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Respiratory failure and pharyngeal hematoma as presenting signs of Moschcowitz's syndrome: a case report and literature review

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Abstract. – Moschcowitz's syndrome or thrombotic thrombocytopenic purpura is a quite rare pathology in childhood, being, as a matter of fact, more frequent among adult people. Often it is hard to distinguish from other pathologies in children both for its rare incidence and for the presence of clinical forms that are very heterogeneous and difficult to be classified. We report on a 13 year-old girl suffering from Moschcowitz's syndrome, in whom respiratory failure and pharyngeal hematoma were the first sign of the disease follone by jaundice, hematoma of the arm and limbs. The girl was treated with plasmapheresis with an improvement of her general condition. Since then we have followed up the girl for two years without any reappearance of the symptomatology. To our knowledge this is the first report of this peculiar presentation in children.

Key Words:
Thrombotic thrombocytopenic purpura, Pharyngeal hematoma, Respiratory failure, childhood.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a condition characterized by thrombocytopenia, microangiopathic haemolytic anemia, and less frequently with neurological deficits, renal failure, and fever. TTP is a rare disease, and has been reported to affect only 3.7 persons per one million annually in the United States[1]. It frequently follows a fatal course; 95% of patients die within three months if not treated[2].

TTP pathogenesis has been associated with deficiencies in the metalloproteinase, ADAMTS13 (A Desintegrin And Metalloprotease with a ThromboSpondin like domain 13)[3]. The principal function of ADAMTS13 involves the cleavage of unusually large forms of von Willebrand factor (ULVWF), thereby, preventing ULVWF multimers from accumulating in the circulation; platelet aggregation in TTP is thought to be the consequence of the binding of the platelets from ULVWF remaining in the circulation[4,5]. Immunoglobulin G (IgG) autoantibodies that block the activity of ADAMTS13 have been detected in patients suffering from TTP; this may account for the impairment of ADMATS13 characteristically observed in cases of TTP[6,7].

In children it is often hardly distinguished from other pathologies with which it can be mistaken, like hemolytic-uremic syndrome, and this difficulty is due to two main factors: scarce incidence of Moschcowitz's syndrome, which makes it little known, and the presence of clinical forms that are very heterogeneous and not easy classified[1,2]. Moschcowitz's syndrome, which takes its name from the discoverer who described it for the first time in 1924, is characterized by multifocal stroke episodes caused by occlusions at microcirculatory level, thrombocytopenia from consumption and hemolytic anemia from mechanical damage with presence of schistocytes (negative Coombs)[3,4]. It is classified as primary or secondary and can manifest itself both under oligosymptomatic forms and under very perilous forms that can take the subject to coma and death[1,2].

Here we report on a 13 year-old girl who come recently to our observation.

Case Report

A.C., 13-year-old girl, was admitted to Emergency Department for the presence of dyspnea with tirage. At the admission she was agitated and diaphoretic. At the physical examination, in both lungs, no wheezes were found but tirage and muscular accessory respiration was noticed. SAO_2 was 94-95%. Thorax RX was normal.

For the respiratory distress associated with a normal lungs function, suspecting an upper-airways problem, a ENT consultation was requested. Rhinoscopy showed several varices of locus

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valsalvae. Fiber optic laryngoscopic exam revealed the presence of a bulky hematoma in the left side of hypopharynx that largely obstructed the glottis (Figure 1). Vocal cords, partially visible, were normal as regards motility and morphology. The otolaryngologist suggested to refer the patient to imaging in order to better assess the extension and the origin of the hematoma.

Laboratory exams showed: platelets 13 × 10^3, red blood cells 3.2 × 10^6, haemoglobin 10.2 g/dl, the percentage of reticulocytes were 0.11%; hepatic functionality tests were within normal range (GOT 27 UI/1; GPT 11 UI/1; gamma-GT 11 UI/1); LHD values were very high (1,413 UI/1; Reference values 240-480 UI/1); kidney function, according to lab data results, was within the norm (urea 28 mg/dl, creatinin 0.60 mg/dl). PT, PTT and fibrinogen were normal.

CT exam was done without and with intravenous contrast medium and allowed to identify an hypodense formation (about 70 H.U.) in hypopharyngeal and paralaryngeal spaces on the left side, with a secondary pharyngolaryngeal dislocation to the right side and a rotation of hyoid bone towards the same side. Such formation extended caudally towards a plane at the level of left upper lobe of thyroid. After injection of contrast agent there was not enhancement.

Because of the severe respiratory symptomatology the patient, after transfusion of three platelets units, underwent tracheostomy in order to obtain a recovery of ventilation function and to protect lower airways from potential hemorrhage. One hour before surgery three platelets unit were transfused. After the surgery the girl was moved to Pediatric Unit where further clinical investigation was carried out.

The girl was second-born to non-consanguineous parents (the mother suffering from hepatitis B), by a spontaneous full term delivery following a normal pregnancy. Birth weight was 3100 grams. History was negative for jaundice at the birth. The first milestones were normal. Thorough anamnesis collection showed that about three weeks before her admission, the girl began to show lower limb hematoma and epistaxis; for this reason she was taken to the family doctor who suggests to made a hematological test, but the parents refused. The day after we found the presence of marked skin and scleral jaundice with arm and limb hematoma. At this time the blood tests showed: platelets 26 × 10^3, red blood cells 2.90 × 10^6 with presence of schistocytes at the peripheral smear, haemoglobin 9.6 g/dl, the percentage of reticulocytes were 0.21%. Total and unconjugated bilirubin agreed with the presence of haemolytic prehepatic icterus (total bilirubin 11.4 mg/dl; unconjugated bilirubin 10.65 mg/dl); hepatic functionality tests were within normal range (GOT 32 UI/1; GPT 23 UI/1; gamma-GT 18 UI/1); LHD values were very high (1,624 UI/1; Reference values 240-480 UI/1); haptoglobin results were significantly below the reference limits (1 mg/dl; reference values 30-200 mg/dl). Kidney function, was within the norm (urea 23 mg/dl, creatinin 0.70 mg/dl), as well as the FR values and antibodies against TORCH agents and other virus (Toxoplasma Gondi; German measles; CMV; Herpes Simplex, Epstein Barr virus (VCA and EBNA. Native anti-DNA antibodies and AMA were absent; within the norm the anticardiolipin and antiphospholipid antibodies, while the ANA were present (1/80), and the ASMA too (1/160).

PT, PTT, were normal; fibrinogen 410 mg (nv 200-400 mg/dl) Thyroid function was within the norm with hormonal values within limits and absence of anti-thyroglobulin antibodies. The abdominal ultrasound exam and the abdominal CT, carried out with contrast, showed a normal liver, biliary ducts and gallbladder not swollen, kidneys in the right position, of normal size for the age.

On the base of the clinical picture and the tests we made a diagnosis of thrombotic thrombocytopenic purpura or autoimmune genesis Moschcowitz's syndrome. Daily therapy with plasma exchange was started, Urbason (40 mg bid intravenously), Persantin and Eparmefolin (1 fl/dl intravenously). The above therapy was continued through which an improvement of the clinical picture had been obtained and a negative conversion of ANA and ASMA. The study of ADAMST 13 activity showed a severe deficiency value (< 10%) with positive anti ADAMTS 13

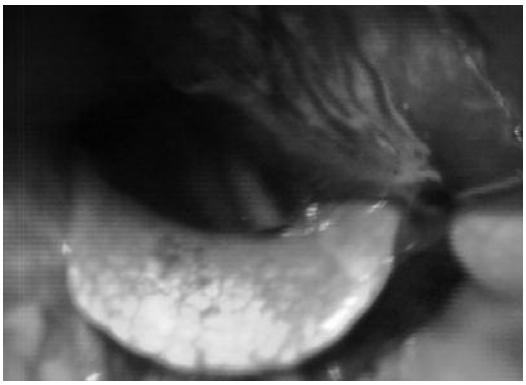

Figure 1.

IgG and inhibitor. The patient underwent 32 sessions of plasma exchange. Following this sessions some nettle-rash manifestations appeared, which disappeared without further complications.

The patient was dismissed with improvement of clinical conditions and normalization of hematochemical tests. Symptomatology improvement was followed clinically and by means of CT imaging, which showed progressive reduction and the definitive disappearance of the pharyngeal hematoma within three months since diagnosis was established. Such condition allowed us to carry out a closure of the tracheostomy, after the normal respiratory function was assessed. We have followed up the girl for two years and no other episodes were seen.

Discussion

Thrombotic thrombocytopenic purpura or Moschcowitz's syndrome is quite rare and it is even rarer in childhood. It is a very heterogeneous syndrome, with different variants described that should be properly distinguished in order to follow a correct therapy. Moschcowitz's syndrome is characterized by scattered thrombosis at micro circulatory level, thrombocytopenia and consumption anemia caused by mechanical damage (negative Coombs). We can distinguish four very similar forms of thrombotic thrombocytopenic purpura: the primary form, the secondary, the hemolytic-uremic syndrome associated to diarrhea and the atypical form[3-4].

The idiopathic form has been studied for a long time in order to find out its pathogenesis and in the recet years a lot of progresses have been made in this field. It ha been in fact noted that the pathogenetic heart of this anomaly lies in the presence of antibodies that inhibit the activity of metalloprotease ADAMST13[3-5]. There are even rarer forms in which changes at ADAMST13 level are present, that cause a deficit of its functionality[1]. In the above clinical case the normal functionality of ADAMST13 has been established, but its quantity was inferior to normal, which has confirmed the autoimmune genesis of the pathology. ADAMST13 is a metalloprotease, synthesized at hepatic level, whose substrate is represented by Von Willebrand's factor, a multimero that is essential in forming the platelet thrombus because it adheres to the endothelial cells and to the connective tissue expounded in the damage place of the vasal wall and the circulating platelets adhere to it through a glycoprotein of a membrane called GPI. This process needs a precise modulation and this role is carried out by metalloprotease ADAMST13 that eliminates the Von Willebrand factor in excess limiting the uncontrolled growth of the platelet thrombus. Its deficiency, as it happens when in presence of autoinhibitor antibodies, or its malfunction, in the even rarer case of genetic changes causes the uncontrolled growth of thrombuses at peripheral level. This process is at the base of thrombocytopenia from consumption and of hemolytic anemia from mechanical damage and can cause vasal occlusions followed by ischemia at different organs level.

In Moschcowitz's syndrome, the most vulnerable organ is the central nervous system, so much that the neurological damage is considered a fundamental characteristic in defining this syndrome. Another part which is exposed to ischemic damage with a resulting functional damage, even severe, is the kidney, which is for the most part typically hit in the hemolytic-uremic syndrome[4-5]. However, in the case previously shown, neurological or kidney functionality deficit have not been noticed during all the stay in hospital. In fact, the patient's neurological test has always been within the norm for the age. Kidney functionality, monitored through hematochemical tests, was within the norm too and this was further confirmed by the reports from abdomen ultrasound and CT.

A very important aspect to evaluate when approaching a patient affected by thrombotic thrombocytopenic purpura is the hepatic functionality. In fact, as already stated, metalloprotease13 is mostly synthetized in the liver and so any hepatic pathology could caused by its not sufficient synthesis[3-6]. In the reported clinical case hepatic functionality has been studied and it was within the norm, as the physiological values of the indexes of hepatic functionality and the report from image diagnostics through abdomen ultrasound and CT show. This case appears particularly interesting since the peculiar presentation, characterized by the unusual finding of a bulky haematoma that obstructed upper airways.

From literature review it is shown the absolute uniqueness of the presented case, as it is seen that the few reports of occluding haematomas at the upper airways level are mainly related to trauma and haemophilia[9,10]. Furthermore the tracheostomy procedure made in order to protect the airways and to recover normal respiratory function is itself atypical if compared with the diffused indications within pediatric patients, that are mainly represented by prolonged mechanical ventila-

tion, craniofacial and neurological syndromes, congenital malformations and trauma. Among airways obstructions the predominant causes are subglottic stenosis, tracheomalacia and vocal cord paralysis[11-16].

The primary forms of Moschcowitz's syndrome respond to the plasma exchange therapy to which immunosuppressant medication is often associated. Plasma exchange therapy allows the removal of the autoantibodies and the reactivation of the quantity of ADAMST13. Immunosuppressant medication is necessary for the modulation of antibody activity, reducing also the production of antibodies against ADAMST13. Secondary forms of thrombotic thrombocytopenic purpura are treated differently depending on the primitive underlying pathology. Hemolytic- uremic syndrome does not benefit anyhow from plasma exchange therapy, except in its atypical form for H factor deficiency.

In conclusion, when approaching a thrombocytopenic patient who is also affected by hemolytic anemia, it is important to pay a particular attention to the clinical-researcher characteristics that allow to state the pathogenesis and then to make a correct diagnosis, to give an effective therapy and make short and long term prognosis[3-9]. As for autoimmune genesis Moschcowitz's syndrome, it is important to keep in mind that the solution of the acute break does not mean complete recovery because the patients affected by this pathology can show a recurring in the short or long term, even after many years, besides, being the pathogenesis immune, it is necessary to keep in mind the possibility that these subjects can in the future show other immune diseases, for example herythematous systemic lupus that, in pediatric age, is more frequently associated with Moschcowitz's syndrome.

Conclusions

We think to report this children because to our knowledge this is the first report in the literature of a thrombotic thrombocytopenic purpura, showing as a first sign of the disease a respiratory failure associated to bulky hematoma of the pharynx; however in our case, the children respond well to the plasmaphereis therapy with an improvement of her general condition and without any worsening in the following two years.

Conflict of Interest

None.

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