

## CONGENITAL MACROTHROMBOCYTOPENIC THROMBOPATHY AND NEPHRITIS (EPSTEIN SYNDROME-VARIANT)

Mohammad I. Quadri, MD, PhD; Muzzafar Ahmad, MD;  
Kefah A. Senan, CABB; Iman H. Al-Sheikh, MBBS, MD

Hereditary macrothrombocytopenic thrombocytopenia is a heterogeneous disorder.<sup>1</sup> Diseases associated with congenital macrothrombocytopenic thrombopathy may be inherited as autosomal recessive or autosomal dominant traits.<sup>1</sup> Epstein syndrome, a variant of Alport syndrome, comprises the triad of macrothrombocytopenia, nephritis and deafness.<sup>2,3</sup> The thrombocytopenia in this disorder is usually severe, and can be misdiagnosed as immune or idiopathic thrombocytopenic purpura in early childhood when other features of the syndrome have not yet appeared. We describe two members of a family (father and son), both with hereditary macrothrombocytopenic thrombopathy, as well as renal failure in the father.

### Case Report

A baby boy was born to a 27-year-old (G3 P2) mother after an uneventful pregnancy in a private hospital. On examination at birth, the infant was found to be completely normal. During a routine checkup at the same hospital at the age of five days, his CBC showed thrombocytopenia (ranging between 10-20x10<sup>9</sup>/L on different samples). He was put on prednisolone 2 mg/kg/day, and was referred to us the next day for evaluation.

The infant's platelet count varied between 4-20x10<sup>9</sup>/L, using Coulter & Sysmex blood cell counters. Prednisolone was continued, and he also received prophylactic platelet transfusions three times in next five days. The direct platelet suspension immunofluorescence test (PSIFT) and indirect PSIFT using normal platelets and the father's platelets were negative. On the infant's 14th day (three days after the platelet transfusion), blood film was examined by the hematologist and all the platelets were found to be large and lymphocytoid. Some of the platelets were irregular and larger than lymphocytes, and almost twice the size of red cells (Figure 1). No leukocyte inclusions were seen. Automatic platelet count was

27x10<sup>9</sup>/L but manual platelet count was 78x10<sup>9</sup>/L. Blood cell analyzers were unable to record the mean platelet volume or platelet distribution width and read these large platelets as clumps. The Sysmex NE 8000 platelet histogram showed most of the platelets as more than 20 fL in size. Bone marrow aspiration revealed an increased number of megakaryocytes, and both mature platelet-producing megakaryocytes and early forms with basophilic cytoplasm were present. Some of the early forms had vacuolated cytoplasm. Otherwise no significant morphological abnormalities were seen. Prednisolone was tapered and stopped after two weeks. The platelet count ranged between 20-35x10<sup>9</sup>/L thereafter.

The infant's family history was reviewed at this stage. The child was born to a young Saudi couple with second-degree consanguinity. The mother denied taking any medication during the pregnancy. The couple's two other children were healthy with no history of any bleeding tendency, appearance of rashes, hearing problems or renal complications. The father, who was 32 years old, had a mild bleeding tendency in early childhood, and had had one episode of severe epistaxis at five years of age. He was found to have low platelet count ranging between 15-20x10<sup>9</sup>/L. He was diagnosed as having idiopathic thrombocytopenic purpura (ITP). His bone marrow aspiration/biopsy was reported to be consistent with ITP. He continued to have recurrent epistaxis and was put on

FIGURE 1. Two large lymphocytoid platelets, along with a normal neutrophil (MGG stain, 1000x).

TABLE 1. Platelet aggregation studies in neonate and his father.

Platelet agonist	% aggregation				
	Working conc.	Neonate	Father	Control	Normal range
Ristocetin					
	1.25 mg/mL	40	59	83	70-90
	1.0 mg/mL	28	46	62	25-50
	0.5 mg/mL	11	09	13	<10
ADP					
	1 µM/L	ND	08	20	20-30 (primary wave only)
	2 µM/L	09	09	32	40-70 (primary/sec. wave)
	5 µM/L	ND	63	>100	70-90 (single wave)
	10 µM/L	33	68	>100	70-90 (intense single)
Epinephrine					
	100 µM/L	ND	36	>100	70-90
	200 µM/L	ND	42	>100	70-90

From the Department of Haematology (Drs. Quadri and Al-Sheikh), Regional Laboratory and Blood Bank, and Department of Pediatrics (Drs. Ahmad and Senan), Maternity and Children's Hospital, Dammam, Saudi Arabia.

Address reprint requests and correspondence to Prof. Dr. Quadri: P.O. Box 3812, Dammam 31481, Saudi Arabia.

Accepted for publication 16 November 1999. Received 11 August 1999.

Arachidonic acid 1000 µg/mL	ND	56	107	70-90
Collagen 1 µg/mL	ND	42	>100	40-60
4 µg/mL	ND	79	>100	60-90
Collagen lag phase	-	<1 min.	<1 min.	<1 min.
Thrombin 1 U/mL	02	0	>100	70-100

Equipment: Bio/Data Corporation (Platelet Aggregation Profiler-PAP-4), Horsham, PA. Reagents: CHRONO-LOG, Havertown, PA. ND=not done.

prednisolone. At 23 years of age, he was discovered to have renal failure. No renal biopsy was done as both kidneys were found to be fibrotic. Three years later, he underwent renal transplantation in India. He also developed diabetes and hypertension, possibly due to the prolonged use of steroids, without any appreciable effect on platelet count and with no major bleeding episode. He was also receiving imuran 12.5 mg on alternate days, cyclosporine 125 mg bid (po), insulin, and antihypertensives, in addition to 15 mg/day maintenance dose of prednisolone.

On the basis of the above findings, we suggested a diagnosis of macrothrombocytopenic thrombopathy with nephritis/renal failure in the father (possibly a variant of Epstein syndrome). Hematological and renal screening was done for three generations (paternal grandfather, two paternal uncles, two sibs and mother of the neonate). No abnormalities were detected. There was no history of hearing, renal or hematological disease in any relative. The ophthalmic and audiometric examination of the father was normal. The latest platelet count in the father was  $21 \times 10^9/L$ , and almost all the platelets were giant forms. No WBC inclusions were seen. The results of platelet functions (aggregometry) of the neonate and his father (using normal adult platelets as control) are given in Table 1. The platelet count of the control platelet rich plasma (PRP) was approximately adjusted with the platelet count of the test PRP. There was impairment of aggregation in response to ristocetin, ADP, epinephrine, arachidonic acid and collagen. Thrombin-induced platelet aggregation was absent. The platelet aggregometry of the mother was completely normal.

### Discussion

The association of hereditary macrothrombocytopenic thrombopathy with other hereditary renal and extrarenal disorders has been reported.<sup>2-4</sup> The triad of macrothrombocytopenic thrombopathy, nephritis and deafness constitutes Epstein syndrome.<sup>2,3</sup> A few reports of an association with leukocyte inclusions (Fechtner syndrome) have been reported.<sup>5,6</sup> We are not aware of any report in the literature where only macrothrombocytopenic thrombopathy and nephritis have been described in Epstein syndrome. In Alport syndrome, deafness may not be seen in all cases, and might skip a few generations.<sup>7</sup> It also appears after the development of nephritis and may appear late. Brivet et al. described cases with macrothrombopathy,

May-Hegglin anomaly, and congenital nephritis, but without deafness.<sup>8</sup>

Hereditary thrombocytopenias are usually diagnosed as ITP in childhood before the detection of other manifestations of Alport or Epstein syndrome. This also happened with the father of this neonate. We excluded the diagnosis of alloimmune and autoimmune thrombocytopenia in the neonate. A careful evaluation of the medical report of the father, along with the presence of macrothrombocytopenic thrombocytopenia, suggested the diagnosis of Epstein syndrome (or a variant of Epstein syndrome, as no deafness was present). Only a careful and long follow-up can exclude the development of deafness and extrarenal involvement in our patients. The inheritance pattern was autosomal dominant in our cases.

Steroids and splenectomy appear to have no role in this disorder, and the prolonged use of steroids should be discouraged, especially once the correct diagnosis has been made. The response to high-dose immunoglobulin and pulsed methyl prednisolone in a case of Fechtner-like syndrome has been reported.<sup>9</sup> The results of platelet functions in Epstein syndrome have been variable, ranging from normal to grossly impaired.<sup>2,5</sup> Both of our cases showed mild derangement of platelet aggregation with ristocetin, ADP, arachidonic acid, and collagen. No aggregation was seen in response to thrombin. As we did not use washed or gel-filtered platelets, absent thrombin-induced aggregation is difficult to explain. Thrombin produces fibrin clot in PRP and obscures aggregation tracing. However, normal aggregation was noted in the control sample. Furthermore, neonatal platelets may not show optimal response to agonists as adult platelets.

### References

1. George JN. Thrombocytopenia due to diminished or defective platelet production. Hereditary and congenital thrombocytopenias. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, editors. *Williams Hematology*, International Edition. New Delhi: McGraw-Hill Inc., 1995:1281-5.
2. Epstein CJ, Sahud MA, Piel CF, Goodman JR, Bernfield MR, Kushner JH, et al. Hereditary macrothrombopathy, nephritis and deafness. *Am J Med* 1972;52:299-310.
3. Bernheim J, Decharanne M, Bryon PA, Lagarde M, Colon S, Pozet N, et al. Thrombocytopenia, macrothrombopathy, nephritis and deafness. *Am J Med* 1976;62:145-50.
4. Sawada Y, Kudo I, Takami H, Aihara M, Yoshida Y, Kimura A, et al. Macrothrombopathy with deafness, nephritis, cataract, short small intestine and double ureter. *Jap J Clin Hematol* 1990;31:1028-31.
5. Peterson LC, Rao KV, Crosson JK, White JG. Fechtner syndrome: a variant of Alport's syndrome with leukocyte inclusions and macrothrombocytopenia. *Blood* 1985;65:397-406.
6. Heynen MJ, Blockmans D, Verwilghen RL, Vermeylen J. Congenital macrothrombocytopenia, leucocyte inclusions, deafness and

- proteinuria: functional and electron microscopic observation on platelets and megakaryocytes. *Br J Haematol* 1988;70:441-8.
7. Ruley EJ. Nephritis. In: Hoekelman RA, editor. *Primary pediatric care*. 3rd edition. St. Louis: Mosby, 1997:1439-40.
  8. Brivet F, Girot R, Barbanel C, Gazengel C, Maier M, Crosnier J. Hereditary nephritis associated with May-Hegglin anomaly. *Nephron* 1981;29:59-62.
  9. Leung TF, Tsoi WC, Li CK, Chik KW, Shing MM, Yuen PM. A Chinese adolescent girl with Fechtner-like syndrome. *Acta Paediatrica* 1998;87:705-7.