Letters to the Editor

Valproate-induced Bleeding: Report of Two Cases and Review of Literature

Case 1

7-year-old boy was diagnosed to have absence epilepsy. VPA (20-mg/kg body weight/day) was started. Three days later, he presented with multiple ecchymotic patches and epistaxis. Hemoglobin was 11.4 mg%, and platelet count-3,52,000/cu.mm. Bleeding time (BT) was >15 minutes. Platelet aggregometry showed normal aggregation with ristocetin and reduced aggregation with epinephrine and collagen. Clotting time (CT), prothrombin time (PT) and partial thromboplastin time (PTT) were normal. Plasma VPA level was 54 µg/ml. VPA-therapy was withdrawn. Fresh platelet concentrates were transfused. Child improved and platelet aggregometry repeated after six weeks was normal.

Case 2

15-year-old girl presented with excessive bleeding from traumatic compound tibial fracture. Twelve hours after surgery, she developed re-bleeding from surgical site. She was on VPA (30 mg/Kg/day) for nine months for epilepsy. Plasma VPA level was 120 µg/mL. Hemoglobin was 9.2 g%, and platelet count-2,10,000/cumm. BT, CT, PT and PTT were normal. Urea clot lysis test was positive, suggesting Factor XIII deficiency. Past history did not suggest prolonged bleeding from umbilical stump after birth, therefore VPA therapy as an acquired cause for factor XIII deficiency was suspected and withdrawn. Cryopreci-pitates were transfused and bleeding stopped. Clot lysis test repeated after ten weeks was normal.

The commonest hematologic abnormality with VPA therapy is thrombocytopenia, however, our patients had normal platelet counts. Frequency of valproate-induced thrombocytopenia is 21%, however 90% remain asymptomatic(1). The incidence of thrombocytopenia is related to VPA dose and plasma drug levels, as 1200-3000 mg/day resulted in thrombocytopenia(2). Most had plasma VPA level >140 micrograms/mL Platelet counts normalized after dose reduction(1). Plasma drug levels were within therapeutic range in our patients. The incidence of thrombocytopenia was also related to VPA-treatment duration(1). Thrombocytopenia results due to combination of peripheral antibody-mediated platelet destruction and bone marrow depression. Platelet dysfunction also occurs with VPA therapy. In a 4-month-old, bleeding from venepuncture sites and multiple ecchymoses occurred two days after starting VPA therapy(3). The cause was platelet dysfunction and hypofibrogenemia. Case 1 had platelet aggregation defect, and onset of symptoms was similar. Platelet aggregation defects correlate well with VPA dose and plasma concentration.

VPA-related factor XIII deficiency (seen in case 2) has been reported earlier(4). Acquired von Willebrand's disease may be the other mechanism of bleeding(5).

In conclusion, the risk of clinical bleeding with VPA therapy appears to be extremely low despite high incidence of laboratory abnormalities. Hematologic toxicities may be reversed by dosage reduction and discontinuation of VPA may not be required.

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Ensuring Correctness of Bone Marrow Reports in Infants: Role of the Pediatrician

Pediatricians generally have little to do with the way bone marrows (BM) are reported by pathologists. This communication is to emphasize the fact that BM of young children, particularly infants, constitutes a special group, where an active involvement of the pediatrician can ensure correctness of the report.

The BM of infants and young children differs from that of normal adults in having up to 75% (mean + 2 SD) lymphocytes and transitional cells(1). These cells, also called hematogones(2), have morphological features that cause them to be often wrongly interpreted as blasts. This occurs typically in two settings. The first is a BM examination done to look for a hematological or non-hematological malignancy. The second setting is evaluation for remission of a child on therapy for acute lymphoblastic leukemia (ALL). The error here is because of a phenomenon, not very common, known as rebound lymphocytosis, wherein lymphocytes and hematogones come to dominate the BM 6-24 months post-therapy(2,3).

In most of our cases where a mistake had occurred due to rebound lymphocytosis, the follow-up BM examination had been done outside in another hospital and the patient had returned to us after the marrow had been reported as being in relapse. Unfortunately, in all but an occasional of these cases, the pediatrician outside had accepted the wrong diagnosis. Morphological features of the BM cells, however, made it apparent to us that the cells were not blasts and a hematological follow-up resolved the issue.

Preventing such errors is obviously crucial. Providing full clinical information to the pathologist helps, as does firm dependence on ones clinical judgment. However, what would help most, is a high index of suspicion among pediatricians. The greatest problem in this, in our view, is a rather poor awareness because pediatrics texts generally do not discuss BM transitional cells/hematogones(4). Books that do, often do not emphasize these cells in the proper context where it matters most, *i.e.*, in relation to management of hematological and non-hematological malignancies(5). Emphasis of great practical value is present only in a few monographs which are liable not to be consulted by many practising physicians.

The unique feature of bone marrow of