

block but is common with associated malformations and symptomatic patients. In asymptomatic patients, prolonged QTc may herald the onset of symptoms(9). The risk of sudden death is twice great in patients who have a prolonged QTc interval. When all the high risk factors are present in a patient, prognosis remains grave. However, prompt treatment with inotropic agents, temporary pacing and decongestive measures may save some babies, if diagnosed *in utero*. On the other hand, congenital heart block due to pure electric discontinuity remains asymptomatic and such subjects do fairly well. There is an approximately 95% twenty year survival of patients without anatomic heart defect(7).

REFERENCES

1. Major RH. Diseases of the Circulatory system. *In: Classical Descriptions of Disease*. Oxford, Blackwell Scientific Publications, 1948, pp 326-339.
2. Morquio L. Sur une Maladie infantile et Familiale caractérisée par des modifications permanentes durables de attaques Syncopales et épileptiformes *et al.* morte subite. *Arch Med Eng* 1901, 4: 467-469.
3. Yater WM. Congenital heart block. Review of the literature: Report of a case with incomplete heterotaxy, the electrocardiogram in dextrocardia. *Am J Dis Child* 1929, 38:112-136.
4. Paul M, Rudolph AM, Nadas AS. Congenital complete A-V block. *Circulation* 1958,18:183-189.
5. Scarpelli EM, Rudolph AM: The hemodynamics of complete heart block, *Progr Cardiovas Dis* 1964, 6: 327-342.
6. Ayers CR, Boineau JP, Spach MS. Congenital complete heart block in children. *Am Heart J* 1966, 72: 381-390.
7. Roberts N, Gelband H. Arrhythmias in heart disease in infants, children and adolescents. *In: Heart Disease in Infants, Children and Adolescents*. Eds. Moss AJ, Adams FH, Emmanouilides GC. Baltimore, Williams and Wilkins, 1977, pp 687-696.
8. Michaelson M, Engle MA. Congenital complete heart block. An international study of the natural history. *Cardiovasc Clin* 1972, 4: 86-101.
9. Esscher E, Michaelsson M. Congenital complete AV block. *In: Diagnosis and Treatment of Cardiac Arrhythmias*. Eds. Bayes A, Cosin J. Barcelona, Doyma, 1978, pp 618-624.

Wiskott-Aldrich Syndrome

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Wiskott-Aldrich syndrome (WAS) is a rare X-linked immunohematological

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disorder which was first described by Wiskott in 1937 and characterized by thrombocytopenia, eczema, immunodeficiency with susceptibility to pyogenic, viral and opportunistic infections(1,2). The primary defect is unknown, although the surface sialoglycoprotein, gpL115 purified from lymphoblastoid cells is defective with reduced platelet glycoprotein Ib (3-4). The immunologic disturbance in this disease is a complex combination of cellular and humoral deficiency. In the first year of life, antibody levels are in the normal range/but later most patients develop low IgM, with high IgE, IgA and normal IgG(1,2). Cell-mediated immunity is decreased as evidenced by delayed hypersensitivity on skin testing, decreased number of circulating T-cells, diminished mitogen and antigen-specific responsiveness and reduced number of T-helper cells(2). WAS has an extremely poor prognosis with fatal outcome in infancy or early childhood(1,2,6). Recently, bone marrow transplantation (BMT) has been shown to be curative in selected cases(7-9). The purpose of this report is to show the clinical and laboratory profile of two boys with WAS and review the clinical, laboratory and recent therapy of this condition.

Case Reports

Case 1: A 2¹/₂-year-old boy was referred to us at the age of 15 months with the chief complaint of recurrent infection and eczema since early infancy. He was the product of a full term normal vaginal delivery following an uneventful antenatal period with a birth weight of 3.2 kg. He was apparently well until 3 months of age when he developed severe bloody diarrhea which required

hospital admission. At 4 months of age, he developed severe broncho-pneumonia with growth of *pneumococcus* from blood culture. Later, he had several admissions due to upper and lower respiratory tract infections mainly otitis media, bronchopneumonia and herpetic gingivo-stomatitis. Eczema was evident and involved the ears, face, neck and lower extremities with secondary infection. At 11 months, he had epistaxis with bruises which was controlled with platelet therapy. There was no history of bleeding during the neonatal period or after circumcision. Parents were first degree cousins with one sibling who died at 11 months with a similar history and two healthy sisters. He received BCG, DPT and polio vaccinations. At the time of referral he was an active, alert, sick-looking, afebrile child with no signs of respiratory distress. Throat was congested with herpetic ulcers. Both ear drums were congested. Eczema involved the face and lower extremities. Liver was 3 cm below right costal margin with ecchymotic patches over both lower limbs. Laboratory features revealed: Hb 8.5 g/dl, WBC 17,800/cu mm with normal differential counts, platelets 45,000 /cu mm, and anti-platelet antibodies negative. Chest X-ray was normal. Renal and liver function tests were normal. ANA and anti DNA antibodies were negative. HIV and PPD test were negative. Serum IgG was 1450 mg/dl (normal 639-1349), IgA 387 mg/dl (normal 70-312), IgM 46.5 mg/dl (normal 56-352), and IgE 19.2 IU/ml (normal 8-15) while C3 and C4 were normal. Cultures from the ear and throat grew *Haemophilus influenzae* type B and *pneumococcus*. Bone marrow aspiration showed active marrow with

abundant platelets forming megakaryocytes with reduced granulopoiesis. The patient was treated with blood, platelets, steroids, antibiotics, and antiviral (acyclovir for herpes infection with a dosage of 5-10 mg/kg/dose every 8 hours for 10 days). Intramuscular (IM) immunoglobulins (400 mg/kg/dose) were given every 3 weeks. The child is being followed up in our clinic and we plan to send him for bone marrow transplantation at King Faisal Specialist Hospital and Research Centre, Riyadh.

Case 2: A 15-month-old boy was referred to us with the chief complaint of purpuric skin rash since 2 months and recurrent eczema since infancy. He was the product of a full term normal vaginal delivery following an uneventful antenatal period with a birth weight of 3 kg. He was apparently well until 4 months of age when he developed eczema over the face, neck, and the back. He had several admissions due to sinopulmonary infections. At 13 months of age, he developed purpuric skin rash and later recurrent epistaxis. There was no history of neonatal bleeding. Parents were first degree cousins and he was the first sibling. He received BCG, DPT, polio and measles vaccines. Pertinent physical findings showed active, alert and afebrile child with no signs of respiratory distress. There was infected eczema over the face with signs of scratching and purpuric skin rash all over the body. There was no lymphadenopathy nor hepatosplenomegaly. Laboratory features included: Hb 9.4 g/dl, platelets 27,000/cu mm, WBC 12,300/cu mm with normal differential counts. PPD test was negative; chest X-ray was normal. Anti platelets antibodies were negative. Serum C3 and C4 levels were normal.

Serum IgG was 604 mg/dl (normal 639-1349), IgM was 39 mg/dl (normal 56-352 mg/dl), IgA was 365 mg/dl (normal 70-312 mg/dl), and IgE was 22 IU/ml (normal 8-15 IU/ml). Bone marrow aspiration showed normal cellularity with abundant platelet forming megakaryocytes. The patient was managed with antibiotics, platelets and steroids. Intravenous (IV) immunoglobulins were given for thrombocytopenia in a dosage of 400 mg/kg/day for 5 days; if the platelet count was below 20,000/cu mm, then intramuscular (IM) immunoglobulin 400 mg/kg/dose was given once every 3 weeks. The child is being followed up at our clinic.

Discussion

The Wiskott-Aldrich syndrome (WAS) varies considerably in its severity and usually manifests in the first weeks or months of life with bleeding due to thrombocytopenia, frequently presenting with bloody diarrhea, epistaxis, hematuria, hematemesis, intracranial hemorrhage or petechial rash on the skin and oral mucosa(1,2,6). Subsequently, recurrent bacterial infections develop commonly as otitis media, pneumonia or meningitis. There is also depressed cell-mediated immunity with increased risk for viral and opportunistic infections(1,2,10). Eczema is the most variable feature and is indistinguishable from atopic dermatitis, although severe bleeding might result after scratching. Later in the course of the disease, complications due to chronic infections arise such as bronchiectasis and chronic keratitis. Autoimmune diseases occur more frequently than in the general population such as Coomb's positive hemolytic anemia, nodular vasculitis,

nephropathy and arthritis(11/12). The most notable serious long term complication is the 100-fold increase in the incidence of malignant disease that occur with aging(6,13). The malignancies are predominantly lymphoreticular and occur in the parenchymatous tissues of non-lymphoid organs such as the brain.

Both of our patients had a history of recurrent infections, bleeding and eczema since infancy. Like all other reported cases of the syndrome, most infections were caused by *Haemophilus influenzae* type B and pneumococcus. We did not encounter fungal or any opportunistic infections. Both had recurrent epistaxis with low platelets, but none had neonatal or intracranial hemorrhage. Serum immunoglobulins showed decreased IgM, and high IgA and IgE levels as described in the literature(1,2). Consanguinity was evident in both families with history of death in one male sibling at 11 months with similar condition.

Until recently, treatment of WAS has been unsatisfactory and included transfusion of blood and platelets, antibiotics, corticosteroids, immunoglobulins and palliative splenectomy(1,2,14). Cure can only be achieved by allogenic bone marrow transplantation (BMT) from a HLA compatible donor(7-9). Complete hematologic and immunologic reconstitution has been observed following this method(15). The number of reported patients who had BMT was limited. Fischer *et al.* reviewed the experience of BMT in patients with immunodeficiency *W* between 1969 and 1985 at 14 European centres and reported disease-free survival in five of eight patients with WAS who had received HLA-identical bone

marrow transplantation and in one of the five who had mismatched transplants(16). Combining these findings with those of O'Reilly *et al.* Vossen concluded that 24 of 27 HLA-identical transplanted cases with WAS were long-term survivals(17,18). Recently, BMT was successful in infants with this disorder(19). Our patients were managed conservatively with blood, platelets, steroids, and antibiotics. Intravenous immunoglobulins were administered for thrombocytopenia and regularly every 3 weeks to prevent infection. Both showed good response but this is only temporary and the ultimate cure is bone marrow transplantation.

In summary, WAS is a rare condition which needs a high index of suspicion for early diagnosis and should be suspected in any male newborn with unexplained rectal bleeding or any infant with recurrent infection, eczema and thrombocytopenia. It should also be suspected in any unexplained recurrent deaths of male infants. Early diagnosis *in utero* could be done by finding thrombocytopenia and small platelet size in fetal blood(20).

REFERENCES

1. Asherson GI, Webster ADB. Wiskott-Aldrich syndrome. *In: Diagnosis and treatment of immunodeficiency disease.* London, Blackwell-Scientific 1980, pp 240-248.
2. Standen GR. Wiskott-Aldrich syndrome: New perspective in pathogenesis and management. *J Royal Coll Physician London* 1988, 22: 80-83.
3. O'Donnell ER, Davis AE, Kenny D, *et al.* Purification and chemical composition of gp LI 15, the human lymphocyte surface sialoglycoprotein that is

- defective in the Wiskott-Aldrich syndrome. *J Biol Chem* 1986, 261: 7526-7530.
4. Reising D, Parkman R. Molecular heterogeneity of a lymphocyte glycoprotein in immunodeficient patients. *J Clin Invest* 1987, 79: 595-599.
 5. Parkman R, O'Donnell ER, Kenny DM, *et al.* Surface protein abnormalities in lymphocytes from patients with Wiskott-Aldrich syndrome. *Lancet* 1981, 2:1387-1389.
 6. Perry GS, Schuman LM, McHugh RB, *et al.* The Wiskott-Aldrich syndrome in the United States and Canada (1892-1979). *J Pediatr* 1980, 97: 72-78.
 7. Parkman R, Rapoport J, Gehar, *et al.* Complete correction of the Wiskott-Aldrich syndrome by allogenic bone marrow transplantation. *N Engl J Med* 1978, 298: 921-927.
 8. Ochs HD, Lum LG, Johnson FL, *et al.* Bone marrow transplantation in the Wiskott-Aldrich syndrome. *Transplantation* 1982, 34: 284-288.
 9. Good RA. Bone marrow transplantation for immunodeficiency diseases. *AMJ Med Sci* 1987, 294: 68-74.
 10. Rosen FS, Cooper MD, Wedgwood RGP. The primary immunodeficiencies. *N Engl J Med* 1984, 311: 300-310.
 11. Spitler LE, Wray BB, Mogeran S, *et al.* Nephropathy in Wiskott-Aldrich syndrome. *Pediatrics* 1980, 66: 391-398.
 12. Filipovich AH, Krivit W, Kersey JH, *et al.* Fatal arteritis as a complication of Wiskott-Aldrich syndrome. *J Pediatr* 1979, 95: 742-744.
 3. Periman P, Callihan TR, Lessin L, *et al.* Hodgkin's disease occurring in a patient with Wiskott-Aldrich syndrome. *Cancer* 1980, 45: 372-374.
 4. Lum LG, Tubergen DG, Corash L, *et al.* Splenectomy in the management of the thrombocytopenia of the Wiskott-Aldrich syndrome. *N Engl J Med* 1980, 302: 892-896.
 5. Kapoor N, Kirkpatrick D, Blease RM, *et al.* Reconstitution of normal megakaryocytopoiesis and immunologic function in Wiskott-Aldrich syndrome by marrow transplantation following myeloablation and immunosuppression with Busulfan and cyclophosphamide. *Blood* 1981, 57: 692-696.
 16. Fischer A, Griscelli C, Friedrich W, *et al.* Bone marrow transplantation for immunodeficiencies and osteopetrosis. European survey 1968-1985. *Lancet* 1986, 2:1080-1083.
 17. O'Reilly RJ, Brochstein J, Dinsmore R, *et al.* Marrow transplantation for congenital disorders. *Semin Hematol* 1984, 21: 188-221.
 18. Vossen JM. Bone marrow transplantation in the treatment of immunodeficiencies. *Ann Clin Res* 1987, 19: 285-292.
 19. Lorraine J, Beard MD, Ian RG, Toogood, *et al.* Early bone marrow transplantation in an infant with Wiskott-Aldrich syndrome. *Am J Ped Hemat Oncol* 1991, 13: 310-314.
 20. Holmberg L, Sustar B, Jonsson A. A prenatal study of fetal platelet count and size with application to fetus at risk from Wiskott-Aldrich syndrome. *J Pediatr* 1983, 102: 773-776.