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Valproate in Psychiatric Practice: Risks to Fertility and Future Generations

Valproato na Prática Psiquiátrica: Riscos para a Fertilidade e para as Gerações Futuras

Keywords: Fertility/drug effects; Mental Disorders/drug therapy; Valproic Acid/adverse effects
Palavras-chave: Ácido Valpróico/efeitos adversos; Fertilidade/efeito dos fármacos; Perturbações Mentais/tratamento farmacológico

Dear Editor,

We are writing to express concerns about the use of valproate or valproic acid (VPA) in psychiatry, particularly its impact on fertility and future generations.

This medicine gained widespread use as a mood stabilizer following reports of teratogenic risks associated with lithium use.[1] However, VPA's significant teratogenic effects, identified since the 1990s – including a 20-fold increased risk of neural tube defects – have led to its contraindication during pregnancy and limited use in women of childbearing age unless other treatments fail.[2]

Besides structural abnormalities, *in utero* exposure to VPA is associated with neurodevelopmental disorders.[3] A French study demonstrated a dose-response relationship between VPA exposure during the second or third trimesters of pregnancy and neurodevelopmental risks.[3] In animal studies, VPA increased the risk of neurodevelopmental disorders up to the third-generation offspring. Additionally, VPA negatively affects fertility, with studies linking it to polycystic ovary syndrome and hyperandrogenism.[4] Given these risks, in 2018, the European Medicines Agency restricted VPA use, contraindicating its use during pregnancy and in women of childbearing potential, unless enrolled in a pregnancy prevention program with pregnancy tests, effective contraception, and specialist reviews.[2] Valproate has also been linked to reversible male infertility, impacting sperm parameters through the effect of gonadotropin , oxidative stress, and mitochondrial dysfunction.[4] Recent studies suggest paternal VPA use within three months before conception may increase the risk of neurodevelopmental disorders in children compared to the use of other antiseizure medications.[2]

Since 2018, the United Kingdoms' (UK) Medicines and Healthcare Products Regulatory Agency has reported a 38% reduction in valproate use among women of childbearing age. However, a concerning plateau in this decline has emerged, with two to three babies per month still exposed to the drug *in utero*. The evidence suggests healthcare professionals may not be consistently informing women of these risks.[2,5] As a result, in January 2024, the UK's medicines regulator mandated that VPA must not be started in new patients (male or female) under 55 years, unless two specialists document that there is no alternative treatment.[2] The decision by the UK regulator to maintain strict controls on valproate prescribing is controversial but reflects ongoing concerns about inconsistent adherence to safety regulations.[5]

In conclusion, while VPA remains important in psychiatric care, its impact on fertility and generational risks requires strict adherence to guidelines, informed patient choices, and the consideration of alternatives. It is essential to address these challenges responsibly.

AUTHOR CONTRIBUTIONS

MA: Conception and writing of the manuscript.
DD, CS: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Infection and Immunosuppression as Causes for Immune Dysfunction Presenting as Hemophagocytic Lymphohistiocytosis and Thrombotic Microangiopathy

Infeção e Imunossupressão como Causas de Disfunção Imune Manifestada como Linfohistiocitose Hemofagocítica e Trombomicroangiopatia Trombótica

Keywords: Lymphohistiocytosis, Hemophagocytic/etiology
Palavras-chave: Linfohistiocitose Hemofagocítica/etiologia

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease associated with a hyperinflammatory state, cytokine storm, and macrophage and lymphocyte activation.[1] Because of its rarity and low specificity of clinical symptoms, the diagnosis is difficult, and the prognosis is bad.

We describe the case of a 35-year-old man with Crohn's disease (CD). The disease had recently flared, requiring treatment with vedolizumab (VDZ), prednisolone (40 mg/d) and azathioprine (100 mg/d).

Ongoing complications led to admission due to a recurrent intra-abdominal abscess. Failure of empirical antibiotic therapy led to right hemicolectomy with direct ileo-colonic anastomosis. On preoperative evaluation, a nasopharyngeal swab for SARS-CoV-2 was positive, when it had been negative on admission, and the patient had no symptoms. Five days after the surgery, fever (maximum 38.5ºC), haematochezia, and a cutaneous rash (Fig. 1) appeared, alongside the development of *de novo* multiorgan failure (Table 1), namely acute kidney injury, acute hepatic failure, and thrombotic microangiopathy. An abdominal computed tomography (CT) scan showed hepatomegaly with no surgical complications. *Enterococcus faecium* was isolated in blood cultures, and therapy was adjusted accordingly. Further work-up led to the diagnosis of HLH given the presence of hyperferritinaemia, hypertriglyceridemia, hemophagocytosis on bone marrow and high serum soluble CD25 (fulfilling six out of eight HLH-2004 diagnostic criteria). Additionally, other aetiologies such as cytomegalovirus, human immunodeficiency virus, thrombocytopenic thrombotic purpura, and haemolytic uremic syndrome were excluded. Suppressive therapy with high-dose corticosteroids was added and the patient steadily recovered with resolution of all organ dysfunctions (Table 1). Predisposing mutations in *STXBP2*, *STX11*, *PRF1* and *UNC13D* were searched and turned out negative.

Hemophagocytic lymphohistiocytosis was assumed secondary to sepsis due to *E. faecium* bacteriemia, probably in the context of intestinal translocation after abdominal