**Case Report**

**Membranoproliferative glomerulonephritis type II and Niemann-Pick disease type C**

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**Introduction**

Niemann-Pick (NP) disease is an autosomal recessive lipid-storage disorder. There are three types, designated types A, B and C. The latter (NP-C) is biochemically distinct from the first two in that it involves defective intracellular processing and transport of low-density lipoprotein (LDL)-derived cholesterol. The clinical manifestations of NP-C are heterogeneous and characterized by hepatosplenomegaly and progressive neurological dysfunction [1]. Renal involvement is uncommon in NP disease, although some cases have been reported in patients with types A or B [2]. We report here a case of membranoproliferative glomerulonephritis type II (MPGN II) observed in a patient with NP-C disease.

**Case**

‘Mr F’, a Caucasian male born in 1965, employed as a civil servant, was first examined in our department in September 1999. He had a complex medical history. The diagnosis of NP disease had been suggested originally when the patient was 3 years of age, because of hepatosplenomegaly with foam cells on the splenogram. However, this diagnosis was later discarded on the basis of normal leukocyte acid sphingomyelinase activity. The patient’s psychomotor development was normal thereafter until adulthood. In 1992, an audiogram revealed a bilateral perception hearing defect.

In 1998, the patient was treated for depression. Renal function was normal at that time, with a plasma creatinine level of 0.84 mg/dl. In April 1999, an annual occupational check-up found evidence of glomerular nephropathy: proteinuria was 4 g/24 h and abundant microscopic haematuria was present. A renal biopsy was scheduled but never performed because the patient developed neuropsychiatric disturbances, including atypical acute delirium and mild pyramidal syndrome associated with increased and diffuse deep tendon reflexes and bilateral Babinski signs. The patient was admitted to the psychiatric ward. A few months later, the neuropsychiatric disturbances had subsided and the patient was referred to our department. On admission, his general status was good and he was of normal morphotype. Despite antipsychotic treatment, mild cognitive disturbances persisted, with psychomotor retardation, mild memory disturbances and dysarthria. The physical examination revealed long-standing hepatosplenomegaly and pyramidal syndrome; oculomotor function was normal. Blood pressure was 150/100 mmHg.

Laboratory tests confirmed the glomerular nephropathy with renal failure: serum creatinine 2.14 mg/dl, serum albumin 35 g/l, proteinuria 4 g/24 h, and haematuria 50 000 RBC/min. Proximal tubular functions were normal [mean maximal transfer (Tm) bicarbonate normal, Tm phosphate subnormal at 2.12 mg/dl, Tm glucose > 200 mg/dl]. The haemoglobin level was 10.5 g/dl, and the platelet count was 128 000/mm³. Investigations of the alternative pathway showed an alternative anti-C3 convertase antibody (C3 NeF) by stabilization of a preformed C3 convertase. HIV and hepatitis B and C serologies were negative. Circulating anticoagulants and antiphospholipid antibodies were negative. All auto-immunity markers were negative as was cryoglobulin.
negative. Brain MRI was normal. Although he had no visual complaints, the ocular findings were drusen scattered in the posterior pole of each eye.

We established a diagnosis of type C NP disease on the basis of a biochemical study of cultured skin fibroblasts which showed intracellular accumulation of unesterified cholesterol following a lipoprotein load, as visualized by filipin staining, and defective intracellular esterification of free cholesterol [3–5]. Leukocyte acid sphingomyelinase activity was normal and an I1061T mutation of the NPC1 gene was not found.

Histology of renal biopsy tissue showed MPGN II with intense mesangial proliferation, increased mesangial matrix, lobular accentuation and capillary wall thickening. The interstitial tissue showed rare foam cells. There was intense C3 staining along the capillary walls with a double-contour linear configuration. Electron microscopy confirmed intramembranous electron-dense deposits, without glomerular foam cells.

Treatment of glomerulonephritis was limited to perindopril without immunosuppressive treatment. One year later, the patient’s course was satisfactory: serum creatinine 120 µmol/l and proteinuria 1 g/24 h with a normal urinary sediment. In contrast, the circulating C3 NeF persisted with a decreased C3. The neuropsychiatric disturbances remained stable.

Discussion

NP disease is characterized by the tissue accumulation of sphingomyelin and other complex lipids. Three types of the disease have been identified: types A and B are characterized by a complete leukocyte acid sphingomyelinase deficiency. Type A is the most severe, and affected individuals die in childhood of severe neurodegenerative disorders. Neurological disturbances are uncommon if not absent in type B, hence the prolonged survival. Visceral localizations of the disease, however, may be severe and lead to chronic respiratory or hepatic failure [6]. Type C, which accounts for 40% of all cases of NP, is biochemically distinct. Leukocyte acid sphingomyelinase activity is normal but is sometimes partially deficient in cultured skin fibroblast. The diagnosis of NP-C disease requires the demonstration of both abnormal intracellular cholesterol processing as defined by impaired cholesterol esterification and intralysosomal accumulation of unesterified cholesterol. The intracellular metabolism of cholesterol is abnormal, but the primary biochemical anomaly remains unknown.

Two genes are involved in type C, but one, the NPC1 gene, is responsible for over 95% of cases. This gene encodes a 142 kDa protein, the function of which is unknown [7]. A variety of mutations are known to occur, the most frequent being the 11061T mutation, found in nearly 40% of the cases of NP-C in Europe [8]. The most common phenotype includes late-onset neuropsychiatric disturbances, which may be the presenting symptoms in adulthood, as was the case for our patient.

Renal involvement is very rarely observed in NP and has only been reported in a few NP-A and NP-B patients, as post-mortem microscopic findings of foam cells in the glomeruli, tubular epithelium or interstitial tissue [2]. Clinical manifestations and alterations of renal function are generally absent. To our knowledge, glomerular nephropathy has never been reported in association with NP. However, Brière [9] reported the case of a young woman with NP-B who developed MPGN I with hypocomplementaemia associated with chronic *Staphylococcus aureus* sepsis. Renal impairment regressed following antibiotic therapy. This case of subacute nephropathy was unrelated to the storage disorder, although the microscopic and histochemical study of the kidney following transparietal biopsy identified the presence of storage cells in the glomeruli and tubular epithelium, with abnormal sphingomyelin and cholesterol accumulation.

Renal involvement is more commonly observed in other sphingolipidoses such as Fabry’s disease, in which endothelial and epithelial glomerular cells and tubes are the site of progressive accumulation of undergraded glycosphingolipid. The result is non-specific lesions of degenerative glomerulosclerosis, interstitial fibrosis and arteriolar sclerosis. Such lesions are observed in other lipid-storage diseases, such as familial lecithin-cholesterol acyltransferase deficiency or Alagille’s syndrome. However, MPGN has never been reported in these diseases as well as in the lipoprotein glomerulopathy. This suggests that the abnormal deposits of lipids and in particular of sphingomyelin do not induce the glomerular lesions observed here. Moreover, in our patient, the electronic microscopy did not show any lipidic deposits. In fact, if there is a pathophysiological link between NP-C and MPGN II, it is probably an indirect one.

In conclusion, the association of these two rare diseases, NP-C and MPGN II, is perhaps fortuitous but should serve to draw the attention of physicians who manage such patients to the possibility of renal involvement.

References


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