Case Report

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Pathology Section

A Case of Macrophagic Activation Syndrome in a Child with Epilepsy Treated with an Excessive Dose of Sodium Valproate

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ABSTRACT

Macrophagic Activation Syndrome (MAS) is a rare disorder and is thought to result from non-malignant activation and proliferation of macrophages and T-cells. It can be of primary or secondary origin and its prognosis is often poor. Authors report a case of a three-year-old boy admitted in the intensive care unit for MAS secondary to an overdose of sodium valproate to remind practitioners to think about it in the presence of a febrile pancytopenia.

Keywords: Bone marrow, Brazzaville, Henter's criteria, Intensive care

CASE REPORT

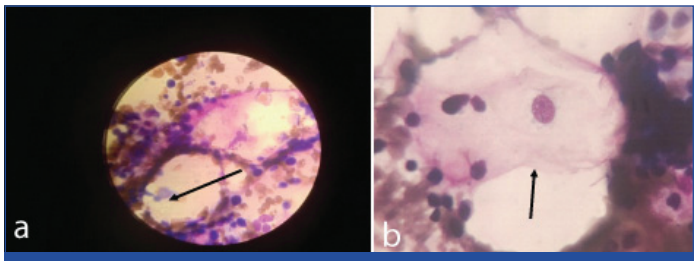
A three-year-old boy was admitted in the Paediatric Intensive Care Department of the University Hospital of Brazzaville for coma. Eight days before admission he had intermittent fever of upto 40°C associated with post-meal vomiting. Symptomatic treatment was administered by the parents with no improvements. Repeated tonic clonic seizures on the eight day, with a frequency of three times in a span of 24 hours, prompted hospital admission. The patient has been followed since the age of eight months for West syndrome. He was given sodium valproate 30 mg/kg twice a day until he was two-year-old. The resumption and recurrence of seizures at this age prompted the mother's gradual increase in the dose of the drug up to 62 mg/kg day.

The clinical examination generally noted a comatose child, feverish at 39°C and dehydrated (stage 3); presenting a frank pallor of the mucous membranes and the integuments; there were petechiae in the thoracic region and a moderate jaundice (15 mg/dL). The blood pressure was 80/60 mmHg, the skin recolouration time was less than three seconds. The Body Mass Index (BMI) was 11.33 kg/m^2.

During clinical examination, Glasgow was 8/15 with no signs of focusing. The stomatological examination noted a spontaneous gingivorrhagia or appearing at the slightest touch of the tongue depressor. The abdomen was soft, with a large splenomegaly stage III of HACKETT (spleen expands to the umbilicus) and hepatomegaly. The examination of other organs was normal.

The paraclinical assessment showed: Pancytopenia with leukopenia at 2300/mm^3 (4000-10000/mm^3), neutropenia at 1100/mm^3 (2000-7500/mm^3), lymphopenia at 980/mm^3 (1500-4000/mm^3); the haemoglobin level was 5.4 g/dL (13-14 g/dL), mean corpuscular volume at 72 fl (80-100 fl) and mean corpuscular haemoglobin at 22.4 pg (27-31 pg); platelets were 31,000/mm^3 (150000-450000/mm^3), i.e., thrombocytopenia. There was also a hyperferritinemia at 1122 µ/l (10-140 µ/l); hypertriglyceridemia at 3.6 mmol/l (0.35-1.5); hyponatremia at 128 mEq/l (135-150 mEq/l). The HIV, Hepatitis B and C serology was negative. C-Reactive Protein (CRP) was elevated with 24 mg/L (<6 mg/L). The Cerebrospinal Fluid (CSF) analysis was normal; and thick drop test was negative.

A bone marrow sample was taken from the iliac crest. The myelogram performed after thin and thick smears were stained with May Grunewald Giemsa noted a hyperplasia of megakaryocytic with a hypoplasia of erythroid and granulocytic lineages, macrophage with tangible bodies containing cellular debris and erythroblasts [Table/Fig-1]. The serum fibrinogen was 1.3 g/L.



[Table/Fig-1]: a) Arrow pointing towards macrophage; b) Containing cellular intracytoplasmic debris.

The diagnosis of secondary MAS was made on the basis of Henter's criteria [1].

The treatment consisted in eviction of sodium valproate, parenteral rehydration; repeated transfusions of platelet concentrates and globular concentrates, corticosteroid therapy (methyl prednisolone: 4 mg/kg/d); and a prophylactic antibiotherapy. Therapeutic milk F75 (75Kcal for 100ml administered 130 Kcal/kg/day) was used as starter formula and F100 (100 Kcal for 100 mL) as a catch-up formula for nutritional recuperation.

The clinical and biological evolution was favourable with normalisation of haematimetric constants from the seventh day. An outing has been scheduled for the twentieth day. The patient has been followed-up several times during a six-month period; he is fine and his check-up was normal.

DISCUSSION

Macrophage activation is a normal and essential step in the immune response; it is mediated by cytokines including GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor), SCF (Stem Cell Factor), FLT3-L (Fms-like Tyrosine Kinase-3 Ligand), IL-3 (Interleukin-3), gamma interferon, Tumour Necrosis Factor (TNF) released by activated T lymphocytes. During the MAS, there is an overwhelming inflammatory reaction due to uncontrolled and dysfunctional immune response and a diffusion to all the tissues of the organism which can be the seat of a histiocytic infiltration [2]. This syndrome was first identified by Risdall RJ et al., in 1979 [3]. It has been rarely reported in the paediatric population. Its incidence would be 1/1000000 children; but this incidence remains underestimated in the absence of consensus on the diagnostic criteria [4,5].

The clinical signs of this syndrome are not very specific and the diagnosis is determined by the combination of at least five Henter's criteria [1]; which was the case in the present patient who had a fever for more than seven days, splenomegaly, pancytopenia, triglyceridemia, hyperferritinemia and signs of haemophagocytosis. Alkoht A et al., in Syria had reported similar findings in addition to immunologic results [6]. This polymorphic clinical feature is often linked to some affection such as acute leukaemia, medullar aplasia. However, the results of the myelogram (lack of medullar blastosis and rich marrow) helped us eliminate those differentials.

The causes of secondary MAS are dominated by mainly viral infections (Cytomegalo virus, Epstein Barr virus, Human Immuno Deficiency Virus, Varicella zooster virus) but the toxic causes have also been reported. In the present case, the toxic agent found was sodium valproate, which was administered at a supra-therapeutic dose (62 mg/kg/day), which reveals an immunotoxic mechanism causing a serious hypersensitivity reaction, as reported by Lambotte O and Méchai F [7].

There is currently no recommendation for the treatment of MAS; currently some authors agree, apart from the treatment of the causative agent, to administer a specific treatment for haemophagocytosis with the aim of attenuating the inflammatory response and controlling cell proliferation [8,9]. This treatment combines corticosteroid therapy, cyclosporin and etoposide VP-16. In the present case, methyl prednisolone was administered at 4 mg/kg/d, which was lower than in Alkoht A et al., study [6]. Cyclosporin and etoposide VP-16 were not used in the patient.

MAS is often associated with poor prognosis with a death rate exceeding 50% as reported by Créput C et al., [10]. Nevertheless, early diagnosis and treatment would have been, among other factors, contributing to the favourable outcome in index patient.

CONCLUSION(S)

MAS is rarely reported in the practice area due to a lack of consensus in diagnostic criteria. Its favourable development is often exceptional. Corticosteroid therapy often allows remission but the high risk of relapse requires close monitoring.

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