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Niemann–Pick's and Gaucher's diseases

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SUMMARY

A short account is presented of the evolution of knowledge concerning Niemann–Pick's and Gaucher's diseases, two autosomal recessive genetic disturbances of lysosomal storage function. This culminated in the intriguing realisation, arising from mounting clinical and molecular evidence, that glucocerebrosidase mutations constitute the most common risk factor for Parkinson's disease identified to date.

1. Introduction

Niemann–Pick's disease and Gaucher's disease are presently subsumed under the rubric of "Lysosomal Diseases". The lysosome is the subcellular membrane-bound organelle containing acid hydrolases, responsible for the catabolism of naturally occurring, intracellular macromolecules. Catabolism occurs within the lumen of the lysosome at an acidic pH. A genetic difference in a lysosomal enzyme, its protein co-factor, lysosomal membrane protein or in a protein involved in the post-translational modification or transport of lysosomal protein, will disrupt lysomal function. As a result, partially digested molecules, resulting from a defect in transport or undigested substrate, accumulate within the lysosome forming intracellular inclusions or "storage bodies".

The concept of lysosome storage disease was established in 1963 by H.G. Hers [1]. Observing that in type II glycogenosis (Pompe's disease), glycogen accumulated within vacuoles as a result of a defect in a specific glucosidase, Hers proposed the notion of an inborn lysosomal disorder. Over 40 distinct different genetic lysosomal diseases have now been identified. Many involve the central nervous system as manifestations of autosomal recessive disorders and are categorised according to the nature of the material that accumulates within the cell, such as sphingolipoidosis.

Brief mention should be made of the three eponymous seminal contributors to the lysosomal diseases. Philippe Charles Ernest Gaucher (1854–1918) was a pioneer dermatologist who submitted his doctorate thesis in 1882, while still a medical student at Paris University. It was entitled "De l'epithélioma primitif de la rate. Hypertrophie idiopathique de la rate sans leucémie" [2]. At that time, he considered that it was a cancer of the spleen and it was not until 1965 that the biochemical nature of Gaucher's disease was understood.

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Table 1
The lysosomal storage disease

1. Stored substrate sphingolipids (x12), e.g.
Tay-Sachs disease
Fabry's disease
Gaucher's disease – infantile, childhood & adult
Niemann–Pick disease types A & B
2. Mucopolysaccharidosis (x6), e.g.
Niemann–Pick disease type C
3. Oligosaccharides/glycopeptides
4. Multiple enzyme deficiencies
5. Stored substrate monosaccharides/amino acids/monomers
6. S-Acetylated proteins

Albert Niemann (1880–1921), a German paediatrician, published the first description of a hitherto unknown disease in 1914, "Ein unbekanntes Krankheitsbild" [3]. Ludwig Pick (1868–1935), a German pathologist, in 1927 published "Über die lipoidzellige Splenohepatomegalie Typus Niemann–Pick als Stoffwechselerkrankung" [4]. He distinguished Niemann–Pick disease from Gaucher's disease and drew attention to Niemann's original description.

2. Salient clinical features of the Niemann–Pick (NP) group of diseases

These encompass a number of fatal inherited disorders involving dysfunctional metabolism of sphingolipids within the generic family of lysosomal storage disorders. Hepatosplenomegaly, thrombocytopenia, and widespread neurological dysfunction including dystonia, abnormal postures, supranuclear gaze palsy, dementia and seizures are the main clinical features.

In 1961, Crocker assigned NP diseases into 4 phenotypes A, B, C and D, based upon the organs involved and age at onset of symptoms. Although sphingomyelin accumulation occurs in all four,

evolving biochemical evidence subsequently supported division into only two main groups.

a. NP types A and B. These are neurovisceral liposomal lipid storage diseases caused by deficiency of acid sphingomyelinase. As a consequence, accumulation of sphingomyeline (a group of crystalline phosphatides, that on hydrolysis yield a fatty acid, sphingoside and phosphoric acid), increased unesterised cholesterol and other phospholipids occurs. Sphingomyelin is a ubiquitous substance in mammalian tissues and is a major component of cell membranes and is one of the principal phospholipids of myelin sheaths.

   Clinically, two types are distinguished by the presence or absence of central nervous system involvement. About 50% of patients develop cherry-red retinal spots. Most are infantile in onset with prolonged jaundice. They rarely live longer than 2 years. Patients become hypotonic and flaccid. Seizures are rare; peripheral neuropathy has been reported.

   Type B patients, with hepatosplenomegaly, present usually in childhood with slow deterioration, and survival to adulthood is usual. Infiltration of the lungs is common. The phenotype may be more variable than type A, and intermediate forms have been reported.

   All types are transmitted by autosomal recessive inheritance. That is, both copies of the gene in each cell have mutations. Types A and B are caused by mutations of the acid sphingomyelinase gene (SMPD1). Assigned to chromosome 11p15.1–15.4, it codes for a protein of 629 amino acids. More than 100 mutations have been identified, including missense, nonsense, frame-shift and in-frame deletions have been reported.

   In the general population, type A is extremely rare (about 1 in 10 million) but it is more common in those of Ashkenazi Jewish ancestry (about 1:40,000); type B about 1 in 5 million; NPC affects all races but is rare. The estimated incidence is 1 in 150,000 births.

   Large lipid-laden NP cells are present in liver, spleen lymph nodes, adrenal cortex and bone marrow. The pathogenesis of cellular dysfunction is not yet well understood [5].

b. NP types C (and D). In these, there is only a modest accumulation of sphingomyelin, and fusion into a single group, type C, has been recommended. The group is characterised by gradual deterioration with variable age of onset and only moderate visceromegaly. Foam cells are present in the bone marrow. Neonatal jaundice is common. Most patients first show signs in childhood; the age of death varies from 3 months to 63 years. However as a group, extreme clinical heterogeneity may be found.

   The most conspicuous signs are cognitive impairment, extrapyramidal dysfunction with dystonia, tremor, choreoathetosis and vertical supranuclear palsy. Cataplexy may occur as well as terminal dysarthria and dysphagia. Many patients develop seizures and later cortical blindness.

   Foam cells infiltrate the spleen and bone marrow. Cortical atrophy, ballooning of neurons, intranuclear inclusions have been described. Intraneuronal neurofibrillary tangles have been seen; in those, illness ran a slow course but without amyloid deposits.

   Type C is characterised by excessive intracellular quantities of unesterified cholesterol derived from extracellular sources. The primary biochemical defect remains to be elucidated and the specific alteration underlying the abnormalities of cholesterol homeostasis in type C is unknown.

   The mutated gene (either NPC1, 95% of families, or NPC2) is located to the pericentric region of chromosome 18 and there is evidence that more than one protein can produce the type C phenotype. Current research, utilising mouse models or cell cultures, aims to determine the pathophysiological mechanisms, aimed at elucidating which stored materials are causative, cholesterol, gangliocides, sphingolipids or other factors [6].

The prognosis and clinical type is determined by the rate of sphingolipid accumulation and the organs affected. For type A disease (approximately 85% of cases) the outlook is poor, with death by the age of eighteen months. Types B and C have a better prognosis, with many patients surviving into their teens or adulthood.

No specific treatment is presently available but current trials include cholesterol-lowering agents and Zavesca, intravenous cyclodextrin (HPbCD). Enzyme replacement has proven difficult. A source of targeted sphingomyelinase, such as implantation of genetically engineered autologous skin fibroblasts, has been proposed [7]. Liver transplantation and bone marrow transplantation have been tried without notable success. Gene replacement may become feasible.

3. Gaucher's disease

The most common of the lysosomal storage diseases, Gaucher's disease is also an autosomal recessive trait and classically exhibits three main clinical variants: onset at childhood or adulthood without neurodegeneration (type 1), infantile onset (type 2), and onset in childhood or early adulthood (type 3); types 2 and 3 show neurodegeneration. The disease is caused by insufficient activity of the lysosomal enzyme acid beta-glucosidase (glucocerebrosidase). This insufficiency arises from more than 300 mutations in the GBA gene on glucocerebrosidase's catalytic function, causing accumulation of its main substrate glucosylceramide with resulting intracellular stability or subcellular trafficking or both. The main clinical effects are hepatosplenomegaly, anaemia, thrombocytopenia and involvement of bone and lungs.

In type 1 disease, which mainly affects primary visceral macrophages, this variant has led to active research into the potential of enzyme therapy by targeting the intravenous enzyme (vide infra). The disease is pan-ethnic with a particularly high frequency of type 1 in Ashkenazi Jews (about 1 in 800 live births) with a probable overall frequency of 1 in 40,000–50,000 live births. About 60% of type 1 patients are diagnosed before the age of 20.

Type 2, the most severe of the classic types, presents in the first few days or months of life with significant CNS involvement, especially with bulbar and oculomotor paresis. It deteriorates rapidly with a median age of death of 9 months. Increasing awareness of the wide range of phenotypes has indicated greater heterogeneity than the previously accepted classical groupings. These limitations have been illuminated by the increasing reports of patients – including those hitherto designated as type 1 – or heterozygote individuals with Gaucher's disease alleles and parkinsonism.

In type 3, juvenile or Norrbottnian, chronic or subacute neuronopathic, there is a less rapidly progressive neurovisceral disease causing death in childhood or early adulthood. There is an increasing tendency to consider the manifestations of Gaucher's disease to be a continuum from mild disease to severe neuronopathic form.

Insufficient catabolism of glucocylceramide and engorgement of macrophages with this substrate account for the visceral manifestations of Gaucher's disease, but the precise pathophysiological mechanisms remain to be elucidated. One proposed mechanism suggests that pro- and anti-inflammatory pathways could be activated through abnormal folding of mutant proteins in the endoplasmic reticulum, an explanation of potential significance to the association with Parkinson's disease.

DNA testing has improved diagnostic accuracy in Gaucher's disease, not only for affected individuals but also for detection