CASE REPORT

Lessons from two cases: is Fabry disease the correct diagnosis?

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SUMMARY

Fabry disease (FD) is an X linked inherited lysosomal storage disorder with complex multisystem involvement; it is caused by deficiency of the lysosomal enzyme α -galactosidase. Deficient enzyme activity leads to a wide spectrum of clinical manifestations consisting of dermatological, ophthalmological, cardiovascular, and urinary and central nervous system findings. As a result, FD should be considered in the differential diagnosis of many systemic diseases. Diagnosis of FD can arise from careful clinical and instrumental investigations, together with family history data and accurate interpretation of genetic and enzymatic analyses. Lack of knowledge on clinical findings of the disease and inept investigation methods unfortunately result in erroneous diagnosis. We present two patients who were referred to our clinic with a suspicion of ED and finally diagnosed as glycogen storage disorder type III and ornithine transcarbamylase deficiency, respectively.

BACKGROUND

Fabry disease (FD) is an X linked inherited lysosomal storage disorder caused by deficiency of the lysosomal enzyme α -galactosidase. Deficient enzyme activity leads to increased storage of globotriaosylceramide in the eyes, kidneys, skin, nervous system, vessels and cardiovascular system. Clinical manifestations of FD include progressive renal and cardiac insufficiency, neuropathic pain, stroke, skin and eye involvement, and gastrointestinal symptoms.¹ Clinical-onset usually starts in childhood whereas diagnosis could be delayed in some patients until adulthood. Although disease is X linked inherited, females often exhibit the same clinical findings as males, and both can die prematurely due to stroke, renal failure or cardiac disease.²

The diagnosis of FD may be challenging due to wide clinical diversity of symptoms. The most frequent misdiagnosis in FD is rheumatic fever. Previous studies revealed that FD is misdiagnosed as many systemic diseases such as gout, gastroesophageal reflux, growing pains, irritable bowel disease and psychogenic diseases.^{3,4} The frequency of misdiagnosis decreases with the rising awareness of FD. However, lack of knowledge on clinical findings of the disease and inept investigation methods unfortunately result in erroneous diagnosis. We present two cases that were misdiagnosed as FD.

CASE PRESENTATION**Case 1**

A 21-year-old man was referred to the paediatric metabolic diseases outpatient clinic of Cerrahpasa

Medical Faculty for treatment of FD. He was the first child of non-consanguineous parents. When the patient was 1 month of age, he had had a seizure that responded well to medication. At the age of 3, hepatomegaly was detected on his physical examination, but no further investigation was carried out. The patient had no further symptoms until the age of 20, when fatigue, weakness and palpitation started. His echocardiography revealed left ventricular hypertrophy, thought to be a cardiac manifestation due to FD. Molecular analysis for FD resulted as hemizygous polymorphism in GLA gene (c.-30G>A).

The patient's initial physical examination at our outpatient clinic revealed 10 cm hepatomegaly and 5 cm splenomegaly. He had no angiokeratomas and his eye examination was normal. His blood biochemical evaluation showed elevated levels of aspartate transaminase 178 IU/L, alanine transaminase 131 IU/L, creatine kinase 3898 IU/L with normal lipid profile. No proteinuria was detected in urine analysis. The patient's physical and laboratory findings were more consistent with glycogen storage disorder type III (GSD) than FD. As his first molecular analysis revealed a hemizygous polymorphism in GLA gene, in order to rule out diagnosis of FD, enzyme analysis was performed and α -galactosidase activity was found to be normal (3.7 μ mol/L/h; N>2.5 μ mol/L/h). Molecular examination revealed a well-known homozygous mutation specific for GSD type III (p.W1327X (C.3980G>A)).

Case 2

A 19-year-old woman was admitted to the internal medicine outpatient clinic with a history of headache and extremity pain from early childhood. The patient's family history was positive for FD. Her seizures had started at 4 years of age and she had undergone hospitalisation in an intensive care unit because of status epilepticus at 18 years of age. Owing to her family history, α -galactosidase enzyme activity was measured and was 148, 88 pmol/spot*21 h (N: 450–2000 pmol/spot*21 h). Because of the decreased enzyme activity the patient was diagnosed as FD and was referred to our outpatient department.

Her physical examination revealed no pathology. Her eye examination was normal; her echocardiography showed no pathology and no protein excretion was found in her urine sample. As her medical history and physical examination were not consistent with FD, mutation analysis was performed to rule out FD, and no mutation on GLA gene was found.

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The patient's brain MRI showed total atrophy of the brain. She had mental retardation with an IQ level of 43. She avoided foods with high-protein content. Investigation for other inherited metabolic disorders that should be thought of in the differential diagnosis was started and a high level of ammonia was detected (336 mmol/L). Plasma quantitative amino acid analysis, acylcarnitine profile and urine organic acid analysis were normal except for high glutamine levels. Orotic acid excretion was detected in the urine. According to clinical and laboratory findings, ornithine transcarbamylase (OTC) deficiency was considered as a diagnosis, and a heterozygous mutation that was well known for OTC deficiency on exon 5 c.422G>C (p.Arg141Pro) was defined.

DISCUSSION

FD is an X linked inherited lysosomal storage disorder. The disease incidence has been estimated at 1/40 000–1/60 000 live births for males. Although the disease is X linked inherited, many heterozygote females often exhibit the same manifestation as males.² FD is a complex disorder with multisystem involvement. Clinical presentation of the disease is highly heterogeneous and includes neurological system manifestations such as acroparesthesia, hypohidrosis, gastrointestinal disturbances and fever attacks. Angiokeratoma and corneal dystrophy (cornea verticillata) are characteristic but not specific findings for the disease. Progressive renal insufficiency, and cardiovascular, peripheral and central nervous system disease, are the main causes of morbidity and mortality in FD.⁵

Misdiagnosis of FD has been mentioned in various reports. Owing to growing knowledge about the disease and its clinical diversity, frequency of misdiagnosis has significantly decreased. As the disease can manifest in a wide spectrum, the patient should first be seen by a cardiologist, internal diseases specialist, paediatrician, neurologist, rheumatologist, dermatologist and ophthalmologist. Physicians should be alert early on for the signs and symptoms of FD because it is a curable disease. The diagnosis of FD is easier with knowledge of a positive family history. However, misdiagnosis is sometimes inevitable if the physician has no experience in recognising and treating FD. There have been several reports of patients suffering from FD being misdiagnosed as familial Mediterranean fever, mucopolysaccharidosis type 1 and familial cavernous cerebral angiomas.^{3 4 6–8}

We present two patients who were referred to our clinic with suspicion of FD, and finally diagnosed as GSD type III and OTC deficiency, respectively. Both cases had specific laboratory and physical examination findings that were not consistent with FD. As a detailed medical history was evaluated carefully in the first case, hepatomegaly and seizure history probably due to hypoglycaemia led us to the definite diagnosis. The second case

had no FD manifestations except extremity pain, however, her family history misled the physician to FD diagnosis.

Diagnosis of FD must be considered after careful medical history taking and physical examination. However, due to the heterogeneous expression of the disorder, absence of classical symptoms does not exclude FD.⁸ In any case, clinicians should avoid erroneous diagnosis of FD in a patient with positive family history when clinical and laboratory findings do not support the disease.

In conclusion, detailed and careful medical history should be taken, and physical and laboratory findings should be carefully evaluated before the definite diagnosis to prevent misdiagnosis, and patients must be followed by units specialised in FD.

Learning points

- ▶ As the clinical presentation of Fabry disease (FD) is highly heterogeneous, clinicians should be watchful for atypical presentations of the disease.
- ▶ Physicians should be alert early on for the signs and symptoms of FD because it is a curable disease.
- ▶ Diagnosis of FD must be considered after careful medical history taking and detailed laboratory examinations to avoid erroneous diagnosis.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Zarate YA, Hopkin RJ. Fabry's disease. *Lancet* 2008;372:1427–35.
- 2 Vanier MT, Caillaud C. Disorders of sphingolipid metabolism and neuronal ceroid-lipofuscinoses. In: Saudubray JM, Van den Berghe G, Walters JH. eds *Inborn metabolic diseases diagnosis and treatment*. 5 edn. 2012:566–8.
- 3 Mehta A, Ricci R, Widmer U, et al. Fabry disease defined, baseline clinical manifestations of 366 patients in the Fabry outcome survey. *Eur J Clin Invest* 2004;34:236–42.
- 4 Marchesoni CL, Roa N, Pardo AM, et al. Misdiagnosis in Fabry disease. *J Pediatr* 2010;156:828–31.
- 5 Eng CM, Fletcher J, Wilcox WR, et al. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *J Inher Metab Dis* 2007;30:184–92.
- 6 Zizzo C, Colomba P, Albegiani G, et al. Misdiagnosis of familial Mediterranean fever in patients with Anderson–Fabry disease. *Clin Genet* 2013;83:576–81.
- 7 Langereis EJ, van den Berg IE, Halley DJ, et al. Considering Fabry, but diagnosing MPS I: difficulties in the diagnostic process. *JIMD Rep* 2013;9:117–20.
- 8 Linthorst GE, De Rie MA, Tjiam KH, et al. Misdiagnosis of Fabry disease: importance of biochemical confirmation of clinical or pathological suspicion. *Br J Dermatol* 2004;150:575–7.

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