

ADULT ONSET CITRULLINEMIA TYPE 2 PRESENTING AS A CASE OF SCHIZOAFFECTIVE DISORDER. CASE REPORT FROM OMAN

Mohammed Al Alawi*, Mundher Al Maqbali, Suha Al Gailani, Hamed Al Sinawi

*Psychiatry Residency Program, Oman medical Specialty Board , Muscat, Oman

Psychiatry Residency Program, Oman medical Specialty Board , Muscat, Oman

Radiology Residency Program, Oman medical Specialty Board, Muscat, Oman

Department of Behavioural Medicine, Sultan Qaboos University, Muscat, Oman

Abstract

Adult onset citrullinemia type II is an autosomal recessive disorder of amino acid metabolism caused by a deficiency of liver specific arginino-succinate-synthetase-activity¹. Cases reported in the literature are few and most of them were from Japan. The adult onset variant is known to present with neuropsychiatric manifestations. The authors report a case of a 30 year old Omani woman who presented with unusual episodic symptoms that mimicked schizoaffective disorder. The patient was admitted under psychiatry initially. Routine investigations were sent along with Electroencephalography which showed continuous epileptiform discharges. Neurology and genetic disorders teams were consulted . After through investigations, the case was diagnosed as adult onset citrullinemia type II.. Such cases necessitates a low threshold for ruling out organic causes in patients presenting with psychiatric symptoms .

Keywords: Adult onset citrullinemia type II, neuropsychiatric manifestations, schizoaffective disorder, Oman.

Introduction

Citrullinemia is a rare autosomal recessive metabolic disorder that results from a deficiency of arginino succinate synthetase (ASS). ASS is one of the five urea cycle enzymes located essentially in the liver. Patients present with increased concentrations of citrulline and ammonia in the plasma². Citrullinemias are classified into three types: neonatal (type I), infantile (type III) and adult (type II). The neonatal and infantile forms , known as the classic types of citrullinemia are caused by mutations of the ASS gene. Whereas citrullinaemia type II(CTLN2) is caused by mutation in the “citrin gene” (SLC25A13)³. Patients with CTLN2 display various neuropsychiatric manifestations that can mimic hepatic encephalopathy⁴. In the past, patients usually followed rapidly deteriorating clinical courses . The condition mainly affects the brain, causing symptoms of delirium, hallucinations, memory changes, episode of restlessness, abnormal behaviors such as aggression, irritability, and hyperactivity. Subsequently it leads to seizures, coma and death if intervention was not instituted at early stages⁶. More recently, prognosis improved with liver transplantation³.

Literature search revealed less than 200 cases reported from 1980 to 2006 with males predominantly affected by this disease. The mean age of onset was 34.4 years, with a wide range from 11 to 72 years. Citrullinemia is found primarily in the Japanese population, where the estimate is 1 in 100,000 to 230,000 individuals⁵. CTLN was also reported in people from East Asia and the Middle East.⁵ The present case, to our knowledge, is the first to be reported from Arab/Islamic population of the Arabian Gulf.

Case report

A 30 years old housewife was referred to our behavioural medicine clinic with 5 years history of episodes of being mute, socially withdrawn and poor self-care. These episodes were usually preceded by neck pain, lasting for 2 to 3 days followed by gradual return to her premorbid self with no recall of the episodes . Her family observed her to have mood swings , disturbed sleep, poor appetite, laughing inappropriately and becoming increasingly forgetful during the episodes. She described hearing voices of children crying and calling her although nobody was around. The voices were not commanding or commenting on her behaviour. She denied having abnormal visual experiences. She was seen at the local psychiatry clinic , diagnosed as a case of schizoaffective disorder and treated

with Risperidone 4mg at night , Fluoxetine 20 mg per day and procyclidine 5 mg three times daily . Her symptoms persisted despite good compliance with medication.

She had uneventful prenatal and developmental history. There was no family history of mental illness. Physical examination was unremarkable. Her speech was reduced to short answers, but was coherent with a low tone. She appeared sad with flat affect and described hearing voices of crying children. The following day she was noted to be mute and responds only to painful stimuli by opening her eyes and moving her limbs.

The Electroencephalography showed continuous generalized epileptiform discharges characterized by 3-22 sharp waves per minutes with parasagittal frontal focus suggestive of non-convulsive status epilepticus.

She was given Diazepam 10 mg IV stat dose, following which she opened her eyes spontaneously and was able to talk coherently. A repeat EEG showed disappearance of the epileptiform discharges. A provisional diagnosis of Autoimmune encephalitis with non-convulsive status epilepticus was made. Blood investigations including Paraneoplastic screen including anti NMDA R antibody, anti LGIa, anti CASPR2, anti GABA B R, anti AMPAR, anti Glycine R, anti amphiphysin, anti Hu, Ma, Ta, Ri, Yo, CV 2. Syphilis serology and PCR for HIV were requested .

Moreover ,TFT, anti TG antibody, Autoimmune thyroid, anti GAB 65, Ceruloplasmin, porphyria work up, Vasculitis panel including ESR, ANA, ANCA, APLA were sent.

She was started on a loading dose of IV Sodium valproate 1200 mg in 100 ml of normal saline followed by 400 mg of Sodium Valproate given three times daily IV and Injection of Acyclovir 750 mg three times daily with good hydration for suspected viral aetiology . Repeated EEG showed recurrence of the epileptiform discharges which persisted despite being of antiepileptic medications. . Levetiracetam 1000mg per day , clobazam 5mg two times daily , phenytoin 200 mg three times daily , Diazepam 10mg as single dose and lorazepam 1 mg three times daily were added . Her level of consciousness deteriorated and Oxygen saturation and blood pressure dropped .She started to spike a high grade fever. Her Prolactin level was 1900 (normal: 2 to 29 ng/mL) and Ammonia level was 1000 (normal range 15 – 45 mcg/dL). Genetic consultation was sought. The abnormal amino acids levels in the plasma and Urine along with confirmatory gene mutation pointed towards the diagnosis of Adult onset citrullinemia type two . Brain Magnetic resonance imaging and lumbar puncture were normal. Ammonia scavengers were started and dialysis was attempted but failed to reduce her ammonia levels. CT Brain showed marked cerebral oedema. She developed multi organ failures which subsequently led to her death.

Discussion

This is the first case of adult onset citrullinemia reported in the Arabian Gulf population. The patient was diagnosed initially with schizoaffective disorder and treated with antipsychotic and antidepressants for five years with no improvement . However, following protracted investigation the case was duly diagnosed with Adult onset Citrullinemia type 2. The delay in diagnosis is not uncommon due to the rarity of the disorder and unspecificity of the symptoms⁷.

According to the literature, the most common clinical manifestation is recurrent encephalopathy with hyperammonemia that could be fatal⁸. Moreover, patients with CTLN2 may present with various neurobehavioral impairment e.g disorientation, delirium, aberrant behavior, convulsions and disturbance of consciousness^{9,10}. Studying the literature revealed several case reports mostly of Asian-Pacific such as Japan where patients exhibited non-specific symptoms before the diagnosis of adult onset citrullinemia could be entertained^{8,10,11,12}. Recently , a 40 years old lady from Japan who has been treated for schizophrenia for 18 years with no improvement till she was diagnosed with CLNT2 after thorough investigation including gene studies¹³ .

In our patient , the episodic nature of the patient's symptoms and altered consciousness level were the main indications for an extensive organic work up. However, metabolic investigations were not included due to the patient's age and absence of pathognomonic signs of common metabolic disorders. Therefore, temporal lobe

epilepsy was suspected and urgent EEG was advised which showed non-convulsive status epilepticus. This prompted the investigation for epilepsy.

Seizures are reported in less than 10 % of patients with adult-onset citrullinemia comprising less than 10%¹³. Despite all efforts to abort the epileptiform discharges, the patient's condition continued to deteriorate. Ammonia levels were high which necessitated a comprehensive metabolic work up and the diagnosis of citrullinemia was made. Hyperammonemia is the hallmark for most of the urea cycle disorders including citrullinemia⁷. Most patients with urea cycle disorder present with elevated ammonia plasma levels in the absence or mild liver enzyme derangement and ketoacidosis¹⁴. Hyperammonemia crisis is often triggered by catabolic events like protein load or certain drugs including sodium valproate. However, in the present case the trigger for hyperammonemia crisis was not clear. Poor response to treatment may be related to the presence of poor prognostic signs such as coma of more than 3 days duration, elevated intracranial pressure and ammonia peaked at > 1000 umol/L⁷. In the reported cases, radiological findings on T2 and diffusion weighted MRI sequences signifying hyper ammonic state are symmetrical hyperintensity in the insular cortex and cingulate gyrus. High levels of glutamine and glutamate and decreased levels of choline and myo-inositol can be seen in MRI spectroscopy.^{15,16}

Conclusion

This case highlights the importance of performing a comprehensive physical assessment in patients who do not respond to conventional intervention. Poor response to psychotropic medications and the presence of features indicating organic causes should alert the treating clinician to request extensive investigations including work up for metabolic disorders. A collaborative work between the treating psychiatrist and the medical team is essential for early detection and effective treatment of such cases.

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