CLINICAL CASE PRESENTATION – FABRY’S DISEASE

The patient

The patient was a 48 year old man who worked as a railway repair man. He presented to his general practitioner suffering from vomiting, general vagueness (which was confirmed by his wife) and loss of coordination. The general practitioner (GP) carried out some blood tests which showed that the patient’s renal function tests were high.

Within ten days of his presentation he was referred to his local hospital. Here the GP’s findings were confirmed. He had a lack of short-term memory, had suffered from frontal morning headaches for a month, he dropped things because of his poor coordination, and his blood pressure was 180/110 for which he was put onto atenolol.

At this time his blood tests were as follows:

- Sodium: 138 mmol/L
- Potassium: 6.2 mmol/L
- Bicarbonate: 22 mmol/L
- Urea: 26 mmol/L
- Creatinine: 650 μmol/L
- Urine protein: 1.5 g/L
- Haemoglobin: 9.4 g/L

Normal white blood cells

- ESR: 8

A chest x-ray showed no abnormalities, but a hint of prominent vasculature with upper lobe venous diversion. An MRI scan showed that the head showed large ventricles, other CSF spaces not compressed, no focal lesions, and appearances consistent with communicating hydrocephalus. An electrocardiogram showed lateral T-wave inversion and left ventricular hypertrophy.

Microbiological and immunological tests were normal.

Ultrasound examination of the abdominal cavity showed that the liver, biliary system, spleen, bladder and prostate appeared to be normal, with no ascites and no lymphadenopathy. His kidneys appeared to be somewhat small (with a bipolar diameter of 9.0 cm) by they were not hydrenephrotic.

His lumbar puncture pressure was high (38 cm of water) and the protein content of the CSF was 1.28 g/L.

He was treated with fluids, dextrose and saline, with insulin, glucose and calcium. This therapy brought his potassium level down from 7.8 mmol/L to 5.4 mmol/L. He was also give frusemide, but this did not increase his urinary output to more than 30 ml/hr. It was then decided to discharge him from the hospital, although his urea level had now risen to 41 mmol/L and his creatinine to 857 μmol/L; at the same time his bicarbonate level had fallen to 18 mmol/L.

However, on his way out of the hospital he fell badly and injured his head, face and right shoulder. He was therefore re-admitted. At this stage it was noticed that he had a skin rash in a “bathing-trunk” distribution. A dermatologist’s advice was sought. The dermatologist’s report stated that: “There are vascular lesions on the buttocks, groin, penis and scrotum. They are small angiomas, probably angiokeratomas. In this case this is either an incidental finding or an indication of Fabry’s disease.”

The rash appeared like that in Fig. 1.

Figure 1 Appearance of the rash

The patient was then transferred to the nearby teaching hospital, where a renal biopsy was performed. The histologist’s report on the biopsy stated: “the only glomerulus available for e.m. is rather collapsed and somewhat sclerosed;

some of the podocytes contain numerous lipid rich vacuoles which have the striped appearance of ‘zebra bodies’ of Fabry’s disease. The possibility of Fabry’s disease should be further investigated biochemically.”

This biochemical investigation showed an α-galactosidase-A activity of 3 units - the normal range being 16-64 units. This finding confirmed the views of the dermatologist and the histopathologist that this is a case of Fabry’s disease.

The patient was then transferred to the renal unit in order that he might benefit from renal dialysis.
Fabry’s disease

Fabry's disease is also known as the Anderson-Fabry disease as both Anderson (1) and Fabry (2) wrote papers about different aspects of the disease in the same year (1898). It is also known as "angio-keratoma corporis diffusum" – a description of the dermatological symptoms - and a-galactosidase-A deficiency – a description of the inherited metabolic defect that causes the condition (3). It is now classed as a glycosphingolipid storage disorder.

The inherited deficiency of a-galactosidase-A leads to an inability to break down glycosphingolipids with a terminal a-galactosyl moiety, mainly globotriaosylceramide (Gal-Gal-Glu-ceramide) or, sometimes, galabiosylceramide (Gal-Gal-ceramide). These glycosphingolipids are deposited in the lysosomes of many visceral tissues, especially in the vascular endothelium.

The disorder is transmitted by an X-linked gene and is therefore more potent in male than in female subjects – but heterozygous female subjects can experience an attenuated form of the disease or they may be totally asymptomatic. Diagnosis is by means of the demonstration of a deficiency of the a-galactosidase-A enzymes. This deficiency can be observed in plasma cells, or white blood cells, but the accumulated glycosphingolipid can also be identified in plasma or urine sediment.

The clinical features of the disease include pain which often occurs in childhood or adolescence (but not apparently in the patient described above).

Other clinical effects include:
- Anaemia – very frequent
- Cataract – very frequent
- Renal failure – very frequent
- Angiokeratoma – almost invariable
- Telangectasia mucous membranes / skin
- Hypertension – frequent
- Emphysema – frequent
- Mild mental retardation - sometimes

Dermatologically, there are skin lesions with characteristic angiokeratoma lesions, especially in a "bathing-trunk" distribution – but there is wide variation between patients.

There are cardiac and renal manifestations. These conditions are due to the build-up of glycosphingolipids in these tissues, causing abnormality of function.
- The renal manifestations are seen both in the renal tubules and in the glomeruli and often lead to renal failure.
- The cardiac manifestations are widespread, causing chest pain, cardiac enlargement and myocardial ischaemia, factors that may be complicated by systemic hypertension. In addition, other cardiovascular signs may be seen, including conduction defects; hypertension and its consequences; ischaemic heart attacks; mitral insufficiency; and thrombosis.

There are ophthalmic complications such as: corneal opacities; cataracts; dilated and tortuous retinal vessels; and papilloedema +/- hypertensive changes.

Neurological complications include ischaemia and infarction in cortical and brainstem areas; strokes, seizures, personality changes and hemiplegia; mental retardation presents rarely and is often fairly minor.

There can be gastrointestinal problems, including abdominal and flank pain; diarrhoea; hepatomegaly; and nausea and vomiting.

Other clinical features include chronic chest problems, with dyspnoea and wheezing. Smokers are particularly prone to such effects. Lymphoedema of the legs and varicose veins can also occur, as can priapism. Patients may also suffer from anaemia due to shorter red-cell survival times.

There are also effects on the musculo-skeletal system.

The treatment of the disease falls into two phases:
1). If the disease is well-established there will be secondary problems, such as renal failure, cardiovascular problems, ocular complications and/or neurological disease. Clearly these must be treated by the standard methods for these conditions.
2). Replacement of the abnormal gene or the abnormal enzyme is a topic that has been studied for some years and some workers believe that we are now at the stage when one or other of these replacement programmes can help the patients, particularly if diagnosed early in life. References to such work are given in the reference list (5,6,7).

In summary, Mendez, Stanley & Medel have stated that "Fabry's disease can present as an insidious dementia in middle or later life. It should be considered in the work-up of otherwise unexplained dementia in males of less than 65".

References

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Suggestions for further reading (the appropriate sections from the following textbooks)

Warrell David A., Cox Timothy M., Firth John D., Benz, Edward J., Smith Richard, and Smith, Susan. Oxford Textbook of Medicine, 4th ed. (2003)
Braunwald, E., Fanci, A. S., Kasper, D. L., Hauser, S. L., Longo, D. L. and Jameson, J. L. "Harrison’s Principles of Internal Medicine" 15th edition, McGraw-Hill, (2001)
Charles R Scriver (Editor), William S. Sly (Editor), Barton Childs, Arthur L. Beaudet, David Valle, Kenneth W. Kinzler, Bert Vogelstein, “The Metabolic and Molecular Bases of Inherited Disease”, 4 volume set (2000) 8th Edition McGraw-Hill

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