

## From Confusion to Autism: When to Think of an Inborn Error of Metabolism?

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Even though, individually, the inborn errors of metabolism are very rare, collectively they are more common than estimated, especially in populations with high rates of consanguinity. These disorders are the last to be considered in most of the lists of differential diagnosis, but when diagnosed early, some of these diseases can have a very good, none disabling, outcome.

The presenting clinical signs can vary from a regular, specific, single organ failure to a global dysfunction that can be classified somewhere in the psychiatric illnesses chapter, and 9.1% of the patients presenting with psychiatric signs have in fact an underlying metabolic disorder [1]. And in an era of trending awareness campaigns focusing on psychiatric disorders and mainly on autism, the social culture plays a major role in orienting the patients to seek an ambiguous, but heard of, psychiatric disorder with the hope of improvement, rather than to reach a clear congenital disease with a clear mutation; yet, most of the time untreatable. And the patient becomes at risk of a late diagnosis.

Despite the advances in psychological descriptions and immense trial in creating criteria and scales to identify psychiatric disorders, accepting these abstract diagnosis remains challenging when compared to the clearness of the evidence based medicine. The continuous search for a genetic cause as well as explaining the physiological basis of the manifestations of these disorders remain essential, while we rely on the psychiatric criteria in order to implement a diagnosis, specially that in some cases of inborn errors of metabolism isolated psychiatric signs may be the only sign present in the early stages of the disease where more treatment options are available [2].

One of the unusual presenting signs of an inborn error of metabolism is confusion, sometimes associated with other symptoms like a none specific abdominal pain, nausea, vomiting, with normal regular paraclinical investigations, in which case we should include in our diagnosis etiologies like porphyria, urea cycle defects, and homocystinuria which are disorders with a curative treatment other than the symptomatic psychiatric medications. An ammonia blood level is a simple widely available test that can give a diagnostic lead, and confusion can be a direct result of hyepammonemia responding to a wide range of medication like sodium benzoate and sodium phenyl butyrate. And when these signs progress to psychosis-like episodes that might be classified as schizophrenia, a brain imaging should be obtained, and even if it shows normal features, the possibility of metachromatic

leukodystrophy should be investigated, because a curative bone marrow transplant can then be proposed as long as the brain MRI shows no anomalies. Another etiology to be considered in schizophrenia is the late onset form of Tay Sachs disease for which many therapeutic trials are taking place currently.

Depression is another usual but common presentation of disorders like Ceroid lipofuscinosis and Fabry diseases. In Fabry disease the patient can present with many unspecific signs like recurrent pain, paresthesia, sometimes provoked by stress or temperature changes, and can be easily attributed to a psychiatric problem, with the ease of appearance of depression and suicidal thoughts. In these patients, the earlier the appropriate enzyme replacement therapy is initiated, the better are the results in correcting the symptoms and in preventing complications like strokes and renal failure.

But the most common psychiatric presentation in inborn errors of metabolism remains is the mental delay with behavioral problems and the diagnosis of autism or autistic spectrum is very easily attributed to these patients. Wilson's disease, monoamine oxidase a deficiency, and of course Sanfilippo syndrome should then be considered. And in the areas where neonatal screening is not a regular practice, phenylketonuria and homocystinuria should be investigated, and with the appropriate diet the results can be spectacular. In these cases a regular brain MRI showing no anomalies does not exclude the possibility of a treatable metabolic disorders, and it should always be completed with a spectroscopy study in order to have an appropriate assessment of the brain myelination, and to avoid missing a diagnosis like the creatine deficiency syndromes, where a treatment can be initiated.

In patients where personality changes are noted, Wilson disease should be eliminated as a diagnosis as well as an X-linked adrenoleukodystrophy, and in both cases the appropriate treatment should be implemented.

But the most commonly involved organelle in psychiatric disorders is the mitochondria. Primary or secondary mitochondrial impairment is proven to be present in most of the psychiatric disorders [3], and lactic acidosis has been found in many patient labeled as autistic [4]. Such observations have been published since the late 90's and the clear genetic basis remains to be discovered in these patients, and the late publications suggest that the administration of carnitine, coenzyme Q10 and other nutrients as a therapeutic trial can be partially beneficial [5,6].

As a conclusion, when faced with a psychiatric disorder, either acute as psychosis or confusion, or chronic in nature like autism, a careful diagnostic attitude should be adopted in order not to miss some very rare; yet, treatable congenital disorders. Simple blood tests might include CPK levels as well as ammonia levels, and a routine double check of the results of the neonatal tandem mass screening. Also a brain imaging should not be the last exam to consider. We should always remember that guidelines usually apply to some communities in the matter of acquired disorders, but when it comes to rare diseases, guidelines and statistics vary a lot from community to another and from a population to another.

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