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Comment on Pancreatitis in Type 1 Tyrosinemia

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To the Editor,

In their interesting, peculiar case report published in the May issue of the Balkan Medical Journal, Uçar et al. (1) reported a rare co-occurrence of acute pancreatitis with type 1 hereditary tyrosinaemia (HT1). This publication caught our attention regarding several relevant points.

First, in the patient details, the authors did not mention the results of any lumbar puncture, as the clinical course could reveal an acute viral encephalitis, especially post-mumps, that may be associated to pancreatitis.

Having normal urinary succinyl acetone is also very questionable after a long (6 months) period of nitisinone discontinuation. In fact, nitisinone 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione, NTBC) is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase, an enzyme that is upstream of fumarylacetoacetase, and most patients present a rapid decrease in the concentrations of succinylacetone (2) when under NTBC.

On the other hand, acute pancreatitis is associated with a strong activation of the pro-inflammatory pathway (3). Local, as well as systemic inflammatory responses are independent of intra-acinar trypsinogen activation (4) and lead to the core inflammatory pathogenesis. A similar hyper-inflammatory state may be seen in HT1. Type 1 hereditary tyrosinaemia is caused by a deficiency of fumarylacetoacetate hydrolase, the enzyme responsible for the hydrolysis of fumarylacetoacetase. This latter metabolite, fumarylacetoacetase, displays mutagenic and apoptogenic activities and elicits an endoplasmic reticulum oxidative, inflammatory stress response (5).

Thus, treatment with NTBC would annihilate the fumarylacetoacetase accumulation, while complete NTBC withdrawal (as seen in this case) leads to a massive accumulation of fumarylacetoacetase.

We think that a possible aetiopathogenic, inflammatory cause of acute pancreatitis due to fumarylacetoacetase accumulating during NTBC withrawal might be considered in HT1 cases, and should enhance consideration of continuous enzyme inhibition with daily NTBC.

Conflict of Interest: No conflict of interest was declared by the authors.

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AUTHOR REPLY

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To the Editor,

We thank Hakim Rahmoune and colleagues for their comments and questions. The clinical pictures of encephalitis and neurological crisis due to tyrosinemia type 1 are extremely different, and it is very hard to confuse these two neurological entities. The first one is an acute serious condition and mostly associated with the clinical findings of central nervous system like altered state of consciousness, convulsions and focal neurological deficits. In contrast, neurological crisis due to tyrosinemia type 1 is generally a sub-acute and gradually settled state associated with peripheral neuropathy, autonomous dysfunction.

Therefore, lumbar puncture was regarded as an unnecessary and invasive procedure for our patient's clinical statement. Neurological crisis was initially considered with clinical and laboratory findings, also discontinuation of 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione. As, the most prominent sign was abdominal pain and electromyography was normal; we had to evaluate the other possible causes which let us to the diagnosis of pancreatitis.

Urinary 5-delta-aminolevulinic acid and succinylacetone were studied in another center and the results were handed to us, these analyses can not be performed in our laboratory. As, succinylacetone is detectable in blood before urine, it is more accurate to determine it in blood. But, the clinical, laboratory and radiological findings pointed out acute pancreatitis without any suspicion.

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