Gaucher disease type I: analysis of two cases with thalassemic facies and pulmonary arteriovenous fistulas

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Here we report two unusual patients with Gaucher disease type I. Both girls admitted with hepatosplenomegaly, growth retardation, and anemia at four and 2.5 years of age, and Gaucher cells were seen on bone marrow aspirates. Thalassemic face was first noted at 8 and 11 years of age, respectively, with frontal bossing and maxillary hypertrophia. Although they had unconjugated hyperbilirubinemia, high reticulocytes, polychromasia, and normoblasts on peripheral smear, other laboratory tests for hemolytic disease were negative. Radiological examination revealed typical bone involvement of Gaucher disease, as well as costal enlargement and obliteration of paranasal sinuses, the latter two reported in hemolytic diseases. Cyanosis, digital clubbing and recurrent lung infections led to contrast echocardiography that revealed diffuse pulmonary arteriovenous shunting in both. Diagnosis was confirmed by low leukocyte beta glucosidase levels and mutations N370S7/L444P (Case 1) and N370S/? (Case 2). These features, all reported for the first time, may show a new clinical course in Gaucher disease.

Key words: Gaucher disease, thalassemia, pulmonary arteriovenous fistulas.

Gaucher disease (GD) is an inherited metabolic disorder caused by the defective activity of acid beta glucosidase and accumulation of glucosylceramide-laden macrophages of the retuculoendothelial system[1]. Three clinical subtypes have been recognized. Type I, the defining feature of which is the absence of neurologic involvement, is the most common. There is great heterogeneity within type I GD. The bone marrow and spleen are two of the more extensively involved organs. Anemia, coagulation abnormalities, visceral enlargement and structural skeletal changes occur at some point during the course of the illness in most patients[2]. In this report we describe two children with GD type I, pulmonary arteriovenous fistulas and some clinical and laboratory findings resembling thalassemia major, a distinct type not found among the 95 patients diagnosed in the same clinic.

Case Reports

Case 1

This four-year-old girl, product of a nonconsanguineous marriage, was first noted to have abdominal enlargement at age one. On admittance to our hospital 1985, growth retardation, hepatosplenomegaly (5 and 7 cm below the costal margins), moderate anemia (9.6 g/dl) and Gaucher cells on bone marrow aspirate were found. Her second visit was five years later, at which time she was subicteric and had thalassemic face with overgrowth of maxilla, prominence of the upper incisors, frontal bossing, flattening of the nasal bridge and separation of the orbits. Her liver was firmly palpable below the right costal margin and a huge spleen filled the whole abdomen. She had severe anemia (5.2 g/dl), thrombocytopenia (45000/mm^3), leukopenia (2400/mm^3) and reticulocytosis (2%). Splenectomy was performed, and histological examination of the liver and spleen also revealed Gaucher cells. Her hematological findings normalized postoperatively for one year. In 1991 she admitted with severe left femoral head pain, which at first could not be differentiated from septic arthritis. Her next visit to our hospital was in 1996, at 13 years of age. She complained of recurrent leg pain, recurrent conjunctivitis, and fatigue. She had a

thalassemic face (Fig. 1a), scleral subicterus, very thin extremities, growth retardation without any development of secondary sexual characteristics,

Fig. 1a. Facial appearance of Case 1.

and firm hepatomegaly 8 cm below the right costal margin. Her Hb level was 10.6 g/dl, mean corpuscular volume 91.6 fl, red blood cell count 3.5 x 10^6/mm^3, red cell distribution width 20.8, reticulocyte count 1.6%, and platelet count 126,000/mm^3. Peripheral smear revealed anisocytosis, poikilocytosis, polychromasia, normoblasts and target cells. Hemoglobin electrophoresis, plasma Hb and haptoglobin, and glucose 6 phosphate dehydrogenase levels were found normal. Direct and indirect Coombs' tests, acid Ham test, and cold agglutinins were negative. Bone marrow aspiration revealed a great number of Gaucher cells and normal erythropoietic activity. Radiological evaluation, reported earlier[3], revealed Erlenmeyer flask appearance on the long bones, bilateral femoral head necrosis, bilateral sacroiliac joint involvement and coarse trabeculation, typical skeletal changes of GD type I[4]. Maxillary and frontal sinuses had no pneumatization on the sinus X-rays (Fig. 2a) and tomography, which may be seen in thalassemia[5], but has not been reported in GD. Chest X-rays demonstrated widening of the ribs and coarse trabeculation of vertebrae. Pseudocyts were present on maxilla, mandibula, and sphenoid, metacarpal and phalangeal bones, together with coarse trabeculation. Biochemical tests were normal except for high triglyceride (326 mg/dl) and unconjugated bilirubin (1.8 mg/dl) levels. Abdominal ultrasonography showed a huge and hyperechoic liver; cirrhosis was not present histologically. Mild cyanosis led to evaluation of blood gases that showed hypoxia. Constrast echocardiography revealed multiple diffuse pulmonary arteriovenous shunting. Leukocyte beta glucosidase activity was found deficient (0.17 mmol/gh, normal range 1-5). She was found to carry N370S and L444P point mutations, as a compound heterozygote.

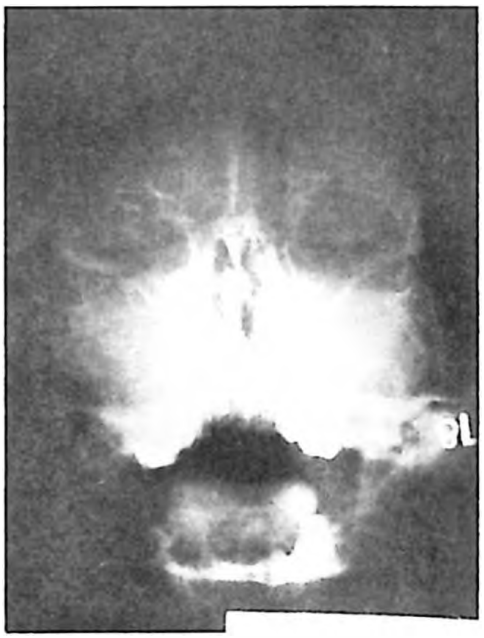

Fig. 2a. Waters radiograph of Case 1 showing no pneumatization in paranasal sinuses and coarse trabeculation of maxilla and mandibula.

Case 2

The girl was first seen in our hospital at the age of 2.5 years, in 1984. She was one of the siblings of a GD patient who died at seven years of age. She was from the same town in the northwest of Turkey as Case 1, but the families were not related. Her complaints were abdominal enlargement, fatigue and paleness. Her parents were nonconsanguineous and her eight siblings were healthy. She had growth retardation, and firm hepatosplenomegaly of 5 and 12 cm respectively, below the costal margins. Hematological examination showed anemia (6.4 g/dl) and thrombocytopenia (100,000/mm^3). Hypochromia, anisocytosis, poikilocytosis, and target cells were seen on the peripheral smear. Bone marrow aspiration revealed Gaucher cells. Biochemical tests were normal except for a high unconjugated bilirubin level (1.3 mg/dl). Long bone radiographs were also normal. Splenectomy was performed, revealing Gaucher cells in the liver and spleen histologically. Although the hematological

values normalized after the splenectomy, the Hb level declined to 7.1 g/dl, and the reticulocyte count increased to 2% one year later. She complained of oral and nasal bleeding episodes, recurrent abdominal pain and fever, and had pyuria. A rectal inflammatory polyp causing hematochezia was removed in 1988. Low serum iron saturation, anisocytosis, poikilocytosis, hypochromia, target cells, and normoblasts on the peripheral smear were detected at that visit, while the Hb level was 9 g/dl and the reticulocyte count 2.2%. In spite of iron supplementation and removal of the polyp, her Hb level declined to 7.2 g/dl. Her first skeletal complaints started at nine years of age, with right pelvic pain. Her sclerae were icteric, extremities cachectic, and abdomen huge. A systolic murmur of third degree was heard on the left sternal margin. Her hemoglobin level was 4.5 g/dl and the aforementioned changes were defined on the peripheral smear again. Femoral X-rays revealed Erlenmeyer flask sign. In 1992, chronic cough, recurrent lung infections, and petechia started. Physical examination revealed an 11-year-old girl with a weight of 23 kg and height of 120 cm. Scleral icterus and digital clubbing were other physical findings. Hemoglobin level was 7.9 g/dl; Hb electrophoresis, plasma Hb and haptoglobin values and peripheral smear for fetal Hb normal; and Coombs' test negative. Low serum albumin, high serum alanine amino transferase and unconjugated bilirubin levels (3.7 g/dl, 63 U/L and 0.8 mg/dl, respectively) were detected. Thalassemic facial appearance was first defined in 1993 (Fig. 1b) when she was 14 years old. Growth retardation (28 kg weight, 136 cm height) without any secondary sexual development, digital clubbing, cyanosis, and facial appearance were very striking. Bleeding episodes, lung problems and pyuria were continuing. Liver was nodularly palpated 20, 15 and 10 cm below the right, mid and left costal margins, respectively. She had moderate anemia (8.9 g/dl), mild reticulocytosis (1.6%), and the same peripheral smear findings defined before with the addition of polychromasia. Except for mild elevations alanine aminotransferase (70 U/L), triglyceride (223 mg/dl), and unconjugated bilirubin (2.1 g/dl), biochemical tests were normal, as well as haptoglobin, G6PD, Coombs', and cold agglutinin studies. Erythrocyte half-life studies demonstrated a normal life span of red blood cells. Prothrombin and partial thromboplastin times were longer than in controls. Radiological evaluation revealed typical changes for GD on femur, tibia and pelvic X-rays. Bilateral maxillary and frontal sinuses also seemed to be obliterated on the Waters radiography (Fig. 2b). Abdominal ultra-sonography revealed a huge, hyperechogenic, nodulated liver. Scintigraphic examination did not show any accesory spleen. Contrast echocardiography revealed multiple diffuse pulmonary arteriovenous shunting. Her leukocyte beta glucosidase activity was found low (0,29 μmol/gh, normal range 1-5) and plasma chitotriosidase activity high (> 180 μmol/gh, normal range 4-76), typical for GD. She was found to carry N370S mutation, as a heterozygote, but no other mutation could be demonstrated after screening for the six most common.

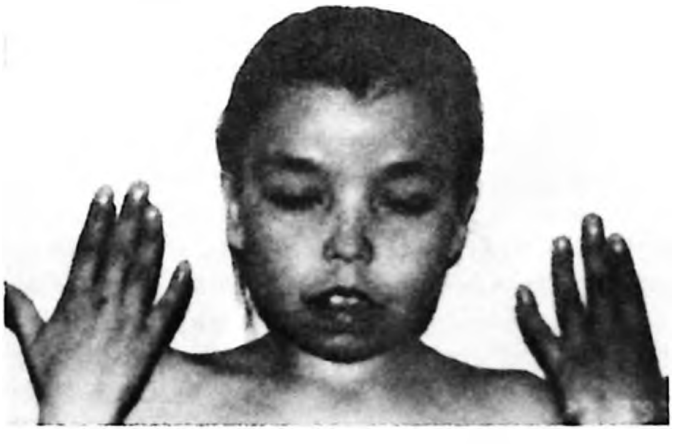

Fig. 1b. Facial appearance of Case 2.

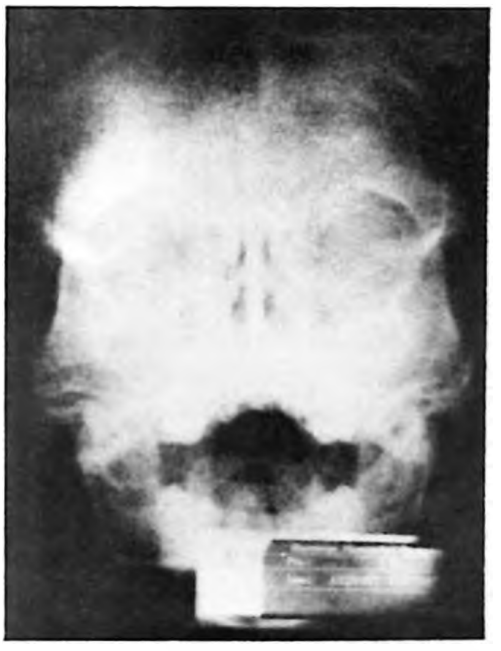

Fig. 2b. Waters radiograph of Case 2 showing no pneumatization in paranasal sinuses and coarse trabeculation of maxilla and mandibula.

Discussion

These two well documented GD type I patients are interesting on two points: the phenotypic and radiological findings resembling thalassemia major and the multiple pulmonary arteriovenous fistulas. Radiological bone changes in chronic adult type GD include failure of remodeling that produces the Erlenmeyer flask deformity, osteopenia, osteosclerosis, joint degeneration, ischemic necrosis, bone destruction, and pathologic fractures[4]. Bone lesions due to Gaucher cell infiltration of the bone marrow are present in 50 to 75% of the patients, and are usually associated with atrophy of marrow cells and fibrosis. Destruction of bone results from multiplication of Gaucher cells packed in the intramedullary spaces, expansion of cortical spaces, pressure atrophy and ischemic necrosis. The femur is the most commonly affected bone. Spine, hips, shoulders, tubular bones, and the pelvis are the other frequent sites of involvement. Mandibular and maxillary involvement is rarely reported in GD[6,7]. Among 16 cases aged between 12-67 years, most discovered incidentally on routine dental radiographs only one patient had pacification of maxillary sinuses by a thick yellow material consisting of Gaucher cells and signs compatible with chronic sinusitis such as fever and headache[8]. This patient did not have any atypical facial appearance or jaw bone changes. Our patients differ from the above-mentioned case as they showed sinus opacification together with maxillary and mandibular destruction, at a relatively young age, and typical facial appearance resembling thalassemia major. Sphenoid bone involvement present in our first case, and severe maxillary and mandibular coarse trabeculation (in both cases) resulting in a foam-like appearance have also not been reported in GD before. The basic process of bone involvement in GD is similar to that in other diseases where proliferation or infiltration of bone marrow takes place. Coarsening of the bony textural pattern may occur in a wide variety of diseases including the congenital anemias. In thalassemias, extreme hypertrophy of the bone marrow in medullary and sometimes extramedullary sites, in order to compensate for chronic hemolysis, is well known. Involvement of the facial skeleton because of the proliferation of bone marrow resulting in severe disfigurement has been described in some reports[5]. The typical facial appearance of thalassemia major in inadequately transfused patients develops as a result of these changes. Maxillary overgrowth, displacement of teeth, prominence of malar bone, retraction of upper lip, malocclusion, and depression of the nose are well known features. Paranasal sinus obliteration and coarse trabeculation of the jaws are also reported[9]. Our two patients showed all these typical findings, but not diploic space widening on lateral skull X-ray, which is an outstanding feature of thalassemia. At the same time, they did not have thalassemia or any other hemolytic condition. The mechanism is probably the same: widening of the bone marrow because of heavy infiltration of Gaucher cells and to compensate for chronic anemia. Severity of skeletal changes due to Gaucher disease does not necessarily correlate with the size of the liver or spleen or bone marrow findings[2]. Splenectomy does not influence the natural course of bone disease, though the opposite was believed for long time. People who undergo splenectomy have the same incidence of significant bone involvement at autopsy, as do those who did not have their spleen removed[4]. However, anemia may contribute to the osseous changes by stimulating the activity of the bone marrow, thus creating more space for the invasion of foamy cells.

Gaucher disease is commonly accompanied by anemia. Its pathogenesis is complex and not well understood. It is usually ascribed to the replacement of bone marrow with Gaucher cells, occasionally due to hemorrhages because of thrombocytopenia and rarely an acquired hemolytic anemia. Another mechanism is that the total circulating red cell mass is in normal limits, but the plasma volume, and thus the total blood volume, is greatly expanded, so that dilutional anemia occurs[10]. Splenectomy corrects the high plasma volume and, therefore, the dilutional anemia. However, some patients become transfusion dependent in spite of the splenectomy. Red cell life span studies have demonstrated normal to reduced levels in GD[11,12]. A huge spleen traps the circulating erythrocytes, including transfused normal red cells, which in hemolysis[13]. Recurrence of anemia after splenectomy is a result of progressive bone marrow infiltration with Gaucher cells, and can lead to myelophthisis, myelofibrosis, and bone marrow failure. The mechanism was probably the same in our patients, as their anemia recurred after some years together with facial changes.

Pulmonary involvement and symptoms are rare in type I GD, and include alveolar infiltration of Gaucher cells and obliteration of gas exchange tissue[14]. Intrapulmonary shunting in cirrhosis was first described in 1956[15], and refers to the entry of systemic venous blood into the arterial circulation without exposure to alveolar oxygen. It has been reported in cryptogenic, postnecrotic, primary biliary cirrhosis; chronic active hepatitis; alpha 1 antitrypsin deficiency; Wilson's disease; and congenital hepatic fibrosis[16], but not in GD. Mechanisms of intrapulmonary shunting are thought to be: 1- an imbalance between vasoconstrictive and vasodilatory substances that are abnormally metabolized by an impaired liver, and 2- unusual regulation of certain pulmonary vessels which results in vasodilatation during hypoxia and thus impaired hypoxic vasoconstriction. Intrapulmonary shunting does not seem to be associated with liver function tests, ascites, splenomegaly, portal or pulmonary hypertension, specific types of liver disease, or digital clubbing[17]. Diagnosis is considered in patients with chronic liver disease and hypoxemia and confirmed by technetium scanning or contrast two-dimensional echocardiography with intravenous injection of isotonic saline or indocyanine dye. The diagnosis was made by echocardiography in our patients. It would be possible to explain intrapulmonary shunting in these children with GD if cirrhosis was demonstrated, but they did not have cirrhosis. Although liver enlargement and dysfunction are common in GD, cirrhosis is seen in relatively few cases and hepatic failure is rare[18]. Osteoporosis and osteomalacia can result in rib fractures and abnormalities of the thoracic cage which may cause reductions in lung volume. Severe rib involvement in both of our cases may have contributed to hypoxia, but is not adequate to explain the development of pulmonary arteriovenous fistulas.

Another interesting point about these cases is that, despite coming from the same region of the country, without any consanguinity between the two families, and having a very unique and similar course, these girls are not similar genetically. The first patient carries N370S and L444P mutations as a compound heterozygote, while the second has N370S mutation as a heterozygote but no other detected mutation after screening for six common ones. Just as considerable heterogeneity in phenotype is sometimes apparent among siblings who have inherited identical disease producing alleles[19], the opposite is also possible: different genotypes can result in similar phenotyhes.

These two cases with thalassemic face, obliteration of paranasal sinuses, and intrapulmonary shunting, all unusual findings in GD, may be examples of a new clinical subtype.

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