Unusual presentation of acute psychosis in a child

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ABSTRACT

Background: Psychosis is often solely described as a psychiatric presentation; however, it is vital that organic causes are eliminated, especially in children.

Case presentation: We report the case of a 14-year-old girl who presented a 2-month history of self-neglect, poor school performance, and a week history of mutism. At initial presentation, her neurological examination was normal except for expressive aphasia, and occasional inappropriate laughing. First-line investigations showed low vitamin B12 and folate and normal magnetic resonance imaging. She was planned for follow up with psychiatrists.

She presented about a week later with worsening symptoms. She had further investigations which revealed high homocysteine, in keeping with homocysteine remethylation disorder. She was started on betaine therapy after which she had a significant improvement in her symptoms.

Conclusion: This case emphasizes the importance of thorough investigations of children with acute psychosis before making an assumption of a psychiatric cause, as reversible causes have better outcomes.

Keywords: Delusion, hallucinations, psychosis, case report.

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Background

Psychotic disorders are known to affect all age groups including children. It was more commonly seen in adults but has also been increasingly reported in children from 3 years and above. The prevalence has been found to be significantly higher in adolescents after the age of 14 up to the early 20s [1]. During the prepubertal years, it is commoner in males while it has equal sex predilection in adolescence [1]. In the UK, In 2012, Kelleher et al, [2] conducted a systematic review of all published literature on psychotic disorders in children and found a prevalence of 17% among children aged 9-12 years and 7.5% among 13-17 years [2].

Before arriving at a diagnosis of Schizophrenia in young children, it is important to perform a full list of investigations to rule out organic causes of psychosis in these children. These investigations include screening for infections, autoimmune disorders, tumors, toxins, drugs, and metabolic disorders [3]. Homocysteine remethylation disorders have been shown to have a causal effect on neuropsychiatric and neurodegenerative problems [4]. Some publications have emphasized the importance of considering homocysteine disorders in patients with psychiatric symptoms [5,6,7].

This case report identifies the need to consider homocysteine remethylation disorders in cases of psychosis in children.

Case Presentation

A 14-year-old young girl presents with a 2-month history of becoming more withdrawn, quiet, and poor school performance. She was accompanied by her mother who was concerned about self-neglect, poor cognition, and a week history of mutism.

On initial examination, she was noted to have occasional unexplained smiling and laughing and lack of speech, other systemic and neurological examination was normal. A prompt referral to the child psychiatry team was made while further investigations and brain magnetic resonance imaging were carried out which were all normal.

A preliminary diagnosis of the first episode of psychosis was made after a psychiatrist assessment. She was discharged with a plan for follow up by the psychiatrists.

She re-attended a week later with a deterioration of symptoms and refusal to eat. She was subsequently admitted to the pediatrics unit for further investigations. On the sixth day of admission, she developed tremors of the right hand after being started on aripiprazole based on the diagnosis of psychosis. She also developed difficulty with walking and required support for mobilization.

Investigations

On the first presentation, the initial investigations were within normal limits except for a low vitamin B12 and folate. A brain magnetic resonance imaging (MRI) also showed no abnormalities. During the second admission, another set of investigations was performed. The key tests aiding diagnosis were plasma amino acids and total homocysteine levels. Electroencephalogram showed severely abnormal brain activity, which was consistent with severe encephalopathy, but no finding consistent with Landau-Kleffner syndrome. This prompted the need for further investigations as electoencephalogram (EEG) does not show encephalopathy in acute psychosis.

Differential Diagnosis

Differential diagnoses that were considered include:
Landau-Kleffner syndrome – this was ruled out by EEG
Drugs and toxins – there was no history suggestive of drug abuse
Intracranial pathologies – ruled out by MRI
Schizophrenia

Treatment

Intramuscular vitamin B12 injections and oral folate supplements were started early on the first admission. Following a diagnosis of Homocysteine Remethylation disorder, oral betaine was commenced at 3 g twice daily, initially via nasogastric tube, as she was not accepting feeds and medications orally. Following betaine therapy, she made a significant improvement, the nasogastric tube was discontinued, and the medication was changed to oral. She was also able to communicate appropriately before discharge. However, she was still unable to weight bear or walk and required physiotherapy input to aid her physical function.

Outcome and Follow-Up

A diagnosis of Homocysteine Remethylation disorder was confirmed following input from the pediatric metabolic team. A general pediatric follow up was arranged for 3 months post-discharge alongside a follow up with the metabolic team. An outpatient follow-up with a physiotherapist and speech therapist was also organized to help her get back to baseline as the betaine treatment improved her basic function.

She made a remarkable improvement in her cognitive function and is doing well in school; however, she still required a walking frame for mobility at the time of writing the case report

Discussion

The term "psychosis" as defined by NICE guidelines includes symptoms associated with significant alternations to a person's perception, thoughts, mood, and behavior. Its presentation ranges from positive symptoms such as delusions, hallucinations, disorganized speech, and behavior/thoughts, and negative symptoms include self-neglect, loss of motivation, reduced speech, emotional blunting, and social withdrawal [1].

Several conditions have been identified as causes of acute psychosis in children. These range from infections, [8] toxins and drugs, autoimmune disorders, [9] metabolic conditions, epilepsy, systemic diseases, and psychiatric disorders [3]. It has also been described following administration of medications such as levetiracetam in patients with epilepsy, [10] and steroids [11]. Metabolic disorders that have been linked to psychosis in children include urea cycle defects, electrolyte imbalance such as hyponatremia, hypoglycemia, Wilson disease, and acute intermittent porphyria. Recent case reports have focused on immune-mediated diseases such as antibodies to N-Methyl-D-Aspartate receptor, Leucine-rich glioma-inactivated 1 (LGI1), Contactin-associated protein-like 2 (CASPR 2), glutamic acid decarboxylase (GAD), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and Gamma-aminobutyric acid B (GABAB) presenting as new-onset psychosis in children [12].

We describe the case of a 14-year-old who presented with acute psychosis secondary to homocysteine remethylation disorder. Remethylation disorders are rare inherited metabolic disorders that occur as a result of impairment of remethylation of homocysteine into methionine. Remethylation is catalyzed by methionine synthase leading to the conversion of homocysteine to methionine. The process of homocysteine metabolism involves transmethylation, methylation, and transulfuration. The most common problems are with the gene encoding the methyl tetrahydrofolate reductase (MTHFR). This results in the accumulation of homocysteine. Also, vitamin B12 is involved in the maintenance of proper function of the MTHFR enzyme while folate is responsible for the provision of the methyl part of the reaction, Hence, folate and vitamin B12 are also involved in the reaction and should be measured while investigating these patients. A few hypotheses have been postulated for the pathophysiology of remethylation disorders. These include accumulation of homocysteine leading to toxicity (hyperhomocysteinemia), folate trapping, oxidative stress, impaired methylation capacity, and impaired nonenzymatic protein functions [5].

Recent publications have proposed that neuropsychiatric disturbances are considered as clinical features of remethylation disorder [5,13,14]. A 15-minute

Table 1. *Summary of investigations with abnormal results in bold.*

Test	Result	Reference range
Full blood count	Normal	-
Urea and electrolytes	Normal	-
Liver profile	Normal	-
Bone profile	Normal	-
B12	88 umol/l	150 - 620
Folate	1.9 umol/l	3.1 - 19.9
Cerebrospinal fluid	Normal	-
Autoimmune screen	Normal	-
Plasma ammonia	21 umol/l	11 - 48
Urine Toxicology	Normal	-
CMV & Toxoplasmosis antibody	Negative	-
Treponema antibodies	Not detected	-
Free carinitine	22.8 umol/l	20 - 40
Very long chain fatty acids	Normal	-
Fixed NMDA receptor antibody	Negative	-
Anti VGKC antibody	<1 pmol/l	0 - 69
MRI	Normal	-
Plasma amino acids		
Taurine	41 umol/l	40 - 160
Aspartic acid	7 umol/l	5 - 30
Threonine	113 umol/l	70 - 190
Serine	128 umol/l	85 - 180
Asparagine	50 umol/l	40 - 130
Glutamic acid	79 umol/l	35 - 190
Glutamine	534 umol/l	390 - 740
Glycine	197 umol/l	160 - 400
Alanine	220 umol/l	190 - 530
Citrulline	15 umol/l	10 - 40
A-Amino N-butyric acid	25 umol/l	10 - 30
Valine	160 umol/l	130 - 300
Cystine	5 umol/l	15 - 50
Methionine	7 umol/l	15 - 40
Isoleucine	52 umol/l	30 - 95
Leucine	114 umol/l	65 - 170
Tyrosine	64 umol/l	40 - 100
Phenylalanine	66 umol/l	40 - 85
Free homocysteine	3 umol/l	-
Total homocysteine	>400 umol/l	5-15
Ornithine	51 umol/l	40 - 150
Lysine	162 umol/l	100 - 260
Histidine	69 umol/l	50 - 100
Tryptophan	29 umol/l	15 - 70
Arginine	86 umol/l	20 - 100
CSF amino acids	Normal	
Genetic studies	MTHFR (methyl tetrahydrofolate reductase) c.584C>T p(Ala195Val) homozygous variant	

consultation published in 2018, on the approach to a child presenting in the emergency department with acute psychosis identifies metabolic disorders as a possible cause of psychosis; however, there was no mention of homocysteine disorder as a possible cause under the metabolic disorders [3]. Another recent publication by Huemer et al, [5] suggested that plasma homocysteine levels should be checked in patients presenting with neurological, visual, hematological, and spinal cord degeneration disorders.

Even though our patient did not present with the schizophrenic type of psychosis, she had self-neglect, mutism, unexplained smiling and laughing. At the initial presentation, the first set of investigations were normal, hence she was discharged to be followed up by the Psychiatrist. It was during her second admission that further investigations were requested after a discussion with the Neurologists and the metabolic team. As listed above, our patient had all the investigations and was noted to have low vitamin B12, this prompted the need for further investigations as vitamin B12 is important in the metabolism of homocysteine. Although, she did not have enzyme studies, she had a genetic confirmation of the MTHFR c.584C>T p(Ala195Val) homozygous variant, alongside her twin sister, who had no symptoms at the time of testing**,** Also, clinical improvement was noted after commencement of betaine confirming the underlying diagnosis of remethylation defects. This was also noted in a previous case report where a child with MTHFR deficiency had a significant improvement in psychosis following regular betaine treatment [15].

Conclusion

This case report highlights the importance of thorough investigation in a child with acute psychosis.

Homocysteine remethylation disorders should be considered in patients with acute psychosis.

A multidisciplinary approach involving general pediatricians, neurologists, and psychiatrists is prudent in the management of patients with acute psychosis.

Betaine is a highly effective medication in the management of Homocysteine remethylation disorder.

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What is new?

There have been a number of causes identified as causes of acute psychosis in children, however, only a few have mentioned homocysteine remethylation disorder. This case report emphasizes the need to ensure all possible medical causes are considered in a child with Acute Psychosis.

Summary of tables

Table 1 shows a summary of investigations. The patient had low vitamin B12 and folate with high methionine levels. She also had a homozygous variant of methyl tetrahydrofolate reductase deficiency which is consistent with homocysteine remethylation disorder.

List of Abbreviations

EEG	Electoencephalogram
MRI	Magnetic resonance imaging
MTHFR	Methyl tetrahydrofolate reductase

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this case report.

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Consent for publication

Written parental consent was obtained.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 14 year old
2	**Final diagnosis**	Homocysteine remethylation disorder
3	**Symptoms**	Self-neglect, mutism, poor school performance, unexplained laughing
4	**Medications**	Betaine
5	**Clinical procedure**	Betaine therapy
6	**Specialty**	Pediatrics