Case report

Hyper-IgD Syndrome and pregnancy

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1. Case Reports

Case 1

A 31-year-old woman of Dutch offspring, gravida 1 para 0, presented to our department because of hyperemesis gravidarum at nearly 7 weeks' gestation. Since her tenth year of age she was suffering from attacks of high spiking fever with mild abdominal pain and arthritis, without any swelling of lymph nodes or skin manifestations; these episodes occurred five to eight times a year. Serum IgD was 257 U/ml (normal < 100 U/ml) and a diagnosis of hyperimmunoglobulinemia D syndrome (HIDS) was made. There were no family members with HIDS. Besides a D & C for metrorrhagia, her gynaecologic history was unremarkable. She was admitted into the hospital for protracted nausea and vomiting without fever. There was ketonuria, but all other appropriate laboratory investigations, including TSH, fT4 and immunoglobulins, were normal. Treatment was delivered by infusion of glucose solutions and guidance by a psychologist. The complaints resolved after 2 weeks and she was discharged. Because of recurrence of symptoms 1 week later, readmission was necessary. After discharge there was a normal obstetrical follow-up. At 38 weeks membranes ruptured spontaneously. Labour was without complications and a healthy male infant was born weighing 3120 g, with good Apgar scores. The placenta was clinically and histologically normal. IgD in cord serum was 0.12 U/ml. Puerperium was uncomplicated. During pregnancy as well as the first 3 months after delivery there were no attacks of fever.

Case 2

A woman of Dutch parentage had her first period of fever after vaccination against measles in her first year of life. After that, attacks of high fever sometimes with skin lesions, arthritis, abdominal pain, diarrhea and swelling of lymph nodes occurred every month. Tetanus vaccination provoked the same clinical picture. Her serum IgD was 4995 U/ml and the diagnosis of HIDS was made when she was 20 years old (patient #1 in a recent review) [1]. Menstruation coincided with or was preceded by attacks [2]. Her family history for the disease was negative. Because of the good results in Familial Mediterranean Fever (FMF), colchicine therapy was started (0.5 mg twice daily) with disappointing results. During her first pregnancy at the age of 27, she had only two episodes of fever, both times in the second trimester, while her serum IgD was 1620 U/ml. A
healthy boy was born. No IgD was detectable in cord serum. Since then, she had monthly attacks again. In her second pregnancy 4 years later, there were only two minor febrile episodes. A healthy boy was born again. After 5 days she was admitted with high fever, due to sepsis with Streptococcus Hemolyticus Group A. At D & C, endometritis was diagnosed and retained pieces of the placenta were removed. Treatment with antibiotics and artificial respiration was started with good result.

2. Discussion

Hyper-IgD Syndrome (HIDS) is a rare disorder, in some aspects resembling Familial Mediterranean Fever (FMF). The syndrome is characterized by recurrent episodes of fever, sometimes preceded by chills, and starting early in life [1]. Typically, these attacks occur every 4–8 weeks and may last about 3–7 days. Associated symptoms may be divergent: lymphadenopathy, mostly cervical, abdominal pain with vomiting and diarrhoea, headache, splenomegaly, recurrent arthritis in large joints and typical skin lesions. Laboratory testing reveals an elevated immunoglobulin D (IgD) (>100 U/ml) and in 80% a concomitant elevated IgA. The combination of the typical clinical picture and the high serum IgD will lead to the diagnosis. Unfortunately thus far no satisfactory treatment is available but apart from the recurrent attacks, prognosis appears to be good.

Until now HIDS has been described in 66 patients (33 males; 33 females). So far the syndrome has never been described specifically in combination with pregnancy. Apart from the hyperemesis gravidarum in our first case, both patients had favourable pregnancies. Including our patients, at least five HIDS patients have been pregnant and delivered healthy children. These limited data may suggest that there is no vertical transmission of the disease. The analysis of clinical data and IgD levels in families favor an autosomal recessive mode of inheritance as well [3].

We observed a diminished frequency of febrile attacks during pregnancy in the two patients with HIDS. This reminds us from similar findings in FMF where pregnancy and lactation have a beneficial influence on the symptoms [4]. These observations, made before the advent of colchicine, led to the employment of estrogens, progestatins or both for FMF with relative good therapeutic results. In HIDS, a hormonal influence cannot be discarded since statistical analysis revealed that menstruations often coincide or precede the febrile attacks [2].

When our first patient presented with nausea, vomiting and abdominal pain, both an attack of HIDS and hyperemesis gravidarum were considered. While 70% of pregnant women have a mild or moderate emesis gravidarum, which starts by 6 weeks of gestation and lasts until 16–20 weeks [5], only patients with hyperemesis gravidarum (severe emesis) have dehydration, electrolyte disturbances and weight loss. An excess of human chorionic gonadotrophin (HCG) is often considered as an important factor in the pathogenesis since women with multiple pregnancies and hydatiform moles have significantly higher HCG concentrations and a higher frequency of hyperemesis gravidarum. Although nausea and vomiting are symptoms of HIDS, an attack was ruled out because of the absence of fever.

The relation between the infection with S. Hemolyticus and HIDS in our second patient is most likely coincidental. An earlier analysis showed that these patients are not immunocompromised and do not carry an increased risk for infections [1].

IgD constitutes only 0.2% of all serum immunoglobulines and so far its function is not fully elucidated but it may be involved in the early antibody response. It has been suggested that IgD rises during pregnancy and in a group of 72 healthy females there was an exponential correlation between maternal IgD levels and gestational age at delivery [6]. In our two HIDS patients we were unable to find a significant rise of serum IgD during their pregnancies and even serum IgD of case 1 decreased to normal values. In healthy pregnancies, the placenta is an effective barrier for IgD [7]. Our observation showed also that in a HIDS patient with very high IgD concentrations, IgD did not appear in cord blood.

This report is the first description of pregnancy in HIDS, but in FMF more data are available. Miscarriage is seen in 25–30% (in healthy individuals in 15%) in untreated patients, but also in patients on colchicine [4,8]. In animals colchicine has shown to be mutagenic. In 1992 a report showed no unusual frequency of fetal abnormality among women with FMF taking colchicine before or during pregnancy [9]. Elaborate experience from Tel Hashomer, where more than 4000 FMF patients are presented, confirmed this. Although a significant increase in the number of cells with abnormal numbers of chromosomes was found in colchicine-exposed men, use of colchicine by the father does not present a significant risk. In FMF it is important to continue colchicine throughout the pregnancy not only because it is effectively suppressing the attacks, but it also prevents the development of amyloidosis.

In summary, our cases illustrate the following points: HIDS is not associated with complications in pregnancy or disturbance in fetal outcome; the frequency of attacks diminishes during pregnancy; HIDS probably inherits via an autosomal recessive trait and is not transmitted to children of patients; lastly, IgD does not seem to cross the placenta even in a patient with very high IgD values.

References

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Abstract

A 27-year-old promipara with acute polyserositis and primary antiphospholipid syndrome developed right upper quadrant pain, massive ascites, HELLP syndrome, and disseminated intravascular coagulation shortly following vaginal delivery. Computed tomography and color Doppler studies were compatible with complete thrombosis of the right hepatic veins, the Budd-Chiari syndrome. Anticoagulation was initiated, along with supportive measures, and the patient recovered completely. Imaging studies 6 months later were normal. This case demonstrates that nearly fatal forms of venous thrombosis may complicate polyserositis in women with antiphospholipid syndrome. Doppler studies of the hepatic vein are of value in establishing the diagnosis.

Keywords: Budd-Chiari syndrome, Antiphospholipid syndrome, Polyserositis.

1. Introduction

The presence of antiphospholipid antibodies is associated with several clinical disorders including recurrent arterial and venous thromboses, autoimmune tissue disorders, pregnancy loss, autoimmune thrombocytopenia, intrauterine growth retardation, and early onset severe preeclampsia. Hemolysis, elevated liver enzymes and low platelet count have been long recognized as complications of preeclampsia. Budd-Chiari syndrome, or hepatic vein thrombosis, complicating pregnancy is extremely rare. This diagnosis may be suspected when there is sudden occurrence of right upper quadrant pain, hepatomegaly and massive ascites.

We report a near-fatal case in a preeclamptic woman with antiphospholipid antibodies, who developed HELLP syndrome, disseminated intravascular coagulation and Budd-Chiari syndrome.

2. Case report

A 27-year-old previously healthy nullipara was admitted at 34 weeks gestation with severe preeclampsia manifesting as blood pressure of 160/110 mmHg and +3 proteinuria. A previous pregnancy had ended in a spontaneous first-trimester abortion. The general physical examination was unremarkable except for the hypertension. The uterus was enlarged to 34 weeks, and fetal heart tracings were normal. The laboratory studies included: white blood cells (WBC) 10 800/mm³, hemoglobin (Hb) 10.5 g/dl, platelet count (PLT) 167 000/mm³, serum creatinine 0.7 mg/dl, prothrombin time (PT) 100%, and partial thromboplastin time (PPT) 35 s. Twenty-four h urine collection had 4.5 g of protein.

Following initial stabilization, the blood pressure increased to 180/110 mmHg, and the patient developed constant epigastric pain. Treatment included i.v. hydralazine, magnesium and induction of labor by oxytocin. The woman delivered a healthy baby girl weighing 2035 g. Histologic examination of the placenta showed...