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Diagnosis of Heterozygous State for Bernard-Soulier Disease

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Bernard-Soulier disease (BSD) is an inherited bleeding disorder characterized by a prolonged bleeding time, with a normal or decreased number of unusually large platelets which fail to aggregate in response to ristocetin. This disease is generally transmitted as an autosomal recessive disorder, but it has also been shown that abnormal platelet morphology is transmitted as an autosomal dominant [1]. In heterozygous BSD patients, giant platelets are found in significantly lesser numbers than in homozygous BSD patients. Heterozygotes of BSD are asymptomatic. Although they have not been well studied, it has been proposed that heterozygous subjects can be

identified by their giant platelets [1–3]. More recently, George et al. [2] described an abnormal platelet membrane glycoprotein I concentration in 3 heterozygotes from two families with BSD. In this study we investigated ristocetin-induced platelet aggregation (RIPA) in heterozygous BSD patients to see if it might be helpful for their identification. 12 members from six families of patients with BSD were investigated. 6 of them were mothers, 4 fathers, and 2 were brothers of our patients. Their ages ranged from 6 to 45 years. With the exception of case No. 4, there was a consanguinity between the parents of all our patients. Platelet aggregation studies were Table I. Ristocetin-induced platelet aggregation in heterozygous subjects with Bernard-Soulier disease

Patients Case No.

Date

Ristocetin-induced aggregation (T_{max}), %?

father

mother

brother

November 20, 1980 October 22, 1982 May 11, 1983

45

26

55

50

28

August 8, 1980 October 6, 1980 May 21, 1981

18 30

13
36 60
16
10
32

December 12, 1980 January 15, 1981 April 16, 1981
22 32 60

April 26, 1983 May 6, 1983

18
38
58
46
32

April 13, 1981 February 28, 1980

21
53
20

Normal values: mean $\pm$ SD, $73 \pm 2.9\%$; range, 56–90%. – = Not studied.

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performed on a chrono-Log aggregometer (Broomall-ly, Pa., USA) using a model 702 strip chart recorder. RIPA was tested using ristocetin (Lundbeck Co., Copenhagen, Denmark) diluted with normal saline to obtain a final concentration of 1.6 mg/ml. Aggregation curves were evaluated according to the percent aggregation (T_{max}) which indicates the maximum percent change in light transmission of platelet-rich plasma after the addition of ristocetin. As seen in table I, except for the father of case No. 4 all hetero-zygotes showed decreased RIPA compared to controls. This decreased rate of aggregation by ristocetin could not be corrected with the addition of normal plasma, which is also characteristic for platelets of patients with BSD [4, 5]. When tests were repeated in some heterozygotes on separate occasions, various degrees of reduced or even normal ristocetin-induced platelet response were observed, possibly due to variation in the number of giant platelets in the circulation. Although the platelet response to ristocetin had not been investigated previously, recently George et al. [2] reported normal RIPA in their 3 heterozygous BSD patients. However, they did not mention whether they had repeated these tests or not.

In conclusion, the present study shows a further defect related to the platelets in heterozygous BSD. In addition to the measurements of platelet size and distribution and of membrane glycoprotein I concentration, the heterozygous state of BSD is recognizable by the abnormal aggregation response of platelets to ristocetin, which is more practical.

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