion of 5265 bp, including 343 bp (exons 1-4 and 5-prime untranslated region) of the 604-bp transcribed region of the TYROBP gene, in Finnish NHD patients. Other patients carrying TYROBP mutations are from Sweden (15), Norway (16,110) and Brazil (16). In TYROBP, a homozygous single-base deletion in exon 3 of DAP12 (141delG) causing a frame shift resulting in a premature stop codon has been also identified in 4 Japanese patients (15,111). In another two unrelated Japanese patients, Kondo et al. (111) found a T-to-C transition in the second nucleotide of the TYROBP gene, changing the start codon from ATG (met) to ACG (thr). All these mutations represent loss-of-function mutations and result in a lack of TYROBP protein. However, in some families no mutation was found in TYROBP suggesting that the disease is characterized by genetic heterogeneity. Paloneva et al. (16) studied the segregation of marker haplotype flanking genes that encode polypeptides interacting with TYROBP, and found that region 6p22-p21 showed complete segregation to NHD. This region contains the TREM2 gene in which different mutations have been identified. In particular, in 2 Swedish families, Paloneva et al. (16) found a homozygous 233G→A mutation changing tryptophan-78 to a translation termination codon (W78X), and in a Bolivian patient a homozygous 132G→A mutation changing tryptophan-44 to a translation termination codon (W44X). These mutations are predicted to result in the generation of a truncated protein. In two Italian sibs, authors identified a mutation in the splice donor consensus site at the second position of intron 3 (482+2T→C) in the TREM2 gene, probably resulting in the skipping of exon 3 from the mature RNA (14,16). In a Norwegian family (41), authors found a 558G→T mutation changing lysine-186 to asparagine (K186N), and in an American family origi-
nating from Slovakia (45), authors identified a 401A→G substitution resulting in an aspartate-134 to glycine substitution (D134G). More recently, in an Italian family, we (13) identified a homozygous C-to-T mutation at position 97 in exon 2 changing glutamine 33 to a stop codon (Q33X). This testing is now available on a re-search basis only.

To date, little attention has been paid to possible minor manifestations in heterozygotes who may present microcystic lesions of the tarsal and carpal bones, focal epilepsy, or EEG anomalies (20), but their specificity and relevance remain to be established.

Pathogenesis

Nasu-Hakola disease pathogenesis is still poorly defined. Before the identification of the molecular defect associated with PLO-SL, two hypotheses had been proposed (20,81, 105,112,113). Kalimo et al. (105) proposed that the main pathogenetic mechanism for leukoencephalopathy is an anomaly in the endothelial metabolism which causes vessel wall damage, with breakdown of the blood-brain barrier leading to the vasogenic brain oedema responsible for oligodendroglial and axonal damage. Abnormal blood vessels have also been reported in the bone, but it is still not known whether they are primary or secondary. The other hypothesis postulates an error in systemic lipid metabolism or a disorder of lipid metabolising cells (79,114,115), and suggests that the basic metabolic defect is responsible for the breakdown of the myelin sheaths and for the formation of membranous structures in adipose tissue.

The novel finding of mutations in two genes does not corroborate either of these hypotheses. TYROBP encodes for a membrane receptor component in natural-killer and myeloid cells; it is expressed mostly in haematological cells and tissues such as peripheral blood leukocytes and spleen (116) and it has been suggested to have a role in the activation of natural killer cells (116) and in myeloid differentiation (117). TREM2 encoding for an immunoglobulin-like receptor, is expressed on macrophages and monocyte-derived dendritic cells and seems to play a role in chronic inflammation (118). TREM2 forms a receptor signalling complex with TYROBP triggering activation of immune responses in macrophages and dendritic cells.

It has been postulated that the TYROBP-mediated signalling pathway plays a role in human brain and bone tissue and provides an example of how mutations in two different subunits of a multi-subunit receptor complex result in an identical phenotype (16). Interestingly, although TYROBP and TREM2 are involved in some immunological functions (116-118), NHD patients were found to show neither immunological symptoms nor haematological abnormalities; in particular, routine leukocyte differential count and natural killer cell functions were normal (14). This can be explained by the presence of additional molecules or of a significant functional redundancy able to replace the inactive TYROBP-TREM2 complex (16). Nevertheless, the expression of these genes in the monocyte-macrophage lineage suggests a link between bone and brain lesions in NHD (15), since both microglial cells in the central nervous system and osteoclasts in the bone share a common differentiation pathway with macrophages (119). In this context it has been postulated that brain lesions might result from a defect of microglial cells unable to remove apoptotic tissue and that bone lesions might result from a chronic dysfunction of osteoclasts causing a defective bone remodelling process (15,16).

More recently Kaifu et al. (120) demonstrated that TYROBP-deficient mice develop osteopetrosis and hypomyelinosi accentuated in the thalamus, suggesting that in the mice the defect in TYROBP arrests osteoclast and oligodendrocyte development, providing a molecular basis for the unique combination of skeletal and cerebral characteristics seen in NHD.

Management

No therapy that can delay or halt the progression of the disease is known. Orthopaedic ankle surgery as well as supportive orthopaedic devices may be of value in individual cases. Symptomatic medication can be useful to control abnormal behaviour and the use of appropriate antiepileptic medication is important since epileptic seizures may worsen the patient’s condition.

Concluding remarks

Nasu-Hakola disease is a very rare and little known condition, but it presents unique clinical features. In our view diagnosis should be based on carefully performed clinical steps, and we suggest the following diagnostic work up:

i) a detailed family and personal history
ii) neurological and neuropsychological assessment
iii) orthopaedic evaluation
iv) radiographic examination of limb bones
v) neuroimaging evaluation

Bone biopsy can be useful to confirm the membranocystic nature of bone lesions. Genetic counselling and genetic analysis of affected patients and probable carriers can be performed to confirm the presence of a known mutation or to contribute to the identification of new mutations. The combination of neuropsychiatric symptoms and bone cysts is unique to this disease, which we believe to be underestimated in Italy. Patients with this disease are likely to go unrecognized partly because they are considered to be affected by other kinds of dementia or by fibrous dysplasia of bone and, partly, because the disease is generally unknown outside Finland and Japan. Thus, we suggest that every case of unexplained presenile dementia should be screened for polycystic bone lesions and that young patients with pathological fractures and bone cysts should be submitted to neuropsychological assessment. Moreover, we propose that all cases of unexplained presenile dementia with a juvenile history of behavioural and personality changes, of psychiatric syndromes with marked frontal components, and of juvenile bone cysts or pathological fractures be reviewed to establish more accurately the prevalence of NHD. The discovery of additional cases followed by appropriate genetic counselling, genetic analyses and careful study of the territorial distribution of affected patients might be a good research strategy that would lead to a better understanding of the disease.
pathogenesis.

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Nasu-Hakola disease: review


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Electronic-Database Information
Accession numbers for data presented herein are as follows:
1. Online Mendelian Inheritance in Man (OMIM): http://www3.ncbi.nlm.nih.gov/Omim (for polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, PLOSL [MIM 221770], tyro protein tyrosine kinase-binding protein, TYROBP [MIM 604412] and triggering receptor expressed on myeloid cells 2; TREM2 [MIM 605082])