Reprinted from the German Journal of Psychiatry · http://www.gjpsy.uni-goettingen.de · ISSN 1433-1055

Case Report

Glutaric Acidemia Type II Associated with Bipolar Affective Disorder

Girish Babu Nanjundappa[1], Geetha Desai[2] and Chaturvedi Santosh Kumar [3]

[1]Senior Resident, Department of Psychiatry
[2]Associate Professor, Department of Psychiatry
[3]Professor, Department of Psychiatry
National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore 560029, India

Corresponding author: Dr. Girish Babu Nanjundappa, Senior Resident, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Hosur Road, Bangalore 560029, India; E-mail: girisha1980@gmail.com

Abstract

Inborn errors of metabolism represent rare but important causes of psychiatric disorders in adolescents or adults. Here we describe a young male presenting with symptoms of bipolar affective disorder with underlying metabolic disorder. During hospitalization he was noticed to have increased sensitivity to antipsychotics, lithium and had poor response to treatment. He was detected to have metabolic impairment in terms of fluctuating levels of serum bilirubin and ammonia. There was family history of early deaths in his siblings. He was investigated for underlying metabolic disorder and Tandem mass spectroscopy of the blood showed increased concentrations of short, medium and long-chain acylcarnitines suggestive of glutaric acidemia type-II (GAII). Although neurological complications have been reported, psychiatric manifestations have not been reported to be associated with GAII. Also the poor response of bipolar disorder to medication and increased sensitivity to side effects of psychotropic medication needs to be understood in the light of the underlying metabolic disorder (German J Psychiatry 2011; 14: 48-50).

Keywords: Glutaric acidemia type II, bipolar affective disorder, inherited metabolic disorders

Received: 14.11.10
Revised version: 28.12.10
Published: 1.7.2011

Introduction

Glutaric acidemia type II (GAII) or multiple acyl-CoA dehydrogenase deficiency is a autosomal recessive disorder of fatty acid and amino acid metabolism (Przyrembel 1976). The heterogeneous clinical features of patients with GAII fall into three subclasses: a neonatal-onset form which is usually fatal and characterized by severe non-ketotic hypoglycaemia, metabolic acidosis, excretion of large amounts of fatty acid- and amino acid- derived metabolites with congenital anomalies (type I); a neonatal-onset form without congenital anomalies (type II); and a late-onset form (type III), which has a variable presentation.

Psychiatric manifestations of inherited metabolic disorders in adulthood, though not uncommon, are identified less often (Sedel 2007). Literature is sparse regarding the manifestations of classic psychiatric disorders and presence of inherited metabolic disorders apart from porphyrias. We report a case of glutaric acidemia type II with bipolar affective disorder and its clinical relevance.

Case Report

Mr. A, a 25-year-old male born of a second-degree consanguineous marriage, presented to our out-patient department with a 5 years history of episodic illness, each episode characterized by pervasive irritability, decreased need for sleep,

increased psychomotor activity, delusion of persecution and delusion of grandiosity. The initial three episodes lasted for 4 to 6 weeks and resolved spontaneously. His mother had a history of five stillbirths before the birth of the index subject. He has a sister who is clinically unaffected. There was a family history of an episodic illness in his paternal uncle, suggestive of bipolar affective disorder. The patient had a history of hepatitis 8 years back, further details of which were not available, but which had resolved spontaneously. He was diagnosed as bipolar affective disorder, the current episode being mania with psychotic symptoms, and was admitted for inpatient care.

As the patient was significantly agitated, parenteral haloperidol (10 mg) was administered, with which he developed acute dystonia. His renal function tests, serum electrolytes and thyroid function tests were within normal limits and he was started on lithium 900 mg/day. After five days, the patient developed significant coarse tremors of bilateral upper limbs. His serum lithium was found to be high (1.9 meq/litre) on two occasions. Lithium was stopped and he was started on olanzapine (20 mg/day). During the course of hospitalization, the patient developed fluctuating hyperbilirubinemia (2.5 to 5 mg/dl) in the absence of fever, which resolved spontaneously over a period of three weeks. Physical examination and investigations (liver enzymes, HBsAG) were within normal limits. After four weeks, the patient developed worsening of agitation with confusion and was found to have fluctuating hyperammonemia on a number of occasions. In view of the above clinical presentation and the family history of early sibling deaths, he was investigated for inherited metabolic disorders. Investigations for Wilson's disease, urine for abnormal metabolites (reducing substances, mucopolysaccharides and amino acids), serum lactate, and blood pH were within normal limits. Computed tomography of the brain and ultrasound of the abdomen were planned, but the patient was uncooperative. Tandem mass spectroscopy of the blood showed increased concentrations of short, medium and long-chain acylcarnitines, which is consistent with the presence of glutaric acidemia type-II (GAII) (Table 1). A diagnosis of late-onset GAII with bipolar affective disorder was made.

Table 1. Blood Acylcarnitine Results

	Blood Acylcarnitine Concentrations (mmol/L)	
	Reference Range	Index patient
Acetylcarnitine (C2)	2.0–29.20	25.6
Proprioylcarnitine (C3)	2.0–2.6	2.7*
Malonylcarnitine(C3DC)	0.04–0.06	0.26*
Butyrlycarnitine (C4)	0.58–0.72	0.35
3-OH Butyrlycarnitine (C4-OH)	0.11–0.16	0.18*
Isovaerylcarnitine (C5)	0.21–0.26	0.41*
Glutarylcarnitine (DC5)	0.04–0.07	0.13*
Hexanoylcarnitine (C6)	0.16–0.21	0.08
Octanoylcarnitine (C8)	0.07–0.11	0.1
Decenoylcarnitine (C10)	0.08–0.15	0.34*
Dodecanoylcarnitine (C12)	0.07–0.11	0.07
Dodecanoylcarnitine (C12:1)	<0.24	0.37*
Tetradecanoylcarnitine (C14)	0.15–0.21	0.24*
Hexadecanoylcarnitine (C16)	1.26–1.84	2.67*
Stearoyicarnitine (C18)	<0.30	0.71*

*Greater or equal to upper limit of reference range.

The patient was given electroconvulsive therapy (ECT) in addition to olanzapine to which patient had responded partially. He was commenced on riboflavin and a low fat, low protein, high carbohydrate content diet. L-carnitine was not initiated, as it was not afforded by the family.

Discussion

The above case had clinical manifestations of bipolar affective disorder with underlying impairment in metabolism of fatty and amino acid. Glutaric acidemia type-II (GAII) or multiple acyl-CoA dehydrogenase deficiency (MADD), an autosomal recessive inherited metabolic disorder, is the functional term for a group of metabolic diseases characterized by defects in the oxidation of acyl-CoA esters in the fatty acids, branched chain amino acids, lysine, 5-hydroxylysine and tryptophan and excretion of metabolites derived from accumulated acyl-CoA esters (Gregersen 1989). Late onset of illness is characterized by intermittent episodes of vomiting, hypoglycemia and acidosis, hyperammonemia, hepatomegaly, proximal myopathy, and few patients have a progressive extrapyramidal movement disorder (Frerman 2001; Gregersen 2001). In several patients with glutaric acidemia type-II, the brain has shown focal dysplasia of the gyri of the frontal, parietal and temporal lobes and microscopic evidence of abnormal neuronal migration (Bohm 1982). Unfortunately, it was not possible to get the neuroimaging of the brain of our patient. The diagnosis of GAII was made from urinary organic acid profiles, which showed corresponding abnormalities of oxidation of fatty acids and amino acids. In some patients, abnormal urinary organic acids excretion is only evident during periods of illness or catabolic stress. Acylcarnitines can be measured from blood spot samples and typically show increased concentrations of various saturated short-, medium-, and long-chain acylcarnitines (Frerman 2001), as noted in this patient (Table 1).

The above case had clinical manifestations of bipolar affective disorder with underlying impairment in metabolism of fatty and amino acid. As GAII has been reported with abnormal neuronal migration, interestingly bipolar disorder has also been reported to be associated with neurodevelopmental anomalies (Relan 2002). As the gene linked for bipolar disorder has been found to be associated on chromosome region 4q35 (Adams 1998), the possibility of shared genetic mechanisms cannot be ruled out. Hence underlying metabolic disorder may have pathoplastic effects on the presentation of mood disorder, but further similar reports could throw more light on this. In the above case, important clinical implications were that of increased sensitivity to lithium and antipsychotic medications, with poor response to medications. The patient responded partially to electroconvulsive therapy and olanzapine, and had minimal complications with

this combination. The patient had less severe metabolic disease; hence urine for abnormal metabolites was negative and perhaps accounts for the fact that he survived till adulthood unlike his younger siblings. To the best of our knowledge, this is the first report of GAII co-occurring with bipolar affective disorder, though cases of progressive neurological illness have been reported. Thus, the clinical presentation and poor response to treatment in the above case could be understood in the light of the underlying metabolic disorder.

References

Adams LJ, Mitchell PB, Fielder SL, et al., A susceptibility locus for bipolar affective disorder on chromosome 4q35. Am J Hum Genet, 1998. 62(5): 1084-91.

Bohm N, Kiebling M, Lehnert W, et al., Multiple Acyl-CoA dehydrogenase deficiency (glutaric acidemia type-II), congenital polycystic kidneys, and symmetric warty degeneration of cerebral cortex in two newborn brothers: II. Morphology and pathogenesis. Eur J Pediatr, 1982. 139: 60-65.

Frerman FE & Goodman SI. Defects of electron transfer flavoprotein and electron transfer flavoprotein–ubiquinone oxidoreductase: glutaric aciduria type II. In: Scriver CR, Beaudet AL, Sly WS, et al., The metabolic and molecular basis of inherited disease, New York: McGraw-Hill. 2001, 2357-65.

Gregersen N. Riboflavin-responsive defects of beta-oxidation. J Inherit Metab Dis, 1985. 8 Suppl 1: 65-9.

Gregersen N, Andresen BS, Corydon MJ, et al., Mutation analysis in mitochondrial fatty acid oxidation defects: Exemplified by acyl-CoA dehydrogenase deficiencies, with special focus on genotype-phenotype relationship. Hum Mutat, 2001. 18(3): 169-89.

Przyrembel H, Wendel U, Becker K, et al., Glutaric aciduria type II: report on a previously undescribed metabolic disorder. Clin Chim Acta, 1976. 66(2): 227-39.

Relan P, Chaturvedi SK & Shetty B. Schizencephaly associated with bipolar affective disorder. Neurol India, 2002. 50(2): 194-7.

Sedel F, Baumann N, Cohen D, et al., Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J Inherit Metab Dis, 2007. 30(5): 631-41.

The German Journal of Psychiatry · ISSN 1433-1055 · http:/www. gjpsy.uni-goettingen.de
Dept. of Psychiatry, The University of Göttingen, von-Siebold-Str. 5, D-37075 Germany; tel. ++49-551-396607; fax: ++49-551-398952; E-mail: gjpsy@gwdg.de