Tyrosinemia type 1 and ADHD-like Symptoms; Similarity or Comorbidity: About a Case.

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Abstract:

Many metabolic diseases influence brain function and are associated with psychiatric symptoms and neuropsychiatric disorders (including autism-spectrum disorders, ADHD and psychotic disorders). Attention-deficit/hyperactivity disorder (ADHD) is among the most common neurodevelopmental disorders in children, with a worldwide prevalence of about 5% in childhood. Tyrosinemia is caused by a genetic mutation in the fumarylacetoacetase gene that leads to a deficiency in the encoded enzyme, which catalyzes the cleavage of tyrosine metabolites to acetoacetic acid and fumaric acid. In recent studies of children with tyrosinemia type 1, a strong correlation was observed between symptoms of ADHD and blood levels of tyrosine, supporting a direct role of this amino acid in the pathogenesis. We report the case of an 8-year-old child, followed since the age of 3 months for a tyrosinemia type 1 who presented symptoms of ADHD with high scores of inattention, hyperactivity and impulsivity on assessment scales.

Keywords: Tyrosinemia type 1, ADHD, symptoms, children, neurometabolic disorders.
Introduction:

Many metabolic diseases influence brain function and are associated with psychiatric symptoms and neuropsychiatric disorders (including autism-spectrum disorders, ADHD and psychotic disorders). Attention-deficit/hyperactivity disorder (ADHD) is among the most common neurodevelopmental disorders in children, with a worldwide prevalence of about 5% in childhood. In about two-thirds of these cases ADHD persists into adulthood. A review of twin studies confirmed high heritability estimates of 70–80 % for the disorder in both childhood and adulthood, and recent large-scale molecular genetic studies have identified the first common and rare genetic risk variants associated with childhood and/or adult ADHD[1,2].

Furthermore, environmental and developmental factors like maternal psychosocial stress during pregnancy, preterm birth, low birth weight and hypoxia during birth as well as childhood maltreatment seem to influence the risk of developing ADHD, sometimes by correlation with genetic variants[3].

Tyrosinemia is caused by a genetic mutation in the fumarylacetoacetase gene that leads to a deficiency in the encoded enzyme, which catalyzes the cleavage of tyrosine metabolites to acetoacetic acid and fumaric acid. Similar to PKU, tyrosinemia patients have increased levels of an aromatic amino acid (tyrosine) which may also interfere with the synthesis of monoamine transmitters, including dopamine. In recent studies of children with tyrosinemia type 1, a strong correlation was observed between symptoms of ADHD and blood levels of tyrosine, supporting a direct role of this amino acid in the pathogenesis [4].

ADHD has high rates of comorbidity with psychiatric or somatic disorders, possibly reflecting shared pathophysiological mechanisms. Knowledge about the relationship between neurometabolic disorders (NMDs) and symptoms of ADHD may provide insight into the etiology of ADHD, as well as improve the clinical management of patients with such conditions[5].

Pathophysiology of tyrosinemia type 1 (HT-1):

In 1977, fumarylacetoacetate hydrolase (FAH) was identified as the deficient enzyme responsible for HT-1 (Figure 1). This enzyme is the terminal step in the tyrosine catabolic pathway. HT-1 is differentiated from another condition with dramatically elevated blood tyrosine levels that produces a severe dermatologic and ophthalmologic condition (tyrosinemia type II). In HT-1 patients, dietary restriction of phenylalanine and tyrosine, even if begun within the first month of life, did not eliminate the development of hepatic, renal, or neurological complications. Orthotopic liver transplantation became the therapeutic option for patients who developed hepatic or neurological complications. An alternative option with apparently fewer complications has become available over the last two decades through the introduction of successful pharmacologic therapy with NTBC.

The mammalian tyrosine catabolic pathway was described in the early 1950s by Edwards and Knox. Fumarylacetoacetate (FAA) is the natural substrate of FAH, but FAH also uses succinylacetate (SAA) as a substrate (Figure 1). Both FAA and SAA accumulate in FAH deficiency. The mechanism of the reduction of FAA to SAA has not been established, but it is probably catalyzed by a yet uncharacterized enzyme, FAA-reductase[6].

Deficiency of FAH would not be expected to result in elevated blood tyrosine, since FAH is five steps removed from the initial catabolic step in tyrosine degradation (Figure 1).
Deficiency of a more proximal enzyme in that metabolic pathway, homogentisic acid dioxygenase, the third enzyme, is associated with the medical condition alkaptonuria and the clinical condition is not associated with any hyper tyrosinemia. Therefore, elevated blood tyrosine levels in HT-1 are more likely due to a secondary inhibition of proximal steps in tyrosine degradation and not the deficiency of FAH.

In FAH mutant mice the mRNA for tyrosine amino transferase (Tat), the rate-limiting enzyme in tyrosine degradation, is absent. The activity of 4-hydroxyphenylpyruvic dioxygenase (HPD), the second step in the tyrosine degradation pathway, is decreased in human HT-1 liver samples. These observations suggest that the clinical effects associated with HT-1 are due to other metabolites resulting from FAH deficiency, not the elevation of tyrosine in the blood.

Clinically, elevated plasma levels of tyrosine observed in conditions associated with deficiencies in the tyrosine degradation pathway other than HT-1 are not toxic to the liver or kidney. Elevated blood tyrosine levels cause only dermatological, ophthalmologic, and possibly neurodevelopmental problems in patients with tyrosinemia type II (TAT deficiency, Richner-Hanhardt Syndrome). Patients with tyrosinemia type III (HPD deficiency) also have highly elevated blood tyrosine levels but do not manifest liver disease or renal tubular dysfunction. Tyrosinemia types II and III variably respond to tyrosine-restricted diet therapies, unlike the liver and renal disease of HT-1. FAA, which accumulates in FAH deficiency, is highly electrophilic and a potent alkylator, causing oxidative damage to the cells in which it is generated by reacting with glutathione and sulfhydryl groups of proteins. FAA appears to directly damage only the hepatocytes and renal proximal tubules in which it is produced and not adjacent cells.

Because of its rapid reactivity, FAA itself is not found in body fluids of patients with HT-1. SAA and SA, derived from reduction of FAA, are the principal diagnostic metabolites of FAA (Figure 1). When effective therapy (i.e., NTBC) to reduce these metabolites is provided to patients with HT-1, the clinical complications associated with FAH deficiency are either prevented (in presymptomatic cases) or ameliorated[7].
**Fig 1:** The abnormalities in the pathway of tyrosine metabolism in tyrosinemia type I.

**Fig 2:** Liver metabolism of phenylalanine and tyrosine. The figure shows the enzymes involved in the catabolism of phenylalanine (Phe) and tyrosine (Tyr) to fumarate and acetoacetate and the diseases associated with deficiencies in the enzymes[8].
Clinical and diagnostic features:

Birth incidence is 1/100,000 in most areas but is more common in some regions, notably in Québec, Canada. In Morocco, sporadic cases are reported in many studies. HT1 is clinically heterogeneous. Symptoms may start during the first few months (acute type), in second half of the first year (subacute type) or in the following years up to adulthood (chronic type). In the acute type, manifestations of hepatic failure predominate (bleeding diathesis, hypoglycemia, ascites etc) with frequent sepsis and rapid deterioration. Mild proximal tubular disease is usually present. Subacute type manifests a similar but less severe clinical picture presenting usually with hepatomegaly or hypophosphatemic rickets (due to tubular dysfunction). Intercurrent illness may precipitate hepatic crisis. Chronic type presents with hepatomegaly secondary to cirrhosis and often tubulopathy, leading to rickets and renal failure. Neurological crises are infrequent presenting symptoms; however, they can complicate any type of the disease when untreated. The crises resemble those of acute intermittent porphyria, manifesting with painful parasthesias (causing patients to assume ophisthotonic position, self-mutilation), autonomic signs (hypertension, tachycardia, ileus) and respiratory decompensation. All patients stand a high risk of developing hepatocellular carcinoma (HCC) secondary to cirrhosis.

The deficiency of fumarylacetoacetate hydrolase, FAH (15q23-q25) results in accumulation of fumaryl- and maleyl-acetoacetate that cause hepatorenal damage. The accumulation of their derivatives (succinyl-acetone (SA) and succinyl-acetoacetate (SAA)) leads to accumulation of delta-aminolevulinate (δ-ALA) resulting in inhibition of porphobilinogen synthesis and porphyria-like crises.

Liver synthetic functions are usually severely affected with coagulopathy and hypoalbuminemia. Elevated levels of SA in dried blood spots, plasma or urine are pathognomonic. Other abnormalities include elevated α-fetoprotein (especially in acutely ill infants), increased plasma levels of tyrosine, phenylalanine and methionine, increased urinary δ-ALA excretion and features of Fanconi tubulopathy. Confirmation of diagnosis is usually by mutation analysis. Differential metabolic diagnoses include classic galactosemia, hereditary fructose intolerance, and fructose 1,6 diphosphatase deficiency, Wilson's disease and some mitochondrial disorders.

Prenatal diagnosis is feasible by mutation analysis on chorionic villus sampling (CVS), if the familial causative mutations are known or alternatively by FAH assay on CVS or amniocytes and determination of SA levels in amniotic fluid. Newborn screening is available in many countries [9].

Clinical phenotypes of tyrosinemia:

Tyrosinemias Several neurocognitive difficulties, as inattentiveness, problems related to working memory and social cognition [4], learning difficulties [10], and lower IQ [11], have been described in treated HT1. Different mechanisms have been suggested to explain these problems, from sequelae from liver disease to toxic levels of Tyr. Van Vliet et al. found that high Tyr levels over the lifespan, especially the last year before testing, were related to internalizing behavior and health-related quality of life [12].

This is in line with a study showing correlations between inattentiveness and plasma levels of Tyr in treated patients with HT1 [13], with a stronger correlation (r = .780) between recent levels of Tyr and inattention than long time levels (r = .707). However, separate pathways for different cognitive outcomes may be present within the same disorder. For
instance, diagnosis of HT1 before eight months of age was related to a decline in IQ over time [14], while this was not found in children diagnosed later. It has therefore been speculated [13] if low IQ and symptoms of inattention in HT1 are affected by different pathways; one by the disorder itself (by affecting the vulnerable infant brain), the other by its treatment [13]. Van Ginkel et al. highlight that close monitoring of patients is important because of uncertain long-term effectiveness and new potential toxicities of the treatment, [13, 8].

**Correlation tyrosinemia et TDAH-like symptoms:**

In a study, they investigated the relationship between plasma tyrosine concentrations and cognitive functions and how tyrosine levels affected enzyme activities of human tyrosine hydroxylase (TH) and tryptophan hydroxylase 2 (TPH2). Eight Norwegian children between 6 and 18 years with HT1 were assessed using questionnaires measuring Attention Deficit Hyperactivity Disorder (ADHD)-symptoms and executive functioning. Recent and past levels of tyrosine were measured and the enzyme activities of TH and TPH2 were studied at conditions replicating normal and pathological tyrosine concentrations. They observed a significant positive correlation between mean tyrosine levels and inattention symptoms. While TH exhibited prominent substrate inhibition kinetics, TPH2 activity also decreased at elevated tyrosine levels. Inhibition of both enzymes may impair syntheses of dopamine, noradrenaline, and serotonin in brain tissue. Inattention in treated HT1 patients may be related to decreased production of these monoamines. These results support recommendations of strict guidelines on plasma tyrosine levels in HT-1. ADHD-related deficits, particularly inattention, should be monitored in HT1 patients to determine whether intervention is necessary [5].

A recent study which aimed to investigate this neuropsychological profile by comparing HT1 patients with healthy controls. Neurocognitive testing was performed in a heterogeneous group of 19 NTBC and dietary treated HT1 patients (five females, fourteen males; mean age 12.9 ± 4.8 years; range 7.9–23.6 years) and 19 age and gender matched controls (five females, fourteen males; mean age 13.2 ± 4.6 years; range 8.1–24.8 years). IQ scores were estimated and all participants performed the Amsterdam Neuropsychological Tasks, measuring executive functions (inhibition, cognitive flexibility and working memory) and social cognition (face recognition and identification of facial emotions). HT1 patients showed poorer estimated IQ, executive functioning (working memory and cognitive flexibility), and social cognition compared to healthy controls. Despite the heterogeneity of the patient group, these data clearly show that IQ, executive functioning and social cognition are affected in HT1 patients, and that IQ screening is not sufficient for cognitive monitoring of these patients [4].

**Case report:**

We report the case of an 8-year-old child, not attending school, from first-degree consanguineous parents (cousins), who is the 4th of his siblings made up of 4 boys, including a brother who died of tyrosinemia. He was brought to a child psychiatry consultation by his mother, who reported irritability, impulsivity, hyperactivity at home and at school, attention disorders and academic difficulties that led to his exclusion from school for his difficult behavior.

In addition, the child has been followed since the age of 3 months for a tyrosinemia type 1 revealed on a hemorrhagic syndrome (epistaxis), diarrhea and icteria. The child was hospitalized and an etiological evaluation was performed, including the determination of
delta aminolevulinic acid and chromatography of amino acids in the urine, which showed the presence of succinyl acetone. The evolution of the disease was marked by the occurrence of several complications, a vitamin resistant rachitis with multiple pathological fractures, a bone hyper trophy with deformation of the feet and a defective walk, a hepatic cirrhosis with increase of alpha fetoprotein and a splenomegaly.

On the developmental side, the mother reported a delay in psychomotor acquisitions, with language acquired at 4 years old, autonomous walking at 4 years old, daytime cleanliness at 3 years old with persistent enuresis until the age of 8 years.

At the end of the clinical interview, scales and questionnaires were used to detect ADHD symptoms, the SNAP IV - Swanson, Nolan and Pelham Teacher and Parent Rating Scale was used with the mother, the items concerning inattention (items 1 to 10) and Hyperactivity-Impulsivity (items 11 to 20) were revealing; The Conners Evaluation Questionnaire was delivered, confirming the same result, a neuropsychological evaluation of the child with IQ evaluation by WISC-IV - Wechsler Intelligence Scale for Children and Adolescents revealed limited intellectual performance with an IQ of 65.

For this child we have scheduled further speech therapy, psychomotor therapy and rehabilitation sessions. We started parenting sessions with the mother based on the BARKLEY Parenting Skills Training Program. We set up school reintegration measures to ensure the child's continued schooling. And we coordinated with his neuropediatrician in order to promote a combined multidisciplinary management, and to be able to monitor and stabilize the levels of tyrosinemia which could condition the psychopathological evolution of ADHD symptoms and weigh the benefit - risk concerning the decision to take specific medication (methylphenidate, amphetamines or others).

**Conclusion:**

NMDs, such as HT-1, constitute a large group of conditions that are often containable with early clinical intervention, but still present lifelong difficulties and high societal costs. many studies suggest that there may be similar biological mechanisms behind the cognitive difficulties seen in ADHD and HT-1. In clinical settings, the impaired dopamine synthesis due to substrate inhibition in treated HT-1 may be compensated for by standard ADHD medication, such as methylphenidate or amphetamine. Similarly, the reduced serotonin synthesis may be counteracted by tryptophan supplementation. In future studies, comparisons of HT-1 and TDAH in addition to other metabolic disorders influencing similar biological pathways, will hopefully provide more insights into possible shared pathophysiological mechanisms and how these affect their treatment.
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