

Teaching Point
(Section Editor: A. Meyrier)

Treat the patient not the lab value

Ramin Tolouian and Hasan Salameh

Division of Nephrology and Hypertension, Paul L. Foster School of Medicine, Texas Tech University Health Science Center, El Paso, TX, USA

Correspondence and offprint requests to: Ramin Tolouian; E-mail: ramin.tolouian@ttuhsc.edu

Keywords: clinical assessment; D313Y; Fabry's disease

Introduction

Remembering back to medical training, it was always stated that it is important to treat the patient and not the lab value. With the advancement of technology, it appears that this concept is fading. First and foremost, proper assessment is of greatest importance to the welfare of a patient. In addition, with the current changing economy and its affects on healthcare, it is of vast significance that we stress the importance of a proper assessment. This case report uses an example to highlight this importance.

Case

In May 2007, a 39-year-old male truck driver was referred by his primary care physician (PCP) to a neurologist for evaluation concerning peripheral neuropathy. The patient stated that he began having numbness in his lower extremities approximately 3 years prior. He described icy cold sensation along with pain in his toes, associated with needle-like pricks that interfered with his sleep. The symptoms at this point had progressed to his left upper extremity. There was no complaint of weakness. The patient had no exposure to recreational drugs or any other hazardous material at work. There was no family history of similar symptoms. The patient's only other medical history consisted of genital herpes and simple removal of super-numerary mammary glands at the age of 13.

The physical examination was significant only for stocking-and-glove sensory deficit on pinprick examination as well as high arches in his feet.

The patient underwent a nerve conduction EMG study; however, the results were not grossly abnormal. The impres-

sion of the EMG study was early sensory-motor peripheral neuropathy (probably demyelination).

The patient was referred to the above neurologist who elected to run several haematologic tests. Of those included are listed below, most of which were within normal range except for a low alpha-galactosidase A (α -Gal A) as well as abnormal lipids. The patient subsequently was further evaluated with urine analysis, EKG, 2D Echo, MRI of the abdomen and ultrasound of the kidneys to evaluate kidneys and other internal organs for evidence of storage disease. The results were only significant for possible hepatic fatty infiltration. No specific focal kidney disease was identified on ultrasound or MRI.

The patient was diagnosed with Fabry's disease and was referred to us to start enzyme replacement therapy. The first striking point was the lack of proteinuria. In fact having normal urine in a 39-year-old man with Fabry's disease was unusual and did not match with the natural course of the classic form of the Fabry–Anderson disease. Therefore, we sent the patient to a dermatologist, a cardiologist and an ophthalmologist. Surprisingly, the ophthalmologic examination under slit lamp was found to be normal, and dermatologist and cardiologist did not find any evidence in favour of Fabry's disease. Table 1 shows the typical signs of Fabry's disease at different stages of life and compares it with our patient. It becomes apparent that the patient does not show significant signs to state that he has Fabry's disease, despite the lab value showing decreased levels of galactosidase A. Therefore, we question whether mutations in the disorder can lead to milder forms of the disease that may not require therapy. Approximately 90% of males have neurologic, dermatologic and cardiac manifestations by the second, third and fifth decades of life, respectively. It is also believed that males with atypical variants may present later in life more with cardiomegaly or proteinuria. Genetic testing at this point was required. We found that the patient did in fact have a mutation. It was the *D313Y* allele mutation. Based on the genetic testing results and the patient's signs and symptoms, we concluded that the patient did not have Fabry's disease.

Table 1. Typical signs of the Fabry's disease at different stages of life, compared with our patient

Stages of Fabry's disease	Our patient
Childhood	No
Pain, numbness of fingers and toes	No
Telangiectasias on ears, conjunctiva	No
Blue-black angiomatic macules or papules	No
Oedematous upper eyelids	No
Raynaud phenomenon	No
Ophthalmologic abnormalities	No
Early adulthood	
Extensive telangiectasias, angiokeratomas	No
Albuminuria, haematuria, oval fat bodies in urine	No
Oedema	No
Fever, heat collapse, anhidrosis	No
Lymphadenopathy	No
Isothermia	No
30 to 40 years of age	
Cardiac disease: coronary conduction defects, mitral insufficiency	No
Renal insufficiency	No
Cerebrovascular attacks	No
Neurologic findings suggesting multiple sclerosis	Yes

Discussion

Fabry's disease, also called the Anderson–Fabry disease, is an X-linked recessive lysosomal storage disease that is caused by the deficiency of the enzyme α -Gal A. This deficiency causes a glycolipid known as globotriaosylceramide (also abbreviated as Gb3, GL-3, or ceramide trihexoside) to accumulate in different tissues that leads to an impairment of proper function of the organelles, hence the manifestation of the disease [1–4].

The prevalence of Fabry's disease is estimated to range from 1:17 000 to 1:117 000 males in Caucasian populations [2,5]. It is important to note, however, that the prevalence of Fabry's disease is probably underestimated. This is most likely due to the fact that the manifestations of the disease are nonspecific. Because of the rarity of the disease, physicians do not often consider Fabry's disease as the diagnosis often resulting in the wrong diagnosis being made initially [3].

Although there is variability in the clinical presentation, most symptoms begin in childhood or adolescence as severe neuropathic pain, which may be precipitated by stress, extremes of heat or cold, and physical exertion [6]. This is followed by telangiectasias and angiokeratomas usually in the groin, hip and periumbilical areas. Some patients may also develop asymptomatic corneal deposits called cornea verticillata that usually do not affect visual acuity, in addition to retinal vascular tortuosity. Finally, during the late stage of the disease, the progressive deterioration of renal, cardiac and nervous system function occurs in these patients more often presenting with renal manifestations such as polyuria and polydipsia or otherwise unexplained renal insufficiency [7,4,8] (Table 1).

The diagnosis is confirmed via blood tests to see if there is low α -Gal A activity in leucocytes or plasma.

Our patient's initial and main presentation was neuropathy. Laboratory investigations ordinarily used to work up neuropathy were performed on our patient with results leading to the diagnosis of Fabry's disease.

We would like to emphasize and remind the readers about the importance of a clinical diagnosis. As a rule in medicine, we make a diagnosis based on clinical assessment and the laboratory is used only as a tool to confirm our clinical diagnosis. We have learned the importance of 'treating a patient, not a laboratory value' over and over again throughout our experience. It seems that this basic rule of medicine has been fading with the emergence of new technologies during the last decade. It appears that these days we are becoming so dependent on technology that we can neglect the clinical presentation, hence making a diagnosis based on the laboratory or other diagnostic tests values.

In our case, although having a low level of Gal-A in the serum of the male subject has a high specificity, the lack of the other clinical signs and symptoms of Fabry's disease in his age make the diagnosis of classic Fabry's less likely. Being persistent in the clinical diagnosis of 'at least not having classic Fabry disease' persuaded us to look further. And in doing so, we found a complementary test to reveal this rare mutation (*D313Y*).

There have been over 400 disease causing α -Gal A mutations but one in particular is stated as having a pseudodeficiency allele: the *D313Y* allele. It has been shown that males with this *D313Y* mutation have decreased α -Gal A activity in the plasma or serum. However, it has also been shown that over-expression studies in the COS-7 cells demonstrated that the *D313Y* enzyme has ~60–70% of wild-type intracellular α -Gal A activity. The problem was that it was shown to be unstable in plasma at neutral pH [9]. This would explain why serum levels in patients with this mutation when measured would be low; however, intracellular activity was found to be normal. The *D313Y* has been found to be in ~0.45% of Caucasian individuals. However, recent studies screening for Fabry's disease detected in patients with deficient α -Gal A activities with only a *D313Y* allele in haemodialysis and hypertrophic cardiomyopathy clinics, raising concern that this mutation may cause Fabry's disease. A renal biopsy was obtained from a male carrying the *D313Y* allele, who was being considered as a kidney donor for his nephew, who had Fabry's disease (α -Gal A mutation, 895del14). The potential donor's α -Gal A enzyme level in plasma was deficient [1.6 nmol/h/ml (normal mean \pm SD: 12 \pm 4.2)], while his leucocyte activity was within normal range [53 nmol/h/ml (normal mean \pm SD: 34.6 \pm 14.6)]. At age 56, he did not have proteinuria or other symptoms of Fabry's disease. On electron microscopy, the glomerular podocytes, mesangial and endothelial cells as well as tubular, arterial medial, endothelial and interstitial cells all lacked the characteristic electron-dense laminated lysosomal GL-3 inclusions. These studies indicate that *D313Y* is a rare α -Gal A coding region sequence variant that does not cause renal pathology and, therefore, is not a disease-causing α -Gal A mutation [9].

The question that still remains unanswered is what was the cause of our patient's neuropathy. Should we consider this mutation as a variant of Fabry's disease or is this a normal variation? Unfortunately, our patient did not give us

consent to obtain a nerve biopsy. In one study, Hoffmann B *et al.* describe a similar case where a child presented with acroparesthesia that was found to have deficient activity of α -galactosidase A in serum with mutation analysis suggesting Fabry's disease. However, analysis of α -galactosidase A activity in leucocytes was found to be within normal limits. The authors suggested that pseudodeficiencies are well recognized in other lysosomal storage disorders and recommend that confirmed analysis of enzyme activity should be performed in patients with reduced enzyme activity in plasma after having had a similar diagnosis in a child suspected of having Fabry's disease [10,11]. It is also important to note that certain drugs such as amiodarone, hydroxychloroquine and chloroquine can cause cellular injury that can be mistaken for Fabry's disease. Therefore tissue biopsies in these cases will show results indistinguishable from classic Fabry's disease [12,13].

Based on the literature review, we consider this mutation as a normal variation and reassured him that he does not have Fabry's disease, therefore concluding that there was no need for enzyme replacement therapy. With the cost of treatment being more than \$100 000 per year, and given the fact that this is a lifelong treatment, it is estimated that he was saved over \$1 000 000 for the next 10 years, and more importantly, his life expectancy, family counselling and his plans for a future changed significantly.

Teaching points

Be aware of the following:

- (1) It's important to treat the patient and not the lab value.
- (2) Fabry's disease is part of the differential diagnosis in patients with neuropathy but the disease remains rare.
- (3) A rare mutation (*D313Y* allele) causes low A-Gal activity in the serum but is considered a normal variant without clinical manifestation and without the need for enzyme replacement therapy.

Acknowledgements. The authors thank colleagues involved in the care of this patient.

Conflict of interest statement. None declared.

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Received for publication: 4.9.09; Accepted in revised form: 29.9.09