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Pulmonary Involvement in Niemann–Pick Disease: A State-of-the-Art Review

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Abstract Niemann–Pick disease is a rare autosomal recessive lysosomal storage disease with three subtypes. Types A and B result from a deficiency of acid sphingomyelinase activity, associated with the accumulation of lipid-laden macrophages (so-called Niemann–Pick cells) in various tissues, especially the liver and spleen. Type A is a fatal neurodegenerative disorder of infancy. Type B Niemann–Pick disease is a less severe form with milder neurological involvement, characterized by hepatosplenomegaly, hyperlipidemia, and pulmonary involvement; most patients live into adulthood. Type C Niemann–Pick disease is a complex lipid storage disorder caused by defects in cholesterol trafficking, resulting in a clinical presentation dominated by neurological involvement. Pulmonary involvement occurs in all three types of Niemann–Pick disease, but most frequently in type B. Respiratory manifestations range from a lack of symptoms to respiratory failure. Progression of respiratory disease is slow, but inexorable, due to the accumulation of Niemann–Pick cells in the alveolar septa, bronchial walls, and pleura, potentially leading to a progressively worsening restrictive pattern on pulmonary function testing. Bronchoalveolar lavage has important diagnostic value because it shows the presence of characteristic Niemann–Pick cells. Radiographic findings consist of a reticular or reticulonodular pattern and, eventually, honeycombing, involving mainly the lower lung zones. The most common changes identified by high-resolution computed tomography are ground-glass opacities, mild smooth interlobular septal thickening, and intralobular lines. The aim of this review is to describe the main clinical, imaging, and pathological aspects of Niemann–Pick disease, with a focus on pulmonary involvement.

Keywords Niemann–Pick disease · Computed tomography · Pulmonary diseases

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Introduction

Niemann–Pick diseases belong to the family of lysosomal storage disorders. Lysosomal diseases are characterized by the inability of lysosomes to degrade macromolecules such as glycolipids, glycoproteins, and mucopolysaccharides, or to release the products of their catabolism into the cytosol [1]. Niemann–Pick disease is a rare inherited autosomal recessive disease without gender predilection, with an estimated frequency of 0.4–1 in 100,000 newborns [1–3]. However, its true incidence is likely to be higher because these estimates are based solely on cases referred to biochemistry laboratories for enzyme studies [3]. Niemann–Pick disease has a familial tendency, with several reports of affected siblings and parents [4–6]. Because it is an

autosomal recessive condition, heterozygous individuals carrying only one causal gene mutation are usually asymptomatic. Carrier family members (parents and siblings) of patients with Niemann–Pick disease should be screened fully to detect signs suggestive of the disease [7].

The disease is heterogeneous and classified into three subtypes. Types A and B are lysosomal storage disorders resulting from deficient acid sphingomyelinase activity that lead to the accumulation of sphingomyelin, primarily in tissues of the reticuloendothelial system [8]. Although type C Niemann–Pick disease shares the eponym of Niemann–Pick disease caused by acid sphingomyelinase deficiency, it is a genetically distinct disorder resulting from defective intracellular trafficking of cholesterol with secondary glycosphingolipid accumulation, and the clinical presentation is dominated by central nervous system involvement [2]. Type A disease, which has an Ashkenazi Jewish predilection, is a severe neurodegenerative disease of infancy characterized by progressive psychomotor retardation, failure to thrive, hepatosplenomegaly, cherry-red macula, and death by 3–4 years of age [2]. In contrast, type B Niemann–Pick disease, which is panethnic, is characterized by hepatosplenomegaly, thrombocytopenia, interstitial lung disease, and dyslipidemia, with little or no neurological involvement in most patients [8]. Liver dysfunction, retinal stigmata, and growth retardation also may be present, but are more variable features [1, 2]. Pulmonary involvement occurs in all three types of Niemann–Pick disease, but most frequently in type B [9] (Table 1).

Diagnosis

Specific diagnoses of types A and B Niemann–Pick disease can be made with the demonstration of reduced acid sphingomyelinase activity in isolated leukocytes and/or cultured skin [8]. Types A and B can be distinguished by the presence and absence, respectively, of early neurological involvement [1]. In type C, acid sphingomyelinase activity in the peripheral leukocytes is within the normal range. The diagnosis of type C Niemann–Pick disease is based on the abnormal intracellular esterification of cholesterol derived from exogenous lipoprotein-derived cholesterol, measured in cultured fibroblasts obtained by skin biopsy [1].

Clinical Course

Symptoms of Niemann–Pick disease are caused by the accumulation of lipid-laden macrophages, the so-called Niemann–Pick cells, in various organs, such as the liver, spleen, bone marrow, organs of the central nervous system, and lung [1]. Tissues that completely lack lipid-laden macrophages are rare in affected patients. In the terminal stages of the disease, the organs of the monocyte-macrophage system, such as the lymph nodes and spleen, are often completely infiltrated with these cells [3]. Thrombocytopenia may appear, which may be secondary to infiltration of the bone marrow by Niemann–Pick cells. Leukopenia may also be a consequence of bone marrow infiltration [1]. Unlike those with types A and C Niemann–Pick disease, patients with type B disease survive into adulthood with little or no neurological involvement. Type B Niemann–Pick disease displays a broad range of phenotypic severity, including hepatosplenomegaly with secondary hypersplenism; mild liver dysfunction; respiratory complications; and an atherogenic lipid profile, usually presenting elevated triglyceride and low-density lipoprotein cholesterol levels, low high-density lipoprotein (HDL) cholesterol level, and sometimes a history of coronary

Table 1 General features of Niemann–Pick disease subtypes

	Type A	Type B	Type C
Gene mutation	SMPD1	SMPD1	NPC1 or NPC2
Deficiency	Acid sphingomyelinase activity	Acid sphingomyelinase activity	Intracellular trafficking of cholesterol
Onset	Early in infancy, failure to thrive, and early death with 3–4 years of age	Childhood/adulthood	Infancy and childhood, with increasing number of adult-onset cases
CNS	Progressive psychomotor retardation, and dysphagia	Little or no neurologic impairment, hyporeflexia, and peripheral neuropathy	Dystonia, speech delay, vertical supranuclear gaze palsy, cerebellar ataxia, dysarthria, and dysphagia
Ophthalmologic	Cherry-red macula	Cherry-red macula	Saccades
Gastrointestinal	Neonatal cholestatic jaundice, hepatosplenomegaly, feeding difficulty, and vomiting	Hepatosplenomegaly, liver cirrhosis, and portal hypertention	Neonatal cholestatic jaundice, and hepatosplenomegaly
Pulmonary	Recurrent respiratory infections, interstitial lung disease, and aspiration pneumonia	Recurrent respiratory infections, interstitial lung disease, and hypoxia	Recurrent respiratory infections, interstitial lung disease, and aspiration pneumonia

CNS central nervous system

artery disease [3, 10]. However, the main manifestations of type B Niemann–Pick disease are hepatosplenomegaly, excessive bleeding and bruising, and growth retardation. Bleeding episodes most often involve recurrent epistaxis [2], and other significant bleeding events, such as subdural hematoma, hematemesis, hemoptysis, hemothorax, and uterine bleeding, may occur [2]. Portal hypertension and esophageal varices have been described secondary to liver failure [2]. Other possible clinical findings include fatigue, joint pain, headache, gastrointestinal pain, and bone fractures [3].

Pulmonary Manifestations

Respiratory involvement occurs in all three types of Niemann–Pick disease, but most frequently in type B [8]. Niemann–Pick cells accumulate in the alveolar septa, bronchial walls, and pleura, potentially leading to a progressively worsening restrictive pattern on pulmonary function testing [1, 11]. Progression of lung disease is slow, but inexorable, due to the accumulation of Niemann–Pick cells in the lung [1]. The key findings of pulmonary involvement in Niemann–Pick disease are presented in Table 2.

Clinical Manifestations

Clinical manifestations of Niemann–Pick disease range from a lack of symptoms to respiratory failure [11]. When present, respiratory symptoms are generally mild, with recurrent cough, moderate dyspnea on exertion, and recurrent respiratory infection [1]. However, rapidly fatal lung disease has been reported [1]. In some patients, progressive pulmonary disease can lead to oxygen dependence and/or reduced exercise tolerance [8]. Some pulmonary symptoms may be secondary to restrictive changes caused by marked hepatosplenomegaly [11]. Pulmonary function tests usually reveal normal lung volumes with a decreased diffusion capacity for carbon monoxide (DLCO) [12]. Lung volumes and flow rates may be preserved, even in patients with advanced Niemann–Pick disease with interstitial infiltrates and severely decreased DLCO [12].

In affected patients, bronchoscopy can reveal lipid-laden macrophages, a characteristic finding of lipoid pneumonia [13]. Testing of bronchoalveolar lavage or lung biopsy specimens can confirm lung involvement by showing large multivacuolated histiocytes containing fine and coarse granules that stain deep blue with May-Grunwald–Giemsa stain (Niemann–Pick cells or "sea-blue histiocytes") [9]. Bronchoalveolar lavage results demonstrate the presence of an important local inflammatory process within the alveolar space, which may contribute to the respiratory manifestations observed in these patients [1].

Imaging

The pulmonary radiographic findings of Niemann–Pick disease consist of a reticular or reticulonodular pattern, with or without septal (Kerley B) lines, and eventually honeycombing, involving mainly the lower lung zones [12, 14]. Infiltrates may initially involve only the base and later progress to involve the entire lung field [12].

The most common changes in Niemann–Pick disease identified by high-resolution computed tomography (HRCT) are ground-glass opacities, mild smooth interlobular septal thickening, and intralobular lines, mainly in the lower lung zones [8] (Figs. 1 and 2). Pleural disease and thoracic lymphadenopathy have not been described in these patients [15]. However, the thymus can be enlarged if its lymphoid tissue is involved [16]. Although the pulmonary features observed in patients with Niemann–Pick disease are often distinct, they are occasionally intermixed [8]. Intermixed regions of

Table 2 Key findings of pulmonary involvement in Niemann–Pick disease

Clinical manifestations	Asymptomatic to respiratory failure (symptoms include recurrent cough, moderate dyspnea on exertion, and recurrent respiratory infections)
Pulmonary function tests	Normal lung volumes with a decreased DLCO
Bronchoalveolar lavage	Niemann–Pick cells, and important local inflammatory process
Pathology	Diffuse infiltration of the lymphatics, subpleural spaces, alveolar walls and alveoli with Niemann–Pick cells, characterizing a type of endogenous lipoid pneumonia
Radiography	Reticular or reticulonodular pattern, with or without septal (Kerley B) lines, mainly in the lower lung zones
HRCT	Ground-glass opacities, mild smooth thickening of the interlobular septa and intralobular lines, and crazy-paving pattern, mainly in the lower lung zones

DLCO diffusion capacity for carbon monoxide, *HRCT* high-resolution computed tomography

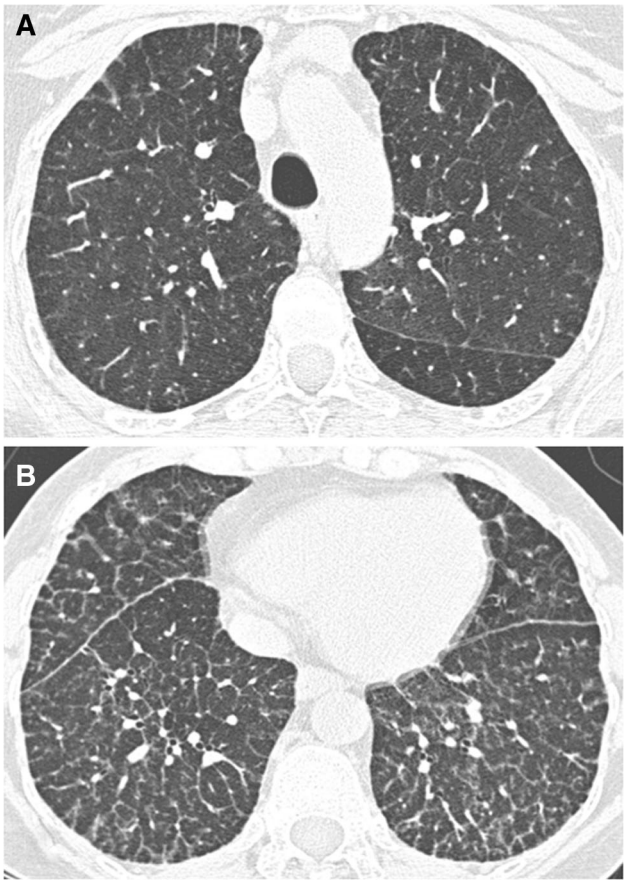

Fig. 1 Axial CT image with lung window settings of the *upper* (**a**) and *lower* (**b**) lung zones show diffuse smooth thickening of the interlobular septa and intralobular lines, mainly in the *lower* lung zones

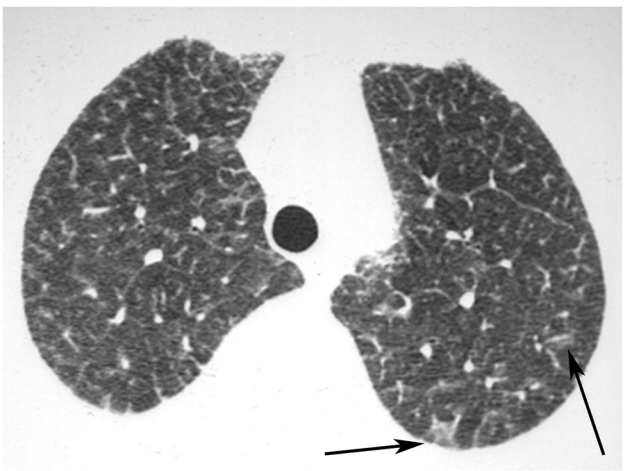

Fig. 2 Axial CT image with lung window settings of the upper lung zones shows smooth thickening of the interlobular septa, associated with focal areas of ground-glass opacity (*arrows*)

ground-glass opacity and interlobular septal thickening could be characterized as the crazy-paving pattern (Fig. 3); although this pattern is not generally

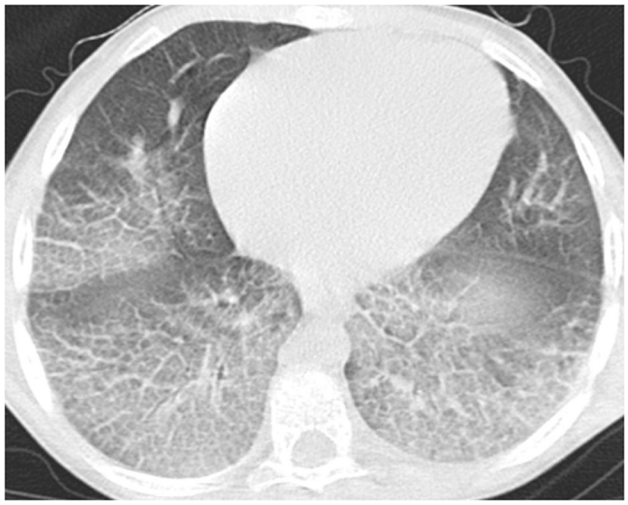

Fig. 3 Axial CT image with lung window settings of the lower lung zones shows intermixed regions of ground-glass opacity and interlobular septal thickening, characterizing the crazy-paving pattern

predominant, Niemann–Pick disease should be included among the entities that can demonstrate it on HRCT [8]. Abnormalities are generally diffuse, but occur more often in the lower lung zones [8]. Ground-glass opacities may predominate in the upper lung zones, usually due to partial filling of the alveoli with Niemann–Pick cells [12, 15]. On the other hand, interlobular septal thickening demonstrates lower lung zone predominance [12]. Peribronchovascular interstitial thickening may be observed in association with interlobular septal thickening [17, 18]. Rarely, pulmonary centrilobular nodular opacities have been described as HRCT findings of Niemann–Pick disease [9, 14, 16]. Other nonspecific HRCT findings, such as segmental atelectasis and bronchiectasis, have been described in many cases [13]. In one reported case, focal areas of low attenuation consistent with cysts were observed in association with ground-glass opacities, predominantly in the lower lung lobes [16]. Other causes of pulmonary cysts, such as lymphangioleiomyomatosis, Langerhans cell histiocytosis, interstitial desquamative pneumonia, and interstitial lymphocytic pneumonia, were excluded [16]. A possible pathogenetic mechanism of cyst development is the migration of Niemann–Pick cells into the bronchiolar lumen, leading to air trapping and airspace enlargement [16]. Moreover, two reports of Niemann–Pick disease in children described areas of low attenuation on HRCT consistent with emphysema [19, 20]. In one report, in addition to interlobular septal thickening, HRCT showed widening of the pulmonary veins, especially in the lower lobes of both lungs of a patient with type B Niemann–Pick disease [13].

Echocardiography and catheter angiography confirmed pulmonary hypertension and multiple pulmonary arteriovenous fistulas [13].

The differential diagnosis of the HRCT pattern of Niemann–Pick disease includes mainly diseases that present ground-glass opacities associated with interlobular septal thickening, such as pulmonary edema, pulmonary hemorrhage, lymphangitis, alveolar proteinosis, amyloidosis, and nonspecific interstitial pneumonia [17].

Interstitial lung disease is visible on chest radiographs in 90 % and on HRCT in 98 % of patients with type B Niemann–Pick disease [8, 9]. However, neither modality has value for the determination of Niemann–Pick disease subtype [1]. The extent and pattern of radiological abnormalities do not correlate strongly with pulmonary function impairment, implying that the interstitial changes do not always significantly affect gas exchange [8, 17]. Therefore, the presence of interstitial lung disease on chest radiographs or HRCT is not necessarily a reliable indicator of the appearance of clinical symptoms or alteration of respiratory function [17].

Pathology

Histopathological features of Niemann–Pick disease include diffuse infiltration of the lymphatics, subpleural spaces, alveolar walls, and alveoli with Niemann–Pick cells, characterizing a type of endogenous lipoid pneumonia [12]. Niemann–Pick cells also infiltrate the interstitium, but the lung architecture is generally preserved [9].

Differential Diagnosis with Gaucher's Disease

In general, childhood interstitial lung disease comprises a large group of rare disorders. Specific diagnosis requires a high index of suspicion, as disease onset is often insidious. Presentation and outcome differ from those in adult patients, and many cases are found to have an underlying cause, making correct etiological diagnosis crucial [21–23]. Nevertheless, the association of interstitial lung disease with hepatosplenomegaly should suggest deposition disease [13]. Furthermore, the associated findings of hepatosplenomegaly, the presence of lipid-laden macrophages in bronchoalveolar lavage and bone marrow aspirate, high angiotensin-converting enzyme levels, and hypercholesterolemia with a low HDL fraction are suggestive of a lysosomal storage disorder [23]. In this clinical scenario, the differential diagnosis includes mainly Niemann–Pick disease and Gaucher's disease [13, 15]. The clinical expression of Gaucher's disease is variable. Lung involvement can occur in all subtypes of Gaucher's disease, with variable frequency [15]. In one study, lung involvement was demonstrated in more than one-third of subjects with this disease examined postmortem [24]. In another study, two-thirds of patients with the adult form of Gaucher's disease had pulmonary function abnormality [25]. Hepatopulmonary syndrome may occur in Gaucher's disease and is associated with severe hypoxemia in the setting of hepatic dysfunction and intrapulmonary vascular dilatation [13]. Radiographic manifestations of Gaucher's disease consist of diffuse reticular, reticulonodular, and miliary patterns [15]. HRCT may show diffuse interstitial interlobular septal thickening and ground-glass opacities, potentially overlapping with the findings of Niemann–Pick disease [13]. Thus, radiographic and HRCT findings are not specific for the diagnosis and cannot differentiate lung involvement in Niemann–Pick and Gaucher's diseases [13]. Microscopic analysis of bronchoalveolar lavage fluid is another diagnostic tool for this differential diagnosis; it may show lipid-laden macrophages, which are suggestive (but not pathognomonic) of Niemann–Pick disease, or Gaucher cells, indicating Gaucher's disease [13]. Lung biopsy provides important diagnostic clues [13]. However, enzyme assay enables the differential diagnosis between Gaucher's and Niemann–Pick diseases and can lead to the final diagnosis, even without lung biopsy [17].

Abdominal Manifestations

Hepatomegaly is a prominent clinical finding in patients with Niemann–Pick disease [2, 10]. The liver enlarges because of the accumulation of lipid-laden macrophages in the hepatic reticuloendothelial system [11]. Biopsy specimens show vacuolated, lipid-laden cells with or without fibrosis [10]. Liver function testing reveals mild elevation of serum transaminase activities and bilirubin concentrations [10]. Although rare, hepatic involvement can lead to cirrhosis and hepatic failure [11]. Several cases of severe liver disease in patients with type B Niemann–Pick disease, ranging from children with fatal hepatic failure to adults with cirrhosis and portal hypertension, have been reported [10]. These clinical descriptions, coupled with findings from pathological examination of the liver, raise concerns about the ultimate contribution of liver dysfunction to the morbidity and mortality of patients with type B Niemann–Pick disease [10]. The liver can be imaged with any cross-sectional technique, including ultrasound, CT, or magnetic resonance imaging (MRI) [3]. CT and MRI enable the quantitative measurement of organ volume [11, 26]. Because many patients with type B Niemann–Pick disease are children and undergo repeated imaging studies to monitor disease status, MRI is frequently used because of its lack of ionizing radiation [11]. However, CT is better for the detection of small calcium foci, occasionally seen in the liver and other organs [11].

Splenomegaly is another prominent clinical manifestation of type B Niemann–Pick disease, also due to the accumulation of lipid-laden macrophages in the reticuloendothelial system. Splenomegaly is more prominent than hepatomegaly in these patients [11]. Splenic infarcts are relatively common [3]. Hepatosplenomegaly is a consistent feature of the disease, with spleen volume increased more than liver volume [2]. Notably, patients who report histories of recurrent bleeding events tend to have larger spleen volumes, but not lower platelet counts, than those without a bleeding diathesis [2]. The degree of splenomegaly has been shown to correlate with several aspects of disease severity, including liver volume, triglyceride and HDL cholesterol levels, hemoglobin concentration, white blood cell count, and percent predicted forced vital capacity, in patients with type B Niemann–Pick disease [2, 11]. Therefore, spleen volume, which can be measured noninvasively at little risk, may be a useful surrogate marker of overall disease severity and treatment response [2]. Unlike in the liver, masses can be seen in the spleen; they are typically echogenic on ultrasound and low density on CT [11] (Fig. 4). Multiple well-defined echogenic nodular lesions within the spleen parenchyma are often seen on ultrasound, and these lesions may be surrounded by ring-like blood flow on color Doppler imaging [27]. These masses can have variable signal characteristics on MRI, with the most common being isointensity on T1-weighted images and hyperintensity on T2-weighted images [11, 28]. On ultrasound, distinguishing histiocytic lymphomas from Niemann–Pick disease may be difficult. These tumors usually show a multinodular pattern in an enlarged spleen, although echoes derived from these nodules show less amplitude than in Niemann–Pick disease [29]. Histologically, hematoxylin–eosin staining shows that the splenic nodules in Niemann–Pick disease are formed by dilated sinuses containing lipid-laden macrophages with large ovoid or lobulated nuclei, but no atypia or mitosis [28]. Giemsa stain may reveal Niemann–Pick cells in the nodules. Outside the nodules, aggregates of foam cells are generally visible in an otherwise normal splenic parenchyma [28, 30]. Several cases of nodular splenomegaly, including the occurrence of hemangiomas, in patients with type B Niemann–Pick disease have been described [3]. Hyperechogenicity of the splenic nodules on ultrasound in Niemann–Pick disease has been attributed to their high lipid content, but hemangiomas in this disease may have a similar appearance [3]. The use of contrast-enhanced imaging modalities, such as ultrasound, CT, and MRI, may allow the diagnosis of hemangiomas, but an atypical hemangioma enhancement pattern has been described in Niemann–Pick disease [3]. Although the predominant abdominal manifestation of Niemann–Pick disease is hepatosplenomegaly, the adrenals, kidneys, and retroperitoneal lymph nodes also can be involved [11].

Skeletal Manifestations

Skeletal involvement occurs commonly in patients with type B Niemann–Pick disease, as has been noted for other lipid storage disorders [22, 31]. Niemann–Pick cells also infiltrate the reticuloendothelial system of the bone

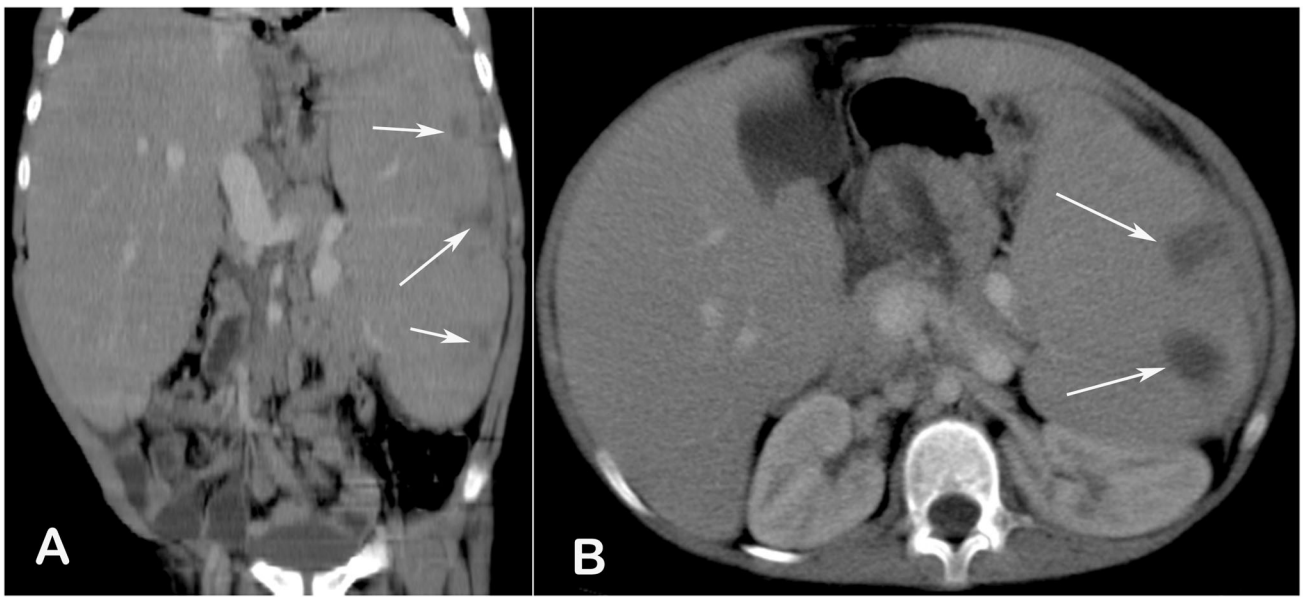

Fig. 4 Contrast-enhanced reformatted coronal (**a**) and axial (**b**) CT images show *marked* enlargement of the liver and spleen. Note also hypodense nodular lesions in the spleen, which although nonspecific, are characteristic findings of Niemann–Pick disease

marrow, which leads to leukopenia and thrombocytopenia while hemoglobin levels remain normal [11]. Most adolescent patients with type B Niemann–Pick disease have delayed skeletal maturation and accompanying growth restriction [11]. Moreover, most patients with type B Niemann–Pick disease also have osteopenia or osteoporosis, which is detectable on radiographs and by dual-energy X-ray absorptiometry [11]. Pediatric and adult patients with type B Niemann–Pick disease have decreased bone mineral density compared with controls, and the majority of adults have lumbar spine, hip, and femur T scores in the osteopenic or osteoporotic range [31]. In one series, 43 % of 46 patients with type B Niemann–Pick disease had histories of one or more skeletal fractures [31]. MRI can be used to evaluate the bone marrow and shows low T1 signal intensity, similar to Gaucher's disease [11].

Treatment

No specific treatment for acid sphingomyelinase deficiency is currently available [2]. However, enzyme substitution therapy and gene therapy may be useful for patients with type B Niemann–Pick disease [17]. Hematopoietic stem cell transplantation can be performed to treat lung involvement [9], and was reported successfully reduce pulmonary infiltrates [13]. Whole lung lavage, a classic treatment for lipoid pneumonia, was also reported to be a relatively effective treatment for type B Niemann–Pick disease, especially in adults [13].

Conclusion

Niemann–Pick disease affects multiple organ systems, all of which can be well assessed using a combination of clinical findings, laboratory tests, and imaging techniques. Pulmonary manifestations are common, and significant respiratory disease can be observed in any Niemann–Pick disease subtype. Patients with type B Niemann–Pick disease survive into adulthood, commonly present pulmonary involvement, have little or no neurological involvement, and have a clinical presentation dominated by hepatosplenomegaly. The most frequently observed radiographic manifestations of Niemann–Pick disease are a reticulonodular pattern on radiographs and smooth interlobular septal thickening, often in combination with ground-glass opacities, on HRCT. Moreover, early atherosclerotic heart disease because of lipid abnormalities is common. Most children with this disease have delayed skeletal maturity. The association of interstitial lung disease with hepatosplenomegaly should suggest deposition disease, especially in children. Furthermore, the associated findings of lipid-laden macrophages in the bronchoalveolar lavage and bone marrow aspirate, and hypercholesterolemia, are suggestive of a lysosomal storage disorder. Diagnostic workup of lysosomal storage disorders should include noninvasive imaging, as well as a sphingomyelinase assay and the analysis of bone marrow aspirate. The specific diagnosis of Niemann–Pick disease can then be achieved with confidence by demonstration of the distinctive sea-blue histiocytes within bone marrow aspirates and low sphingomyelinase activity, detected by enzyme assay of cultured skin fibroblasts.

Compliance with Ethical Standards

Conflict of interest None.

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