Teenager Male with Burning Pain in Extremities – Suspect Fabry Disease, 2 Case Reports

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Abstract

Introduction: We present 2 cases of teenager males presented with burning pain in extremities and turned out to be cases of Fabry disease. The purpose of presenting this case is to highlight the fact that suspicion of Fabry disease in patients presenting with these symptoms will lead to early diagnosis and treatment of this condition before occurrences of complications.

Case Report 1: A 14-year-old male presented with severe burning pain in both hands and feet since last 4 yrs which persisted despite consumption of painkillers and becoming more disabling and without having any family history for such condition. On general examination patient had small reddish coloured lesions around the umbilicus, appearing like angiokeratomas. Skin biopsy confirmed the lesion. On enzyme assay his alpha galactosidase activity found to be ‘0’ nmol/hr/mg of protein, confirming his diagnosis. Patient's creatinine and 2 D ECHO were normal and urine had 1+ proteinuria. Patient started on carbamazepine tablets for pain and referred to higher centre for genetic diagnosis and enzyme replacement therapy.

Case Report 2: An 18-year-old male referred to our hospital by general practitioner for fatigue and pedal oedema with deranged renal function tests. On history taking patient gave history of severe burning pain in both hands and feet since age of 9 yrs. Patient’s general examination revealed hypertension with pallor, pedal oedema along with angiokeratomas in bathing suit distribution. Patient’s ultrasonography of kidney revealed bilaterally normal sized kidneys with altered echotexture and urine examination showed fine granular foamy cells with sub nephrotic range proteinuria. 2 D ECHO revealed concentric left ventricular hypertrophy. Skin biopsy report supported the diagnosis of Fabry disease. Patient advised to undergo renal biopsy to confirm Fabry nephropathy but patient denied any further diagnostic workup for nephropathy or Fabry disease. Patient started on conservative treatment and carbamazepine in renal dose given for acroparaesthesias. On discharge patient has been advised to visit higher centre for further diagnostic work up and enzyme replacement therapy.

Conclusion: Suspicion of Fabry disease in teenager males presenting with symptoms of burning pain in extremities may lead to early diagnosis and treatment of this condition before occurrences of complications.

Introduction

Fabry disease is X linked lysosomal storage disease. It results from deficiency of enzyme alpha galactosidase and causes lysosomal deposition of globotriaosylceramide in cells throughout the body. It has its onset in childhood with severe pain in extremities (acroparaesthesias). It is associated with vascular cutaneous lesions (angiokeratomas), hypohidrosis, characteristic corneal opacities (cornea verticillata) and proteinuria which in untreated patients progress to end stage kidney disease. Cardiovascular and
cerebrovascular diseases also cause mortality and morbidity in later years of life. We present 2 cases of teen aged males presented with burning pain in extremities which turned out to be cases of Fabry’s disease. The purpose of presenting this case is to highlight the fact that suspicion of Fabry’s disease in patients presenting with these symptoms will lead to early diagnosis and treatment of this condition before appearances of complications.

Case Report 1

A 14-year-old male born to parents with third degree of consanguinity presented with severe burning pain in both upper and lower extremities. He was asymptomatic till about age of 10 yrs, when he started complaining burning sensations in both feet which gradually progressed upwards and which later also accompanied by similar sensations in hands. The symptoms were intermittent and not associated with any swelling or increase in local temperature. Symptoms gradually increased in frequency and intensity, particularly during summer months. Patients had shown to general practitioner, who diagnosed his condition as arthritis and prescribed different painkiller medications which were ineffective for controlling pain of the patient. As pain gradually became disabling, patient came to us. No history of similar disorder in family present. On examination no coarsening of facial features seen but reddish cutaneous vascular lesions seen around the umbilicus which appeared like ‘angiokeratomas’, nervous system examination was suggestive of small fibre sensory neuropathy. Patient’s serum uric acid, creatinine were normal and tests for antinuclear antibody and rheumatoid factor were negative. Urine examination revealed 1+ proteinuria. Slit lamp examination of cornea revealed corneal opacities named as ‘cornea verticillata’. Skin biopsy confirmed the diagnosis of angiokeratomas. On enzyme assay, his alpha galactosidase activity was ‘0’ nmol/hr/mg of protein (normal range: 1.23-8.20 nmol/hr/mg of protein) and patient’s diagnosis confirmed as case of Fabry disease. Patient’s ECG and 2 D- ECHO were normal as his ultrasonography of kidneys. Patient started on carbamazepine tablets for pain to which response was ineffective for controlling pain of the patient. Patient’s general examination revealed blood pressure of 146/92 mm of Hg with pallor, minimal pedal oedema over shin along with classical angiokeratomas in bathing suit distribution (Figure 1). Investigations revealed haemoglobin of 8.0 gm%, WBC count of 8600 cells/ cumm and normal platelet count, creatinine 3.0 mg/dl and blood urea 64 mg/dl, creatinine clearance was 32 with Cockcroft and Gault equation. Patient’s ultrasonography of kidney revealed right kidney 10.3 x 3.2 cms and left kidney 10.3 x 4.8 cms with altered echogenicity and urine examination revealed fine granular foamy cells on smear and proteinuria of 1167 mg/24 hrs of urine. 2 D ECHO revealed left ventricular hypertrophy with good left ventricular function. Slit lamp examination revealed few corneal opacities. Skin biopsy report confirmed the diagnosis of angiokeratomas and supported the diagnosis of Fabry disease. Patient advised to undergo renal biopsy to confirm Fabry nephropathy but patient denied any further diagnostic workup for nephropathy or Fabry disease. Patient started on conservative treatment and carbamazepine in renal dose given for acroparaesthesias. On discharge patient has been advised to visit higher centre for further diagnostic work up and enzyme replacement therapy.

Case Report 2

An 18-year-old male born to non-consanguineous parents referred to our hospital by general practitioner for deranged renal function tests. Since last 6 months patient noticed on and off swelling of both lower limbs, mainly present in morning which decreases as day passes and mild fatigability, for which patient shown to general practitioner and undergone some blood tests. On history taking patient revealed severe burning pain in both hands and feet since age of 9 yrs. He was asymptomatic till about age of 9 yrs, when he started complaining of burning sensations in both feet which gradually progressed upwards and which later also accompanied by similar sensations in hands. The symptoms were intermittent and not associated with any swelling or increase in local temperature. Symptoms gradually increased in frequency and intensity for which patient had shown to general practitioner and started taking painkiller medications which gave some relief to the patient. Patient’s general examination revealed blood pressure of 146/92 mm of Hg with pallor, minimal pedal oedema over shin along with classical angiokeratomas in bathing suit distribution (Figure 1). Investigations revealed haemoglobin of 8.0 gm%, WBC count of 8600 cells/ cumm and normal platelet count, creatinine 3.0 mg/dl and blood urea 64 mg/dl, creatinine clearance was 32 with Cockcroft and Gault equation. Patient’s ultrasonography of kidney revealed right kidney 10.3 x 3.2 cms and left kidney 10.3 x 4.8 cms with altered echogenicity and urine examination revealed fine granular foamy cells on smear and proteinuria of 1167 mg/24 hrs of urine. 2 D ECHO revealed left ventricular hypertrophy with good left ventricular function. Slit lamp examination revealed few corneal opacities. Skin biopsy report confirmed the diagnosis of angiokeratomas and supported the diagnosis of Fabry disease. Patient advised to undergo renal biopsy to confirm Fabry nephropathy but patient denied any further diagnostic workup for nephropathy or Fabry disease. Patient started on conservative treatment and carbamazepine in renal dose given for acroparaesthesias. On discharge patient has been advised to visit higher centre for further diagnostic work up and enzyme replacement therapy.

Discussion

The diagnosis of Fabry disease among the children in absence of family history is difficult. The average age at diagnosis is 29 yrs which in our cases were 14 and 18 yrs and average duration between onset of symptoms and age of diagnosis is around 10.8 yrs which in our cases were approximately 4 and 9 yrs respectively. Initial presentation as nonspecific symptoms leads to misdiagnoses and delays the diagnosis of Fabry disease. Some patients do not have classical angiokeratomas which were present in both our cases which leads to rare consideration of this disease as a possibility. Fabry disease accounts for about 1% of end stage kidney disease, 6.3% of the late onset hypertrophic cardiomyopathy and 4.9% in males and 2.4% in females of cryptogenic stroke.2-4 The
vascular involvement of heart, kidneys, brain leads to mortality and morbidity.

Enzyme replacement therapy (ERT) is available. Reversal of the metabolic and pathologic abnormalities in the cells and tissues are the key therapeutic goals of ERT. These changes should, in turn, result in improvement of symptoms and prevention of disease complications. Recombinant α-Gal A (agalsidase β) [Fabrazyme], agalsidase alfa [Replagal] are approved for use. Replagal is intravenously administered at a dose of 0.2 mg/kg every 2 weeks, and Fabrazyme is intravenously administered at a dose of 1 mg/kg every 2 weeks.

Current proposed guidelines for starting enzyme replacement therapy in Fabry disease patients

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Guidelines for onset of ERT</th>
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<tbody>
<tr>
<td>Adult males (over 16 years)</td>
<td>At time of diagnosis of Fabry disease</td>
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<tr>
<td>At time of development of significant symptoms or if asymptomatic, consider at 7-10 years</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>Symptoms or evidence of progression of organ involvement</td>
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<tr>
<td>Females (all ages)</td>
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In clinical trials, patients treated with agalsidase had a lower annualised rate of GFR decline compared with those in the placebo group. Agalsidase may help stabilise kidney function in Fabry disease. Clinical trials with recombinant α-Gal A showed that ERT is safe and well tolerated, except for mild-to-moderate infusion–associated reactions, which have been managed conservatively. Fabrazyme was shown to clear globothriasoylceramide from the plasma and capillary endothelium of the major sites of pathology, such as the kidney, heart, and skin. The rate of progression of renal, cardiac, and cerebrovascular complications and death among patients who received ERT was reduced.

**Conclusion**

Suspicion of Fabry disease in teenager males presenting with symptoms of burning pain in extremities will lead to early diagnosis and treatment of this condition before occurrence of complications.

**References**