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Letter to the Editor

Before attributing "encephalopathy" to mitotane toxicity, paraneoplastic immune encephalitis and others need to be ruled out

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We read with interest the article by Heo *et al*. about a five years-old female with adrenocortical carcinoma (ACC), which was treated with extirpation, radiotherapy, hydrocortisone, and mitotane at a low dosage [1] Despite this treatment, the disease course was not only complicated by hormonal dysfunction but also be neuro-cognitive and neuro-behavioural dysfunction, which was attributed to mitotane since the neuropsychological abnormalities resolved upon discontinuation of mitotane [1]. The study is appealing but raises concerns that should be discussed.

We disagree with the diagnosis mitotane-induced encephalopathy as long as not all differential diagnoses had been appropriately ruled out. The first differential diagnosis that needs to be ruled out is paraneoplastic autoimmune encephalitis. Although the patient had undergone MRI of the pituitary gland, there is no mentioning if the remainder of the brain had been investigated and if contrast medium was applied. Ruling out autoimmune encephalitis is crucial as neurocognitive decline of the index patient started already at a time when mitotane levels were in the sub-therapeutic respectively normal range [1]. Ruling out immune encephalitis requires in addition to contrast-enhanced MRI, determination of antibodies associated with autoimmune encephalitis, which include antibodies against NMDA. NMDAR, AMPA, MDAR, Caspr2, LGI1, GABAbR, GABAaR, mGluR5, glycine-R, IgLON5, and others [2]. These antibodies can be found in about half of the cases with autoimmune encephalitis [2] and may be present even if cerebrospinal fluid (CSF) findings are normal, as in the index patient.

A second differential diagnosis that has to be ruled out is non-convulsive status epilepticus (NCSE). Because electroencephalography (EEG) revealed "continuous, generalised, fast activities" it is crucial that these EEG recordings are presented and that NCSE is completely ruled out. NCSE can be a complication of autoimmune encephalitis but can also develop in the absence of autoimmune encephalitis or other cerebral pathology, including paraneoplastic encephalopathy. We should know if creatine-kinase was ever elevated in the index patient.

A third differential diagnosis that has to be ruled out is steroid-induced encephalopathy [3]. Therefore, we should be informed whether hydrocortisone was started prior to onset of the neurocognitive abnormalities and if there could be a causal connection. We should know if the patient developed features of Cushing disease.

A fourth differential diagnosis is SARS-CoV-2 associated encephalopathy. Because the manuscript was submitted in February 2021, there is a need to rule out SARS-CoV-2 associated encephalitis. CSF findings can be normal as it is regarded as an autoimmune disease. There is no mention of a negative PCR for SARS-CoV-2 [1]. Was hypophysitis ruled out? Hypophysitis can be also a complication of SARS-CoV-2 infections.

We disagree with the statement that the presented patient is the first developing sided effects to mitotane [1]. Several pediatric patients with mitotane side effects have been reported [4, 5].

A limitation of the study is that no results of a follow-up EEG were provided. Given the fact that the first EEG was abnormal, it is crucial to confirm normalisation of the investigation with clinical improvement.

Overall, the interesting study has limitations that call the results and their interpretation into question. Addressing these limitations could further strengthen and reinforce the statement of the study. Before attributing encephalopathy to mitotane, a number of differential diagnoses need to be appropriately ruled out.

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