Case Report

Unusual Association of Facioscapulohumeral Dystrophy with Heterozygous Methylene Tetrahydrofolate Reductase and Prothrombin Gene Mutation in the Same Patient: A Case Report

Mahmoud R*, Gendy HE and Ali S

Internal Medicine Department, Faculty of Medicine, Cairo University Hospitals, Al-Saray St., El-Manyal, 11562, Cairo, Egypt

*Correspondence: Rabab Mahmoud, Internal Medicine Department, Faculty of Medicine Cairo University Hospitals, Al-Saray St., El-Manyal, 11562, Cairo, Egypt, Tel: +20 106 013 9196; Fax: +20 233380345; E-mail: ruby_mahmoud_555@yahoo.com

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Abstract

We report a case of 38 years old female with familial Facioscapulohumeral Dystrophy (FSHD) associated with heterozygosity of Methylene Tetrahydrofolate Reductase (MTHFR) and prothrombin gene mutation who presented with transverse cerebral sinus thrombosis.

Keywords: Facioscapulohumeral dystrophy, Sinus thrombosis, Thrombophilia, Headache, EMG

Abbreviations: CPK: Creatine Phosphokinase; EMG: Electromyography; FDP: Fibrinogen Degradation Products; FSHD: Facioscapulohumeral Dystrophy; INR: International Normalized Ratio; LDH: Lactate Dehydrogenase; MD: Muscular Dystrophy; MRI: Magnetic Resonance Imaging; MRV: Magnetic Resonance Venography; MTHFR: Methylene Tetrahydrofolate Reductase; N: Normal; NCV: Nerve Conduction Velocity; SNHL: Sensorineural Hearing Loss; U/L: Unit per liter

Introduction

There is little literature on thrombosis associated with hereditary muscular disorder despite these patients are more prone to thrombosis because the disease itself can cause limitation of their activities and leads to sedentary life [1]. No recommendations were set in the guidelines for this possible risk of thrombosis [2].

By reviewing literature, double genetic abnormalities were rarely reported in those patients. We present her a FSHD patient with heterozygosity for the MTHFR and prothrombin gene mutation, which lastly was responsible for the unusual presentation of this patient.

The reported case aged 38 years, Caucasian female from consanguineous parents presented with complaints of persistent headache, blurring of vision and diminution of visual acuity. After noticing little improvement of her symptoms with conservative management, including the use of analgesics, the patient was referred to Cairo University hospital for further evaluation.

While reviewing the history of the present illness, the patient told us that, her illness started at the age of 24 by facial muscles weakness when she noticed deviation of the angle of the mouth to the left side, dripping of saliva with inability to close her eyes completely (Figure 1). Two years later; the disease progress to involve the shoulder girdle muscles when she noticed that her scapulae were not at their place and she cannot work with lifted arms.
Figure 1: Bilateral LMN facial palsy more prominent on the right side.

At the age of 29, she developed weakness of both upper and lower extremities, which progressively worsened by time especially after her last delivery. During her illness, she also reported diminution of both hearing and visual acuity. She also claimed that her grandmother had the same condition.

Examination revealed normal vital signs, weakness of the orbicularis oris, lateral rectus, superior oblique muscles of the eyes and trapezius muscles (the weakness exists bilaterally and more evident on the right side), winging of scapulae (Figure 2) and bilateral shoulder dislocation more on the left side were observed (Figure 3). Bilateral proximal muscles weakness (grade 3) was present in upper extremities with sparing of deltoids and (grade 4) in lower extremities with more affection of tibialis anterior muscle bilaterally. No fasciculations, intact sensations, normal cerebellar functions or urine and stool incontinence. The patient cannot stand up from a squatting position without assistance and she cannot easy walk. Deep tendon reflexes and muscle tone of the arms and legs revealed hyporeflexia and hypotonia.

Investigations revealed normal blood, urine analyses and Serum Creatine Phosphokinase (CPK), mildly elevated Serum Lacto-Dehydrogenase (LDH) it was 247 U/L (our hospital lab reference was N: 90-190 U/L) and severe vitamin D deficiency (3.2 ng/ml). Other chemistry panel and ECG were also unremarkable. NCV in median, ulnar, peroneal and tibial nerves on both sides: showing normal NCV while EMG concluded that, there is a picture of diffuse myopathic disease affecting both upper and lower limbs more proximal. MRI of the left thigh muscles showing: extensive muscle wasting and diffuse fatty infiltration of the muscles (Figure 4). Pure tone audiometry: showing bilateral mild SNHL (Figure 5).

Figure 4: MRI of the left thigh showing extensive wasting and fatty infiltration of posterior compartment of both thigh partially sparing the left biceps femoris muscle, similar changes involving the right rectus femoris and gluteus maximus muscles.

Figure 5: Audiometry of the patient.

Patient's symptoms together with signs and investigations favor the diagnosis of FSHD and as she initially presented by headache, blurring of vision and decreased visual acuity; fundus examination (to exclude Coats' disease) done but it was normal. This result did not explain the symptoms of our patient. Therefore, MRI
brain and MRV ordered for work-up of headaches that shows transverse sinus thrombosis (Figure 6).

Figure 6: MRV showing: Transverse sinus thrombosis.

However, it is unusual site for thrombosis and our patient has no provocation factor. The second point is that by reviewing literature, the incidence of thrombosis associated with FSHD is unclear and no data published as regards this issue. Unlike thrombosis associated with Duchenne and myotonic muscular dystrophies, which were reported in literature in many case reports. Therefore, another hypothesis to explain the cause of thromboembolism is hypercoagulable state.

Screening tests for hypercoagulable state including protein C, protein S and anti-thrombin III were normal. Lupus anticoagulant, anti-cardiolipin antibodies and factor V Leiden mutation tests were also negative but it was positive for heterozygous MTHFR and prothrombin gene mutation (Figure 7).

Discussion

Albeit each of the individual muscular dystrophies is relatively uncommon, they altogether influence a huge number of individuals around the world [3].

One of the most common form of these Muscular Dystrophies (MD) is the Facioscapulohumeral Muscular Dystrophy (FSHD) which characterized by a distinctive, initially regional distribution of muscle involvement. The prevalence of FSHD is estimated at approximately one in 20,000 individuals. Therefore, it should be considered in patients with complaints of progressive weakness. It is believed that the disorder characteristically results from a partial deletion of an integral number of 3.3 kb polymorphic repeats, identified as D4Z4, within the sub telomeric region of chromosome 4q [4].

Low molecular weight heparin was started and she was maintained on warfarin 5 mg/day together with physiotherapy. The patient was discharged with improvement of her symptoms and general condition. She was scheduled for a follow-up visit after two weeks for follow up of INR level and for genetic testing.

However, by reviewing literature, we found that, hereditary myopathies could be associated with thrombosis but there is limited information about the exact cause of thrombosis in those patients.

Several factors may explain this predisposition to thrombosis as we mention they had more sedentary life. Also, an elevation of serum Fibrinogen Degradation Products (FDP) which significantly correlated with creatine kinase, plasma D-dimer and an upregulation of utrophin (dystrophin-related protein) which may have an unexpected influence on coagulation factors such as thrombomodulin in those patients [6].
Saito et al. give another explanation when they report a case of Duchenne muscular dystrophy showing coagulation cascade activation induced by muscle destruction due to convulsion [7].

Moreover, Everado Cobos et al. demonstrate that 96% of Duchenne muscular dystrophy had abnormal coagulation tests [1].

Cobos et al., described the first case of protein C deficiency, factor V Leiden, and myotonic dystrophy in 1999 and Joong-Yang Cho et al., reports the second case of myotonic dystrophy presented with Pulmonary thromboembolism despite a negative standard hypercoagulable work-up and the last case was reported in 2015 by Josef Finsterer and Claudia Stöllberger when they describes another case of Myotonic Dystrophy-1 Complicated by Factor-V (Leiden) Mutation [8-10].

The presented patient is interesting because she is only reported case with FSHD and two heterozygous thrombophilia gene mutations, which is rare. This was supported by results observed in earlier studies, which demonstrate that, recognition of two or more unrelated mutations in one person observed rarely because of a significant risk of spontaneous abortion in fetus with accumulation of genetic “Errors”, and this child, born with a combined genetic pathology, usually cannot live to verify all diagnoses.

In literature, one heterozygosis mutation rarely cause thromboembolism in absence of provocative factors. In addition, many studies concluded that; the presence of greater than one of the prothrombotic polymorphisms was associated with a substantial risk of venous thromboembolism [11].

The only reported case of FSHD with another inherited disease was 6 years old girl from Russia with FSHD and cystic fibrosis [12].

Extra muscular manifestations may occurs in FSHD and can include retinal vascular disease that leads to exudative retinopathy and visual loss. Therefore, headache, blurring of vision and deceased visual acuity can be referred to retinal affection or Coats’ disease that occur in these cases. Surprisingly only 25% of patients with FSHD had abnormalities on retinal, examination and only 0.6% had symptoms [2].

In our case Fundus, examination did not explain the patient’s persistent symptoms and headache work up were done that revealed transverse sinus thrombosis; and heterozygosis MTHFR and prothrombin gene mutation.

By reviewing literature it was found that, a homozygous abnormality or combination of two or more heterozygous abnormal factors can prompt clinically obvious thrombotic disorders at an early age. However, milder heterozygous traits, when existing alone, are more often discovered by laboratory investigation [5].

**Conclusion**

Facio-scapulo-humeral Muscular dystrophy is not uncommon in our region. Unlike many other types, these cases have better outcome and near normal life expectancy. The findings in our patient illustrate that, thrombosis may occur in FSHD patients. Thrombotic events are increasingly recognized as a significant source of mortality and morbidity. Therefore, further studies must go ahead understand the possible relation between the two pathologies.

If FSHD patients present with unusual or persistent manifestations, search for causes other than the expected from the disease spectrum related symptoms with caution particularly when no explanation was found. Lastly, the physicians should be alert to the possibility that individuals having two separate mutations in unrelated genes and this may develop unusually phenotypes.

**References**


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