Refsum's disease in an Arabian family

Refsum's disease is a rare, autosomal recessive neurometabolic disease, characterised biochemically by accumulation of phytanic acid in blood and tissues.[1] This is due to deficiency of the peroxisomal enzyme phytanoyl-CoA-hydroxylase (PAHX), caused by mutations of the PAHX gene on chromosome 10.[2] As phytanic acid is exclusively of exogenous origin, patients with Refsum's disease are treatable by a diet low in phytanic acid and the phytanic acid precursor.[3] A clinical tetrad of peripheral neuropathy, retinitis pigmentosa, cerebellar syndrome, and increased CSF protein concentration was reported in most patients with Refsum's disease.[1 4]

We present long term clinical and biochemical findings in an Arabian patient, finally diagnosed as having Refsum's disease. In 1991, this 34 year old man from Egypt presented with progressive gait disorder and visual field constriction. Born in Souhag, he descended from a consanguineous union. At 19 years of age, he sustained thyphoid fever; since then he had noted hyposmia. At 31 years of age, he emmigrated to Austria. Symptoms started insidiously 1 year later. Neurological examination showed bilateral sickle form restriction of temporal visual fields, wasting of leg muscles with foot drop, absence of tendon reflexes, and loss of proprioceptive sensation. Laboratory findings were normal, except for mild neutropenia (white cell count 3.2 g/l) and raised creatine phosphokinase (113 U/l). Bone marrow biopsy and immunological typing of leucocytes were normal. Tests for tuberculosis, borreliosis, brucella abortus and mellitensis, leishmaniosis, HIV, herpes simplex, cytomegaly, Epstein-Barr virus, syphilis, and antinuclear antibodies were all negative. Chest radiography, ECG, funduscopy, and brain MRI were normal. Electromyography disclosed a severe sensorimotor demyelinating polyneuropathy (for example, median nerve motor conduction velocity 32 m/s). Protein concentration in CSF was increased (1.01 g/l). Sural nerve biopsy confirmed the occurrence of a combined axonal and demyelinating neuropathy with moderate onion bulb formations and a severe reduction of myelinated fibres. Hence, a diagnosis of hereditary sensorimotor neuropathy type I was made.

In 1998, the patient was readmitted because neuropathy had progressed (median nerve motor conduction velocity 27 m/s). Bilaterally, short fourth toes were noted. Pathological laboratory findings (neutropenia, raised creatine phosphokinase) were unchanged; ECG, EEG, visual evoked potentials, and brain MRI were normal. Skeletal radiography showed bilateral shortening of the fourth metatarsal bones. Funduscopy and electroretinography confirmed the presence of retinitis pigmentosa. Molecular genetic testing for Charcot-Marie-Tooth disease type 1A and hereditary neuropathy with liability for pressure palsies was negative. However, markedly raised phytanic acid concentrations (778 μmol/l) and occurrence of diphytanyl and monophytanyl triglyerides (8% and 36% of total triglycerides) were detected in plasma by gas and thin layer chromatography.[5] Thus, on the basis of clinical and biochemical findings, the diagnosis of Refsum's disease was established. A dietary treatment low in phytanic acid and phytol, avoiding fat dairy products as well as plant fats and oils containing phytol, was given. Within a 2 year follow up neuropathy remained unchanged. Subsequently, gonarthritis and, finally, arthritis of both shoulders became apparent. Biochemically, there was fluctuation of raised plasma phytanic acid and phytanyl triglyceride concentrations.

Plasma samples for phytanic acid and phytanyl triglyceride assays in the patient's relatives became available in 1999. The family has lived in the same location in southern Egypt for several generations; the father's mother and the mother's grandmother were sisters. The patient has two brothers (born 1951 and 1962) and two sisters (born 1952 and 1954). The elder brother has symmetric weakness of legs starting at 28 years of age and night blindness. Neurological examination at the Cairo University Hospital in 1986 documented severe sensorimotor neuropathy with wasting and weakness of both legs. Concentration of phytanic acid in plasma was increased (994 μmol/l) and diphytanyl and monophytanyl triglycerides (1% and 12% of total triglycerides) were found, substantiating a diagnosis of Refsum's disease. Both children of the newly detected patient as well as both sisters and their children are healthy. Our patient's younger brother seems healthy, but plasma samples were not available. Our patient's father, born 1928, has diabetes mellitus type II and mild Parkinson's disease; his mother, born 1931, is healthy. In all these persons normal phytanic acid and trigylceride values were obtained.

Refsum's disease is predominantly found in Scandinavians and the populations originating from northern Europe, but is also seen among other ethnic groups and locations where any connection with the Vikings is unlikely.[1] In Austria (8 million inhabitants), 11 patients with Refsum's disease were detected within six families. To our knowledge, this is the first report on the occurrence of Refsum's disease in an Arabian family from Egypt, manifestating in two brothers from consanguineous antecedents. Thus, neurologists should be alert in diagnosing and treating Refsum's disease in this population.

Our patient's clinical phenotype was that of classic adult Refsum's disease, however, without a cerebellar syndrome. Absence of cerebellar and other brain lesions was substantiated by repeatedly normal brain MRI imaging, a finding not reported hitherto in Refsum's disease. Our findings therefore seem to question the validity of cerebellar involvement as a component of the clinical tetrad in Refsum's disease.[1 4] There is ample evidence that Refsum's disease is an affection of the peripheral nervous system, and gait ataxia caused by loss of proprioceptive sensation may mimick cerebellar ataxia.

Skeletal abnormalities, particularly the bilateral shortening or elongation of the third and fourth metatarsal and metacarpal, are common findings in Refsum's disease[1]; in our patient only symmetrically short fourth metatarsal bones were present (fig 1). Obviously, the short toes were overlooked at the first presentation, because monosymptomatic neuropathy was falsely suspected. Thus, the finding of short toes in a patient with otherwise unexplained demyelinating neuropathy may prompt the clinical diagnosis of Refsum's disease.

Recurrent neutropenia occurring in our patient could not be explained by common causes of neutropenia such as chronic infection, toxic drug effects, inflammatory diseases, or hypersplenia. A toxic effect of phytanic acid on leukopoetic bone marrow cells might be considered; however, neutropenia has not been described in Refsum's disease hitherto.[1] Speculatively, there might be a coincidence of idiopathic granulocytopenia and Refsum's disease in our patient.

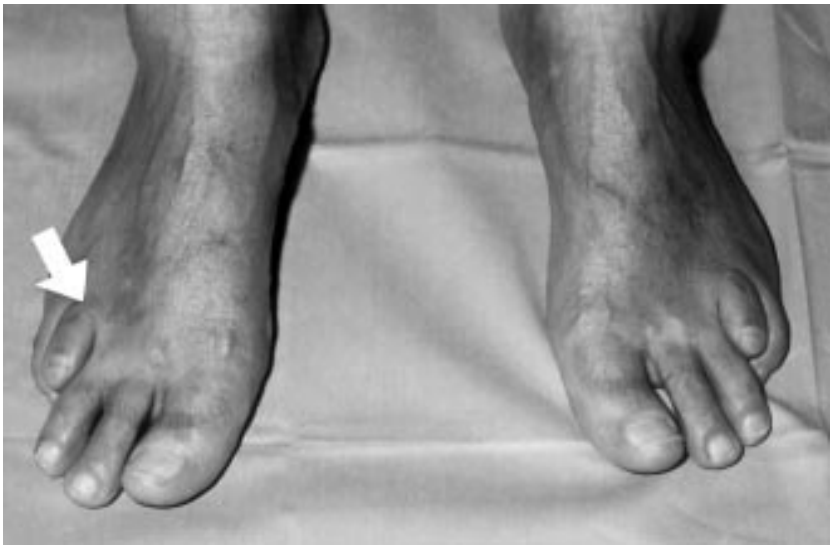

Figure 1 Refsum's disease in an Arabian patient. Symmetric short fourth toes (arrow).

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A case of malignant lymphoma exhibiting multiple cranial nerve enhancement: leptomeningeal metastasis? Or another lymphoma associated event?

The frequency of the involvement of non-Hodgkin's lymphoma in the CNS has been reported to be less than 10%.[1–3] Moreover, as those patients have often been resistant to both chemotherapy and radiation therapy, their prognosis has been very poor.[1–3] We report herein a rare case of malignant lymphoma showing bilateral homogenous and symmetric enhancement of multiple cranial nerves, with the patient's postmortem examination providing controversial pathological findings. A 50 year old woman developed supraclavicular lymph node swelling about 1 year ago, and was diagnosed as having malignant lymphoma (non-Hodgkin's lymphoma, diffuse large B cell type) after pathological examination of the lymph node. She then received systemic chemotherapy and peripheral blood stem cell transplantation. After six courses of CHOP therapy, she achieved complete remission and was discharged. A few weeks later, she gradually lost her appetite and her temperature remained consistently raised above 38°C for several days. One day before readmission, she noticed double vision, dysphagia, and hoarseness. Neurological examination demonstrated bilateral ptosis, dilatation of bilateral pupils being sluggishly reactive to light, paralysis of extraocular movement, paralysis of soft palate movement, and bilateral hearing disturbances. Except for the involvement of cranial nerves, no other neurological deficits were evident. Intriguingly, her cranial MRIs demonstrated marked bilateral swelling of oculomotor nerves and trigeminal nerves, both with homogenous gadolinium (Gd) enhancement (fig 1A and B). The facial and acoustic nerves showed Gd enhancement partly in the their canals. The accessory nerves also demonstrated homogenous enhancement without definite swelling. Within the spinal cord, some of the cauda equina showed partial Gd enhancement (figure E). Cerebrospinal fluid examination disclosed pleocytosis (64/mm^3) and raised protein content (586 mg/dl). Cytological examinations demonstrated class V, which were compatible with malignant lymphoma cells. On the basis of these findings, we suspected the recurrence of malignant lymphoma in the CNS system, and performed whole brain irradiation and intrathecal administration of both methotrexate (MTX) and cytosine arabinoside (Ara-c). Even after a total of 20 Gy irradiation and four courses of intrathecal chemotherapy, her clinical symptoms did not improve, and lymphoma cells still remained in the CSF. The number of cells (8/mm^3) and protein content (84 mg/dl) in the CSF, however, had very much improved, repeated MRI studies could not detect any Gd enhancement in the cranial nerves, and previously recognised swelling in the oculomotor nerves and trigeminal nerves had been fully resolved. During the course of her treatments, she developed multiple organ failure, disseminated intravascular coagulation, and finally she died. Postmortem examination disclosed massive infiltration of lymphoma cells into the liver, kidney, bone marrow, and visceral lymph nodes. Lymphoma cells were recognised histologically in the dura and cauda equina, which had previously exhibited Gd enhancement in the spinal cord (fig 1E and F). Immunohistochemical examinations of that specimen indicated that these infiltrating cells were positive with L26, and were subsequently determined to be B cell lymphoma. However, despite our further extensive investigations of other parts of her CNS, no lymphoma cells could be detected, even in the cranial nerves that had shown previous Gd enhancement. Additionally, we could not detect even the smallest traces of the previous tumour infiltration including their necrosis affected by the irradiation or intrathechal chemotherapy (fig 1C). Without any infiltration of lymphoma cells, the oculomotor nerves and trigeminal nerves had markedly lost Luxol fast blue (LFB) staining and indicated a wide range of myelin damage (fig 1D). Until now, the enhancement of cranial nerves or spinal nerve roots on MRI has often been reported in inflammatory neuropathies, such as chronic inflammatory demyelinating

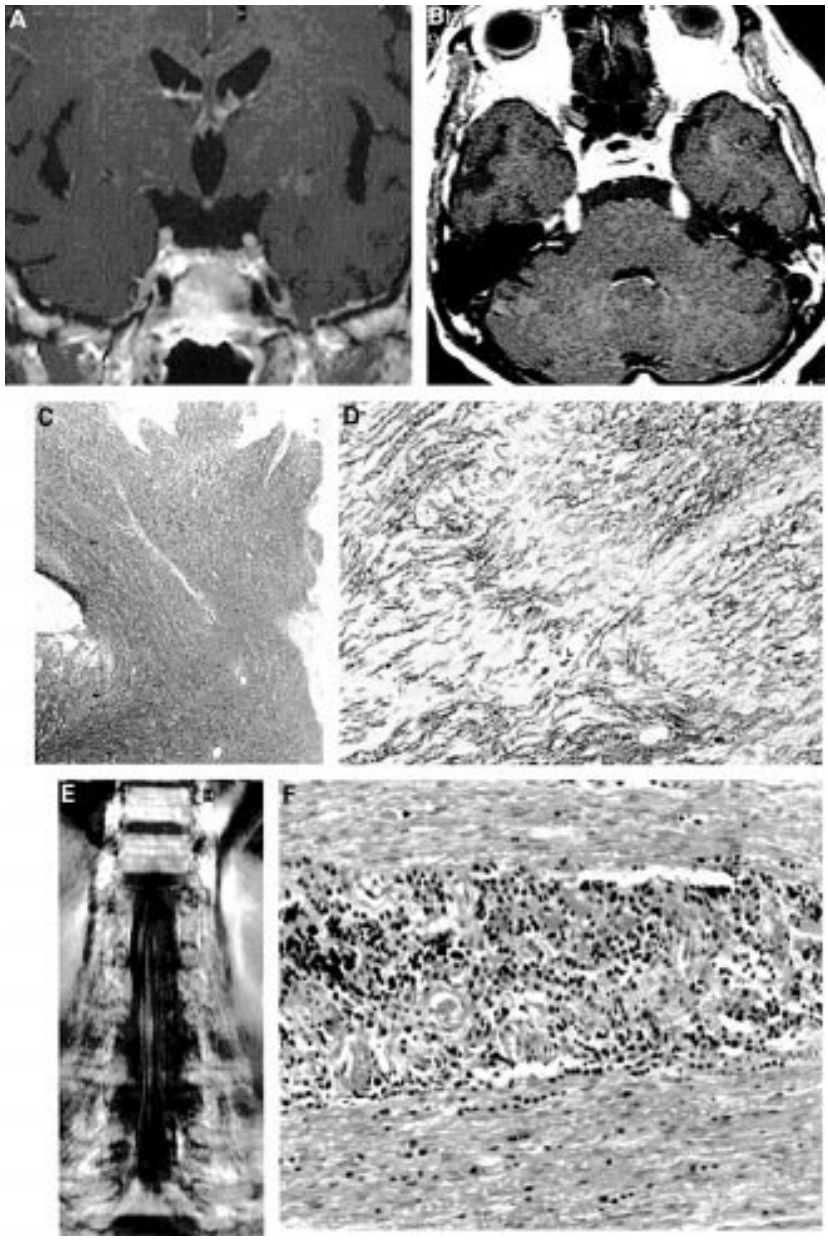

Figure 1 (A) Bilateral oculomotor nerves show homogenous Gd enhancement with marked swelling. (B) Bilateral trigeminal nerves exhibit symmetric homogenous Gd enhancement with marked swelling. (C) Microscopically, no lymphoma cells are evident in the trigeminal nerves. Moreover, neither inflammatory cell infiltrates nor vasculitic changes are seen (haematoxylin and eosin staining). (D) In addition to the loss of myelin staining, myelinated fibre connections are disrupted in the trigeminal nerves (Luxol fast blue staining). (E) Some of the cauda equina exhibit partial Gd enhancement without swelling. (F) Histological examinations disclosed that malignant lymphoma cells were infiltrating into the cauda equina in which the spinal MRI demonstrated partial Gd enhancement.