Bipolar and Related Disorders Induced by Sodium 4-Phenylbutyrate in a Male Adolescent with Bile Salt Export Pump Deficiency Disease

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INTRODUCTION

PFIC are an heterogeneous group of autosomal recessive disorders of childhood that present with intrahepatic cholestasis, characterized by defects in biliary proteins, involved in the synthesis and transport of bile[1], leading to portal hypertension, liver failure and transplantation within the first ten years of life. Up to now three different type of PFIC have been identified: type 1, 2 and 3. PFIC2, also known as BSEP deficiency disease, involves ABCB11 gene, encoding the bile salt export pump (BSEP), a liver-specific adenosine triphosphate binding cassette transporter that mediates the excretion of bile monovalent salts.[2] Current treatments available are high-dose of ursodeoxycholic acid (25–30 mg/kg/die) in initial management, rifampicin for itching and fat-soluble vitamins (A, K, D, E) supplementation.[2] Some patients with PFIC2 may also benefit from biliary diversion, and endoscopic nasobiliary drainage, maintained for a few weeks, may help to select potential responders to biliary surgery.[2] If these medical and surgical therapies fail, liver transplantation remains the only alternative treatment.[2] 4-PB is an orphan drug (AMMONAPS; Swedish Orphan AB Inter, Stockholm, Sweden), routinely used to treat ornithine trans-carbamylase deficiency (OTC). In last years, reports in vitro and in vivo, emerged about the effective use of the 4-PB in PFIC, able to improve liver tests and itching by increasing the hepatocanalicular expression of BSEP and the biliary excretion capacity of bile salts.[6] Dosage was 500 mg per kilogram of body weight per day or total dose of 10 grams per day.[9,10] Results of clinical trials have shown that 4-PB has few side effects and it is safe for patients: grade 3 neuro-cortical toxicity, consisting of excessive somnolence and confusion, was sudden, dose-dependent, accompanied by metabolic changes (hyponatremia and hypocalcemia) and reversible after discontinuation of the drug.[4] Even when pilot studies were conducted in patients with cystic fibrosis or thalassemia, severe adverse events were not reported.[5,6] There are limited information on side effects of long-term administration of drug to patients with OTC deficiency. In this case, the most common adverse event was amenorrhea in 23% of post-pubertal females treated; other problems included anorexia and vomiting.[11] When 4-FB was used in patients with PFIC2, no severe...
side effects were observed during or after these studies. Finally, the leaflet of the drug reported only two common psychiatric adverse effects, depression and irritability. Considering OTC deficiency provides per se to the development of neurological symptoms such as lethargy and irritability, related to hyperammonemia, the adverse events are to be analysed in this clinical setting.

CASE

Mr. N., a Caucasian boy of 18 years, suffering from a genetically diagnosed late onset PFIC2, dyslexia and dyschromia, was listed for a liver transplant in January 2013 without evidence of psychiatric contraindications or mental disorders, detected during a specialist evaluation, performed as part of the examinations for inclusion in the waiting list.

From August 2014, he presented a recurrent jaundice with progressive increase in total bilirubin (until to 14.5 mg/dL) without liver failure. Ultrasounds and endoscopy excluded complications such as ascites, esophageal varices and portal vein thrombosis. An off-label treatment with 4-PB was started at the initial dose of 200 mg per kilogram of body weight per day, refracted in four times. Concomitant therapies were ursodeoxycholic acid (25 mg per kilogram of body weight per day), rifampin, taken for the itching (300 mg per day) and regular supplementation of fat-soluble vitamins (A, D, E, K). Systematically, after taking the drug, the patient complained dysphoria with uncontrolled irritability.

Laboratory tests didn’t show electrolyte or metabolic abnormalities and infections were excluded. These manifestations caused a significant negative impact on his quality of life and on interpersonal relationship. Furthermore the family referred that Mr N. appears very different and showed behaviors related to other-directed verbal aggressiveness, never occurred before taking the drug, repeated consistently after each 4-PB intake. In particular, the patient reported that after 30 minutes of the drug administration, he felt a sense of “nervous tension” that could not control nor to manage with coping activities. After these episodes, intense asthenia and fatigue were reported. Then, recurrent headache and nausea and, occasionally, feeling of retrosternal weight with features not suggestive of angina were also complained. After two weeks, the treatment was discontinued and a psychiatric consultation was requested. A comprehensive psychiatric evaluation was performed by administering the Toronto Alexitymia Scale (TAS-20) cut off scores for psychopathology >50), the State Trait Anger Expression Inventory (STAXI-II) (range of normality between 25° and 75° percentile), the Disability Scale and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). For an initial analysis, the psychodiagnostic exam provided few relevant elements. In fact we excluded the alexitymic disease for TAS score <50 and 5/8 subscale of the STAXI-II presented subthreshold scores (<25° percentile). After careful analysis of the STAXI-II, we note very much subthreshold scores but out of the range for the subscale concerning the control of anger (Ax/Con >75° percentile). These results reported a picture of a boy who may use excessively psychological defenses such as negation and repression that prevent uncomfortable or unacceptable feelings of anger. Mr. N. tended to invest a lot of energy controlling and preventing the experience and expression of the anger. He referred an ego-dystonic perception of the behaviors acted out. Even if not confirmed by SCID II scores, the hypothesis of a passive-aggressive personality disorder emerged clearly and the psychiatric symptoms completely regressed immediately after drug discontinuation. The interview revealed that the study activities was strongly influenced by the disease, however considering the diagnosis of dyslexia, instead the social and family life have not been affected by the health problem. Despite these psychological analyses, were not present evident symptoms of psychopathology, so the psychiatric evaluation excluded the presence of mental disorders in progress. The absence of disturbance in attention and awareness, an additional disturbance in cognition, finally, psychomotor behavioral disturbances ruled out alternative diagnosis of delirium. Instead, according with the DSM-5 criteria, the psychiatric manifestations occurred in this boy were suggestive of bipolar and related disorders induced by 4-PB; the clinical features are: A) a significant and persistent altered mood that dominates the clinical situation, characterized by irritable mood; B) the symptoms developed immediately after drug exposure and this drug can produce psychiatric symptoms; C) the distress is not explained by a bipolar disorder or related disorders not induced by drugs; D) the disturbance does not occur during a delirium; E) alteration causes clinically significant distress.

DISCUSSION

4-PB is a chaperone orphan drug that has been recently indicated for the treatment of BSEP deficiency disease because is able to improve the quality of life through the reduction of itching, the episodes of jaundice and the need for invasive treatment, including liver transplantation. Psychiatric side effects as depression and irritability have been reported but no cases of bipolar and related disorders have been described until now in patient with PFIC2. We do not know the influence of personality traits and psychological factors on the development of symptoms, but can hypothesize in this case the presence of a psychological predisposition to a dysfunctional functioning concerning the expression of anger. So it is possible
that this drug has also amplified a silent psychological tendency. Moreover, the drug obviously has effects other than just being a substrate for an alternate pathway of ammonia excretion and because it penetrates well into cerebrospinal fluid. Also, 4-FB was been studied in many diseases affecting the CNS such as spinal muscular atrophy, multiple sclerosis and cerebral ischemia where it seems to have helped, being able to slow cell apoptosis.

Early researches showed that bipolar disorder is accompanied by the activation of immune-inflammatory pathways as indicated by the increased levels of pro-inflammatory cytokines, positive acute-phase proteins, such as multiple changes in oxidative and nitrosative stress, tryptophan and tryptophan catabolites, neurotrophins, circadian dysregulation, hypothalamic pituitary adrenal, axis dysregulation activation markers.

The drug crosses the blood-brain barrier and influences the brain activity in different ways including tryptophan metabolism, but the exact mechanisms of the 4-FB related CNS adverse effects, have not yet been identified.

New studies should investigate aspects of neuropharmacology and possible relationships with the psychological aspects of subjects taking this drug. This is the first report documenting other psychiatric manifestations related to 4-FB administration, recurring regularly after re-taking the drug, and reinforce the need of a careful psychiatric evaluation before starting the treatment in patients with PFIC.

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