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Research paper

MTHFR 677TT: Clinical Relevance and Diagnostic Limitations: A Case Report

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Abstract

Introduction: The c.677C>T mutation of the MTHFR gene, in the homozygous state (677TT), leads to reduced activity of methylenetetrahydrofolate reductase, a key enzyme in folate metabolism and methylation reactions. Its clinical expression is heterogeneous and may manifest as atypical psychiatric presentations, even in the absence of hyperhomocysteinemia, thereby limiting the diagnostic value of standard biological markers.
Methods: We report the case of a female patient presenting with atypical psychotic symptoms partially resistant to conventional treatment. The biological workup was complemented by genetic analysis, including genotyping of the MTHFR gene.
Results: Genotyping revealed a homozygous MTHFR c.677C>T mutation. Targeted metabolic management was initiated, based on supplementation with active folates (5-methyltetrahydrofolate) combined with vitamins B12 and B6, with biological monitoring. A gradual clinical improvement was observed, allowing a reduction in antidepressant treatment.
Discussion/Conclusion: This case illustrates the value of MTHFR genotyping in identifying an underlying metabolic vulnerability in patients presenting with atypical or treatment-resistant clinical features. The clinical relevance of the 677TT genotype lies in an integrative and personalized approach, while its diagnostic limitations require cautious and contextualized interpretation of genetic findings.

Keywords: *MTHFR 677TT; Folate Metabolism; Homocysteine; Atypical Psychiatric Disorders; Personalized Medicine; Clinical Genetics.*

1. Introduction

Atypical neuropsychiatric disorders in young adults represent a major diagnostic challenge, particularly when they follow a fluctuating course and show resistance to standard psychotropic treatments. Certain metabolic or genetic abnormalities, especially those involving folate and homocysteine metabolism, may mimic primary psychiatric conditions, leading to prolonged diagnostic delay. In this context, adopting a comprehensive etiological approach is essential to identify potential underlying biological causes. We report the case of a patient presenting with progressive pseudo-psychiatric symptomatology, in whom further investigations revealed both biological and genetic abnormalities. This case highlights the diagnostic complexity of such presentations and underscores the potential role of folate metabolism disorders in these clinical settings.

2. Clinical observation

A 31-year-old woman presented with neuropsychiatric symptoms evolving over approximately one year, in a context of chronic diffuse headaches associated with persistent anxiety. Her past medical history included a treated goiter, currently well-controlled under replacement therapy. Family history could not be assessed due to her status as an adopted child, with no available information regarding her biological family's medical background. The patient exhibited atypical depressive episodes, intermittent and of variable intensity, associated with marked mood lability. This was characterized by rapid alternation between anxiety, sadness, and irritability, as well as unexplained panic attacks. These attacks were characterized by a sudden onset of intense fear, accompanied by psychomotor agitation, palpitations, a sensation of loss of control, and severe anxiety, without any identifiable triggering factor. This symptomatology occurred in a context of emotional hypersensitivity, with disproportionate reactions to environmental stimuli and significant variability in symptom intensity, as reported by relatives. The clinical course was marked by the progressive development of these polymorphic symptoms, which initially led to psychiatric referral. At first, the patient was considered to have a psychosomatic or pseudo-psychiatric disorder, given the absence of clear neurological findings and the fluctuating nature of the clinical manifestations. Successive antidepressant treatments resulted in only partial and incomplete responses, without sustained improvement. This thereby reinforced the initial hypothesis of an atypical psychiatric disorder. Neurological examination revealed mild flattening of the right nasolabial fold, associated with a subtle drooping of the right labial commissure, suggestive of a possible residual central facial deficit. Deep tendon reflexes were brisk and symmetrical in all

four limbs, with no objective abnormalities of the long tracts. In addition, the patient was overweight, with a body mass index of 29 kg/m², while the general physical examination was otherwise unremarkable. Given the presence of subtle neurological signs in a young patient, the hypothesis of a mild and possibly previously unrecognized cerebrovascular etiology was initially considered. This justified the performance of an extensive etiological workup.

3. Results

The biological workup included an investigation for thrombophilia, comprising antithrombin level assessment and testing for antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies), all of which were normal. An autoimmune panel was also unremarkable. Cerebrospinal fluid analysis showed normal cytochemical findings and a normal profile, with no oligoclonal bands detected. Serum vitamin B12 levels were within the normal range, whereas plasma homocysteine was decreased at 5.49 µmol/L (reference range: 6-15 µmol/L). Similarly, serum vitamin B9 (folate) levels were reduced, measured at 3.24 ng/mL (normal range: 4.20-19.02 ng/mL). In this context of folate metabolism abnormalities, further investigations included genetic testing. This revealed the presence of the MTHFR c.677C>T mutation in the homozygous state. Brain magnetic resonance imaging revealed two small, non-specific punctate demyelinating lesions, appearing as T2-FLAIR hyperintensities, without diffusion restriction or contrast enhancement (Figure 1). Finally, the cardiovascular evaluation was strictly normal, with no evidence supporting an emboligenic cardiac source. The patient was started on supplementation with active folates, combined with vitamins B12 and B6, with regular biological monitoring of folate, vitamin B12, and homocysteine levels. The clinical course was marked by a progressive improvement, allowing a reduction in antidepressant treatment.

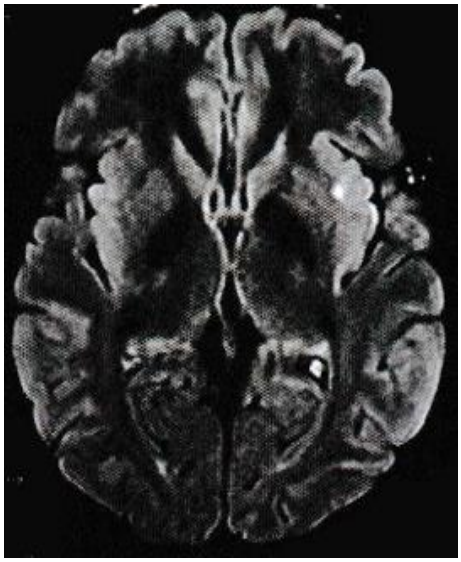

Fig. 1: Brain MRI (Axial T2-FLAIR Sequence) Showing Nodular Hyperintense Abnormalities Located in the Bilateral Frontal Subcortical White Matter and in the Left Insular Region. The Lesions Are Non-Specific In Appearance, With No Diffusion Restriction Or Post-Contrast Enhancement, And Without Mass Effect Or Perilesional Edema, Suggesting A Metabolic Or Small-Vessel Vascular Mechanism Rather Than An Inflammatory Demyelinating Process.

4. Discussion

This case illustrates the limitations of a strictly psychiatric interpretation in the presence of an atypical, polymorphic, and treatment-resistant clinical presentation. Indeed, the persistence of chronic headaches, associated with fluctuating anxiety and depressive symptoms, marked mood lability, and unexplained panic attacks, despite appropriately conducted therapeutic strategies, constitutes a warning sign suggestive of an underlying organic etiology. Several neurological hypotheses may be considered in this context. First, a metabolic encephalopathy, particularly related to a disorder of folate metabolism, should be suspected, especially in the presence of atypical and fluctuating neuropsychiatric manifestations. Similarly, an abnormality in homocysteine metabolism could account for this clinical picture, combining subtle cognitive impairment, emotional instability, and headaches. Other differential diagnoses include autoimmune encephalopathy, inflammatory involvement of the central nervous system, and certain forms of limbic dysfunction.

Successive antidepressant treatments resulted in only partial and incomplete clinical improvement. As a first-line approach, a selective serotonin reuptake inhibitor (SSRI), sertraline, was initiated with gradual dose escalation. It was maintained for approximately 12 weeks, in combination with a short-acting anxiolytic, alprazolam, prescribed on an as-needed basis for anxiety attacks. This strategy led to only partial improvement, with persistence of headaches and anxiety symptoms. Given this insufficient response, a switch to another SSRI, escitalopram, was implemented and continued for 8 to 12 weeks. However, symptoms persisted, particularly mood lability and panic attacks, with no significant overall clinical improvement. In light of this partial treatment failure, a switch in therapeutic class was undertaken, with the introduction of a serotonin-norepinephrine reuptake inhibitor (SNRI), venlafaxine. It was continued for approximately 12 weeks. This adjustment resulted in a moderate, but incomplete improvement, with persistent emotional instability and marked hypersensitivity. Subsequently, due to the persistence and fluctuating nature of symptoms, a combination therapy strategy was implemented. This associated venlafaxine with an adjunctive mood stabilizer such as lamotrigine, targeting mood lability, emotional hypersensitivity, and treatment-resistant anxiety.

In this context, the lack of response to appropriately conducted psychiatric treatments, together with the atypical, fluctuating, and polymorphic nature of the symptomatology, should raise suspicion of a non-psychiatric origin. This should prompt diagnostic reassessment toward an underlying neurological etiology.

Table 1 summarizes the clinical course and the successive therapeutic strategies implemented in this patient.

Table 1: Chronological Evolution of Clinical Features and Therapeutic Strategies

Stage	Main Clinical Features	Therapeutic Intervention	Treatment Duration	Clinical Response
Initial phase	Chronic diffuse headaches, persistent anxiety, atypical depressive episodes, mood lability, panic attacks.	-	-	Fluctuating and polymorphic clinical presentation.
First-line treatment	Persistence of anxiety-depressive symptoms.	Sertraline (SSRI) + Alprazolam	Approximately 12 weeks	Partial improvement; persistent headaches and anxiety.
Second-line treatment	Persistent mood lability and panic attacks.	Escitalopram (SSRI)	8-12 weeks	No significant improvement.
Third-line treatment	Persistent emotional instability.	Venlafaxine (SNRI)	Approximately 12 weeks	Moderate but incomplete improvement
Global evolution	Atypical, polymorphic, and treatment-resistant clinical picture.	-	-	Failure of appropriately conducted therapeutic strategies.
Diagnostic reassessment	Suspicion of a non-psychiatric etiology.	Referral for neurological evaluation.	-	Need to reconsider the initial diagnosis.
Fourth-line treatment (after antidepressant failure)	Fluctuating symptoms, emotional hypersensitivity.	Venlafaxine combined with supplementation with active folates, vitamin B12, and vitamin B6, with regular monitoring of folate, vitamin B12, and homocysteine levels.	Variable	Progressive clinical improvement with reduction of anxiolytic medications.

In this context, a metabolic workup was progressively undertaken following the failure of multiple psychiatric therapeutic lines, approximately 12 months after the onset of symptoms. This evaluation included measurement of folate, vitamin B12, and homocysteine levels. Given the persistence of atypical symptoms and suspicion of a folate metabolism disorder, further investigation was completed with genetic analysis. This revealed the presence of the MTHFR c.677C>T mutation in the homozygous state. The MTHFR gene, located on chromosome 1p36.22, encodes an enzyme essential for folate metabolism and methylation reactions, which are crucial for normal brain function. The c.677C>T mutation in the homozygous state leads to a marked reduction in enzymatic activity, resulting in decreased production of 5-methyltetrahydrofolate. The alteration disrupts neuronal methylation processes and may occur independently of plasma homocysteine levels.

Although this mutation is classically associated with hyperhomocysteinemia, normal or even paradoxically low homocysteine levels may be observed, related to compensatory mechanisms, prior supplementation with B vitamins, or intracellular redistribution of homocysteine. Therefore, the absence of hyperhomocysteinemia does not exclude neurometabolic dysfunction, particularly at the cerebral level, where methylation disturbances may manifest as atypical neuropsychiatric syndromes. The clinical presentation of this patient paradigmatically illustrates the diagnostic challenges posed by certain neurological and metabolic disorders with predominantly neuropsychiatric expression. The prolonged and fluctuating course, dominated by atypical affective and anxiety symptoms, initially oriented the diagnosis toward a primary psychiatric disorder. This thereby delayed the identification of the underlying pathology. This type of pseudo-psychiatric presentation is widely described in the literature, particularly in disorders of folate and homocysteine metabolism, as well as in certain genetic conditions involving the central nervous system [1] [3]. Pseudo-psychiatric disorders are defined by affective, cognitive, or behavioral manifestations secondary to an organic, metabolic, or genetic disorder, without an identifiable primary psychiatric lesion.

In this context, diagnostic delay is frequent, especially in young adults, when symptoms are fluctuating, poorly systematized, and partially responsive to psychotropic treatments [4]. In the present case, the initial absence of clear neurological signs, the normality of standard investigations, and the predominance of emotional symptoms favored a psychosomatic interpretation. Several studies have shown that patients with neuropsychiatric disorders related to abnormalities of folate metabolism consult for several years on average before an accurate etiological diagnosis is established [5]. The depressive episodes described in this patient differ from classical forms by their temporal instability, variable intensity, and lack of continuity, features suggestive of so-called atypical or secondary depression. Unlike primary major depressive disorders, these presentations are often associated with preserved emotional reactivity, rapid mood fluctuations, and an incomplete response to antidepressants [6]. From a neurobiological perspective, abnormalities in folate metabolism disrupt cerebral methylation, an essential process for the synthesis of monoamines (serotonin, dopamine, noradrenaline). Folate deficiency or dysfunction of the MTHFR enzyme leads to reduced availability of S-adenosylmethionine, the principal methyl group donor required for effective neurotransmission [7]. This dysregulation explains the atypical depressive symptomatology and the limited efficacy of conventional antidepressant treatments, which act downstream of these metabolic mechanisms. The panic attacks described in this patient were characterized by their abrupt onset, the absence of identifiable triggering factors, and marked emotional intensity.

Such features are frequently reported in metabolic disorders affecting the limbic system, particularly the amygdala and the prefrontal cortex [8]. Hypofolatemia and abnormalities of homocysteine metabolism may induce neuronal hyperexcitability, related to NMDA (N-methyl-D-aspartate) receptor dysfunction and an imbalance in the glutamate-GABA (gamma-aminobutyric acid) system. Homocysteine, even at moderate concentrations, exerts excitatory neurotoxic effects, promoting aberrant neuronal discharges within emotional circuits [9]. This hyperexcitability may explain the occurrence of paroxysmal anxiety attacks that are often resistant to conventional anxiolytics. The mood lability observed in this patient represents a central feature of the pseudo-psychiatric presentation. The rapid alternation between anxiety, sadness, and irritability reflects instability of emotional regulation circuits, particularly fronto-limbic connections.

Brain MRI in T2-FLAIR sequence showing two non-specific white matter lesions with hyperintensity, without diffusion restriction or post-gadolinium enhancement. The absence of signs of inflammatory activity or an expansile process gives these lesions a non-specific character and, in the clinical and biological context, may suggest an underlying metabolic or vascular mechanism. Functional neuroimaging studies have shown that abnormalities of folate metabolism are associated with altered activity of the ventromedial prefrontal cortex, a key region involved in emotional control and inhibition of excessive affective responses [11].

Clinically, this dysfunction manifests as emotional hypersensitivity and disproportionate reactions to environmental stimuli, often misinterpreted as personality traits or primary anxiety or depressive disorders. The variability in symptom intensity reported by relatives constitutes a major source of diagnostic confusion. This fluctuating character is typical of cerebral metabolic dysfunctions, in which clinical expression depends on a dynamic balance between biological factors, environmental constraints, and individual adaptive capacities [12]. In contrast to primary psychiatric disorders, which tend to follow a relatively stable syndromic organization, pseudo-psychiatric presentations of organic origin are often polymorphic and poorly reproducible, erroneously reinforcing the hypothesis of a functional disorder.

Furthermore, the partial or incomplete response to antidepressants provides additional support for a secondary etiology. Conventional antidepressants primarily modulate synaptic neurotransmission, without addressing the upstream metabolic mechanisms involved in neurotransmitter synthesis, methylation, and regulation [13]. In the presence of folate deficiency or dysfunction of the MTHFR pathway, monoamine production remains limited. This accounts for transient or partial improvement, the absence of sustained remission, and the need for repeated therapeutic adjustments. Several studies have shown that folate or L-methylfolate supplementation significantly improves the response to antidepressants in patients carrying MTHFR mutations, confirming the central role of this metabolic pathway [14].
However, it should be emphasized that the MTHFR C677T polymorphism is common in the general population and that its clinical significance remains debated. Several recent studies suggest possible associations with certain psychiatric disorders, particularly depressive and psychotic conditions, but with heterogeneous and non-specific findings [15]. Moreover, synthesis data confirm the central role of MTHFR in folate metabolism and its involvement in various pathologies, without establishing a direct causal link with psychiatric disorders [16]. Recent translational approaches also suggest a potential role in the identification of neuropsychiatric biomarkers, with perspectives for monitoring and prevention, although their clinical relevance remains to be clarified [17]. Finally, interactions between MTHFR gene polymorphisms and biological abnormalities, particularly vitamin deficiencies, may constitute a key interpretative element in selected cases, especially in the context of vitamin B12 deficiency [18]. Current data suggest a potential role for folate metabolism abnormalities in certain psychiatric presentations. However, the evidence remains evolving and not yet sufficiently consolidated. The clinical impact of MTHFR gene polymorphisms, particularly on treatment response, remains heterogeneous and requires further large-scale studies. Consequently, routine screening for MTHFR variants in clinical practice remains controversial and is not currently recommended by consensus [19]. In our case, the indication for genetic testing was not applied systematically. It was part of a targeted approach, driven by the atypical nature of the clinical presentation, its resistance to conventional treatments, and the presence of biological evidence suggestive of a folate metabolism disorder, as proposed in recent approaches to personalized medicine.
Based on these findings, folate replacement therapy was initiated, marking a turning point in the management of the patient. The introduction of treatment was followed by a progressive clinical improvement. A reduction in panic attacks and anxiety was observed within the first weeks, followed by a decrease in emotional lability and mood stabilization over the subsequent 1-2 months. Chronic headaches also gradually subsided, in parallel with the overall improvement in the patient's clinical status. This favorable evolution under targeted treatment suggests a possible underlying metabolic mechanism, without establishing a definitive causal relationship. It highlights the importance of individualized treatment-resistant psychiatric symptomatology.
Thus, this case highlights the need for an integrative approach at the interface between psychiatry and neurology, and supports the need for a thorough diagnostic reassessment in cases of treatment non-response, while taking into account the current limitations in knowledge regarding genetic polymorphisms such as MTHFR.

5. Conclusion

The MTHFR c.677C>T mutation, through its effects on folate metabolism and cerebral methylation pathways, provides a plausible explanatory framework for both the clinical symptomatology and the partial response to antidepressant treatment. The integration of genetic testing may help reduce diagnostic delay; however, it should only be considered in selected cases presenting with atypical symptoms or treatment resistance.

Conflicts of Interest

The authors state that they have no conflict of interest.

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