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DIVERSE CLINICAL PRESENTATIONS OF METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) DEFICIENCY IN CHILDHOOD: A CASE SERIES

Dr. Alex Turner
Department of Molecular Genetics, Stanford University School of Medicine, Stanford, California, USA

Prof. Isabella Dubois
Unit of Rare Diseases, Necker-Enfants Malades Hospital, Paris, France

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ABSTRACT

Methylenetetrahydrofolate reductase (MTHFR) deficiency is an inherited metabolic disorder that impacts how the body processes folate, a crucial nutrient, and can lead to a wide range of health challenges. While the severe forms are often recognized by significant neurological issues, the full picture of how this condition can present is incredibly varied and can make diagnosis very difficult. This report shares the stories of three children diagnosed with severe MTHFR deficiency, each showing unusual and diverse symptoms. One child experienced early-onset neurological decline and problems with coordination. Another developed a persistent, difficult-to-treat skin rash alongside subtle delays in development. The third presented with striking psychiatric symptoms, like psychosis and aggression, coupled with weak bones from a young age. These cases highlight that MTHFR deficiency isn't always confined to classical brain-related problems; it can affect skin, mental health, and bones too. Catching this condition early, through careful observation and comprehensive metabolic tests, is essential. Timely treatment with specific supplements like betaine, folic acid, and vitamin B12 can dramatically improve outcomes and help prevent irreversible complications. Our hope is that by sharing these experiences, medical professionals will become more aware of the many faces of MTHFR deficiency in children.

Keywords: Methylenetetrahydrofolate Reductase, MTHFR deficiency, Homocystinuria, Inborn errors of metabolism, Pediatric, Atypical presentation, Case series, Neurological regression, Eczematous rash, Psychiatric symptoms, Osteoporosis.

INTRODUCTION

Imagine a crucial biochemical assembly line inside our bodies, constantly working to keep us healthy. Methylenetetrahydrofolate reductase (MTHFR) deficiency (listed in Online Mendelian Inheritance in Man (OMIM) as #236250) is like a hiccup in this vital line, specifically in the folate pathway. This pathway is incredibly important for countless jobs our cells perform every day, from building and repairing our DNA to managing essential "methylation" processes [1, 2, 4]. The MTHFR enzyme itself acts as a key player, transforming one form of folate into another (5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, or 5-MTHF). This 5-MTHF is the primary form of folate circulating in our bodies, and it's absolutely necessary for a critical step: recycling homocysteine, a potentially harmful substance, back into methionine, an amino acid vital for overall health [2, 4].

When MTHFR isn't working properly, this recycling process falters. The result is a distinct chemical imbalance: homocysteine builds up to high levels in the blood (a condition called hyperhomocysteinemia), while methionine levels often drop or stay on the lower side (hypomethioninemia) [4]. This also impacts S-adenosylmethionine (SAM), a "universal methyl donor" involved in over a hundred different methylation reactions. These reactions are fundamental for brain development, neurotransmitter production, and even the insulation around our nerves (myelination) [7, 10]. Interestingly, unlike some other related metabolic conditions, MTHFR deficiency usually doesn't cause blood cell abnormalities like macrocytic anemia [3, 4].

The way MTHFR deficiency shows up in children is incredibly varied – it's like a spectrum with many different shades. Some individuals might have mild, almost unnoticeable biochemical changes found by chance, while others can experience severe, life-threatening neurological problems and other body-wide issues [2, 4, 13]. Historically, doctors primarily recognized the severe forms in newborns or infants, characterized by profound brain-related problems like significant developmental delays, difficult-to-control seizures, a shrinking head size (acquired microcephaly), severe muscle weakness (hypotonia), and a progressive decline in brain function [1, 4, 13]. Other, though less common, features in severe cases have included blood clots, eye problems, and megaloblastic anemia [4]. However, as doctors continue to learn and share new observations, we're seeing a much

broader and more diverse range of symptoms. These "atypical" presentations can often make getting a diagnosis incredibly challenging [6, 13]. The diverse ways this condition can manifest often lead to delayed diagnosis, especially when symptoms are subtle or don't fit the classic picture of brain issues [13].

Adding to the diagnostic puzzle is the inconsistent nature of newborn screening programs around the world. Not all regions routinely screen for all metabolic errors affecting the folate pathway, including severe MTHFR deficiency [18, 20]. Yet, even though effective treatments are available – typically involving strong doses of betaine, folic acid (or its active form, 5-MTHF), and vitamin B12 – how well a child fares in the long run is highly dependent on how quickly the diagnosis is made and treatment begins [9, 12, 21]. Early intervention has proven to significantly improve brain outcomes and survival rates, underscoring how vital it is for doctors to have a high level of suspicion [10, 12, 21]. This collection of case studies aims to contribute to our growing understanding of MTHFR deficiency by sharing the unique experiences of three children in Ireland. By detailing their varied and sometimes surprising clinical journeys, we hope to empower medical professionals to recognize the broad spectrum of MTHFR deficiency, paving the way for earlier recognition, accurate diagnosis, and prompt, life-changing treatment for more children. These cases reinforce the message that MTHFR deficiency should be considered in a wider range of childhood conditions, even when the classic brain-related signs aren't the main concern.

METHODS

This report is a careful look back at the medical histories of three children who were diagnosed with severe MTHFR deficiency. All these young patients received care at the National Centre for Inherited Metabolic Disorders (NCIMD) at Children's Health Ireland at Temple Street in Dublin. This center is the main hub for children with inherited metabolic disorders across the Republic of Ireland. We identified these cases by thoroughly reviewing the NCIMD's patient records, specifically looking for children with MTHFR deficiency confirmed by both their biochemical tests and genetic findings, diagnosed between 2008 and 2023.

How We Selected Patients and Collected Information

To be included, a patient needed a clear diagnosis of severe MTHFR deficiency, supported by their unique biochemical markers and the identification of genetic changes (pathogenic or likely pathogenic variants) in their MTHFR gene. For each chosen case, we conducted a meticulous and systematic review of their electronic and paper medical files. The information we gathered covered a wide range of details to build a complete picture of their health journey, including:

- Who They Are: Their age when symptoms first appeared, age at diagnosis, gender, ethnic background, and any family history of the condition.
- What Symptoms They Had: Detailed descriptions of their initial and evolving health issues. This included neurological symptoms (like developmental delays, seizures, muscle weakness, small head size, coordination problems, and psychiatric concerns), skin problems (rashes), and bone issues (fractures, weak bones).
- Their Blood and Fluid Test Results: Measurements of various substances in their blood, such as total homocysteine, free homocystine, methionine, cystine, folate, vitamin B12, and methylmalonic acid. We also looked at spinal fluid (CSF) tests for 5-methyltetrahydrofolate and brain chemicals like 5-hydroxyindoleacetic acid, if available.
- How Well Their Enzyme Worked: In some cases, we looked at how much MTHFR enzyme activity was present in their cells (fibroblasts or lymphocytes) to see how severe the deficiency was.
- Brain Scans and Other Imaging: What Magnetic Resonance Imaging (MRI) scans of their brain and other body parts (like their wrist or thigh bone) showed. We specifically noted changes like brain shrinkage, white matter abnormalities, and cerebellar changes. We even compared scans over time to see how they responded to treatment.
- Brainwave Tests (EEG) Results: Descriptions of their brain activity patterns, including any evidence of seizure activity or general brain dysfunction.
- Genetic Confirmation: The specific genetic changes found in their MTHFR gene through genetic sequencing. We also confirmed if their parents carried a single copy of these gene changes, which is typical for this inherited condition.
- What Treatments They Received: Specifics about the medications and supplements given, including the dosages and how often they were administered. This included oral betaine, folic acid (or 5-MTHF), hydroxycobalamin (vitamin B12), pyridoxine (vitamin B6), and other supportive medicines (like anti-seizure drugs or anti-inflammatory medications).
- Their Progress and Outcomes: Notes on how they responded to treatment, changes in symptom severity, how their development progressed, and any additional hospital stays or complications.

How We Confirmed the Diagnosis

Diagnosing severe MTHFR deficiency involved a combination of specific blood tests and genetic evidence, following international medical guidelines [4]. Here's what we looked for:

- High Total Homocysteine in Blood: Consistently elevated levels, much higher than what's expected for their age (usually above 15,mumol/L). Because free homocysteine can quickly break down in blood samples,

we made sure to specifically request a "total" plasma homocysteine test to capture all forms of this substance [4, 6].

- Low or Borderline Low Methionine in Blood: Methionine levels typically fell at or below the lower end of the normal range (e.g., 5–77,mumol/L). This pattern helps distinguish MTHFR deficiency from other forms of homocystinuria, where methionine levels are usually high [3].

- Low 5-Methyltetrahydrofolate in Spinal Fluid: Low levels in the fluid surrounding the brain and spinal cord directly indicated that folate transport and metabolism were impaired in the central nervous system.

- MTHFR Enzyme Activity Tests: For some cases, laboratory tests on cells (fibroblasts or lymphocytes) showed significantly reduced MTHFR activity (e.g., less than 5% of normal), which further confirmed the severe enzyme deficiency [8].

- Normal Red Blood Cell Size: Their mean cell volume (MCV) and blood film appeared normal. This helped us differentiate MTHFR deficiency from other internal vitamin B12-related disorders, which often cause larger-than-normal red blood cells (macrocytic anemia) [3, 4].

Genetic Analysis: Pinpointing the Cause

Confirming the diagnosis at the genetic level meant identifying specific changes in the MTHFR gene. We used various genetic testing methods, sometimes starting with a focused "Sanger sequencing" test, and for more complex or atypical cases, using broader "next-generation sequencing (NGS) panels" that look at many genes related to folate and vitamin B12 metabolism. We also tested the parents to confirm that each carried one copy of the faulty gene, consistent with how this condition is passed down through families (autosomal recessive inheritance).

Protecting Patient Privacy

We took great care to protect the privacy of all patients involved. All personal information was removed from their medical records to ensure confidentiality. Since this study looked back at existing records and didn't involve any new treatments or interventions for the patients, ethical approval was granted by the Children's Health Ireland (CHI) Research/Ethics Committee, and we didn't need individual patient consent for this specific retrospective analysis. However, written informed consent forms were obtained from the parents or families for their children's ongoing clinical care and diagnostic procedures. We can confirm that the data supporting our findings is available within this article.

RESULTS

This collection of cases tells the stories of three different children with severe MTHFR deficiency. Each one highlights a unique and sometimes surprising set of symptoms, further revealing the wide range of ways this rare metabolic disorder can manifest. We've summarized their key demographic details and important biochemical findings, both before and after they started treatment, in Table 1.

Case 1: Early Challenges with Brain Development, Movement, and a Persistent Rash

Our first patient, a girl, was born full-term to Irish parents, with no close family relations, and her pregnancy and initial newborn period were uneventful, aside from mild jaundice. She was referred to us at 19 months old because she was experiencing significant delays in all areas of development, severe muscle weakness, a head circumference that was too small (noted to be below the 0.4th percentile at 11 weeks of age, and still only 48.2,cm at 14 years old), involuntary eye movements (nystagmus), and a history of a widespread, stubborn rash [6].

The rash first appeared at 6 weeks of age, was red and scaly, and required constant use of moisturizing creams. Later, at 18 months, her left wrist became swollen and painful. MRI scans of her wrist suggested inflammation in the joint lining and thickened tissues around the wrist bones, which improved with strong anti-inflammatory medications and injections into the joint. Interestingly, a blood test for autoimmune issues (antinuclear antibodies, ANA) was positive (1:400), adding another layer of complexity to her diagnosis. Later, a new, severe, sharply defined "peeling paint" rash developed, and a skin biopsy showed significant skin thickening and abnormal shedding of skin cells.

From a neurological perspective, at just 11 weeks old, she showed muscle weakness, tremors in her upper limbs, and episodes where she seemed to stare blankly. While she initially reached milestones like sitting unassisted at 15 months, her development stalled, and she never began to speak words. An MRI of her brain around the time of diagnosis (Figure 1a) revealed small brain hemispheres with fluid collections under the dura (bilateral subdural collections), a thin corpus callosum (the bridge connecting the two halves of the brain), and extensive bright spots in the white matter surrounding the brain's fluid-filled spaces. These findings pointed to significant brain damage. An eye exam showed crossed eyes (convergent strabismus), delayed visual development, and problems with how her brain processed visual information. An electroencephalogram (EEG), which measures brain waves, showed widespread seizure activity with immature patterns, leading to the start of anti-seizure medications and vitamin supplements (pyridoxine and folinic acid) for suspected vitamin-responsive seizures. Over time, she developed generalized tonic-clonic seizures that required a combination of multiple anti-epileptic drugs.

Our metabolic investigation, prompted by her collection of symptoms, revealed critical clues. Her blood amino acid test showed a strikingly low-normal methionine level of

5,mumol/L (normal range 5−77,mumol/L) and a very high total homocysteine level of 149,mumol/L (normal range 3−8,mumol/L). Her serum folate was low at 2.6,mug/L (normal range 3.8−18.2,mug/L). Importantly, her red blood cells were of normal size (MCV 77,fL, normal range 73−86,fL), with a normal blood film, which helped distinguish her condition from other vitamin B12-related disorders [3, 4]. A crucial test of her spinal fluid (CSF) showed very low levels of 5-methyltetrahydrofolate (MTHF), less than 5,nmol/L (normal range 52−178,nmol/L), strongly indicating MTHFR deficiency.

The diagnosis was confirmed by genetic testing of her blood, which identified two significant changes in her MTHFR gene: c.386C>A (p.T129N) and c.757G>T (p.V253F). Testing her parents confirmed that each carried one of these gene changes, consistent with how this recessive condition is inherited. Further laboratory testing of MTHFR enzyme activity in her skin cells (fibroblasts) showed very little activity, only about 1% of what's normal, confirming a severe enzyme deficiency.

We quickly started her on treatment, which included high doses of folinic acid, followed by 5-methyltetrahydrofolate (gradually increased up to 15,mg three times a day), vitamin B12, and Betaine. Her metabolic markers showed good improvement, with total homocysteine levels dropping to below 100,mumol/L (Table 1) and free homocysteine returning to less than 5,mumol/L. Follow-up MRI brain scans at age 9 (Figure 1b) showed remarkable improvements in the brain atrophy and white matter changes, suggesting a positive response to the targeted treatment. However, despite these biochemical and imaging improvements, her overall neurological progress has been slow. At one point, her CSF 5-hydroxyindoleacetic acid was slightly low (70,nmol/L; normal range 89−367,nmol/L), which might suggest issues with serotonin production, a problem that can be seen in MTHF deficiency [7]. But, direct clinical benefit from addressing this specifically wasn't clearly observed, and performing follow-up spinal taps was challenging. At 14 years old, she walks with a stooped gait and needs ongoing monitoring for scoliosis. She continues to require a special needs assistant at school. Her juvenile arthritis was also managed with a specific medication (adalimumab), which helped her arthritis symptoms improve.

Case 2: A Surprising Bone Fracture with Hidden Nutritional Gaps

Our second patient, a boy, was born at full-term in India to parents who were not related. His newborn period was unremarkable. His family moved to Ireland when he was 10 years old. Before this, he had no significant medical history, though he was known to have a poor appetite and little interest in food, which in hindsight might have been subtle clues.

He came to the hospital at 12 years old after a simple fall on a couch at home resulted in a painful leg injury. An X-ray (Figure 2) showed signs of osteopenia (thinner, weaker bones) and a fracture in his left thigh bone (femur) near the knee – an unusual injury from such a minor fall for a child. When he presented, his body measurements were concerning: he weighed 23.05,kg (below the 0.4th percentile), was 149,cm tall (50th percentile), giving him a very low body mass index (BMI) of 10.4,kg/m2 (normal range 15−24,kg/m2).

Initial rapid blood tests showed slightly low plasma calcium levels (2.24,mmol/L; normal range 2.25−2.7,mmol/L) and a low corrected calcium (2.06,mmol/L), along with elevated alkaline phosphatase (488,IU/L; normal \<300,IU/L), which can indicate bone problems or metabolic stress. His complete blood count, including red blood cell size (MCV) and blood film, was essentially normal, initially steering us away from other B12-related disorders [3, 4].

However, more detailed biochemical investigations revealed widespread nutritional deficiencies. His vitamin D levels were very low (less than 13,nmol/L; normal above 50,nmol/L), folate was low at 2.1,ng/mL (normal 3.8−18.2,ng/mL), vitamin B12 was low at 107,ng/L (normal 211−760,ng/L), and ferritin (an iron storage protein) was low at 12,mug/L (normal 15−80,mug/L). Despite these multiple deficiencies, his initial total homocysteine was moderately elevated at 86,mumol/L, while his methionine and cystine levels were within the normal range. Urine tests showed no other abnormalities.

Given the weak bones and the overall metabolic picture, MTHFR deficiency was suspected. Genetic testing confirmed two likely disease-causing changes in his MTHFR gene: c.589T>G (p.Tyr197Asp) and c.1072C>T (p.Arg258*). His parents were confirmed carriers. An initial MRI of his brain showed only mild cerebellar atrophy (Figure 3), a less severe neurological finding compared to our first patient. We opted to defer spinal fluid tests for brain chemicals and folate at his parents' request, as he was responding well to initial treatment.

He received excellent orthopedic care for his fracture, which healed without any issues. We immediately started him on a wide array of nutritional supplements, including high-dose vitamin D and calcium, a general multivitamin (with folate, vitamin B12, and vitamin B6), and specifically, betaine and 5-methyltetrahydrofolate for his confirmed MTHFR deficiency. After starting this targeted metabolic treatment, his appetite significantly improved, and he made remarkable progress. His weight and height growth normalized. By 15 years old, his BMI had returned to a healthy 17,kg/m2. He now enjoys playing cricket and participating in gymnastics at school, showing a full return to normal physical activity and overall well-being. This case highlights a previously less-described symptom of severe MTHFR deficiency – a bone fracture from minor trauma – and emphasizes how important it is to consider metabolic disorders when children experience unexplained bone fragility.

Case 3: Acute Behavioral Crisis and Weakened Brain Function

Our third patient, a girl, was born full-term to Irish parents, with no known issues during her newborn period. Her health journey began at 5 years old when she started having focal seizures. During these episodes, she would become pale and unresponsive, her right upper limb would twitch, and she would have a fixed stare for several minutes. She also had a slight tremor when at rest, difficulties with coordination (developmental coordination disorder), and was already known to have learning difficulties, for which she received support at school.

Previous investigations, including a genetic array test (array-CGH), had not provided a diagnosis. An earlier MRI of her brain showed an unclear bright spot in the white matter of her left frontal lobe, along with some apparent loss of brain volume in certain areas and reduced white matter in the back of her brain. Her EEG at that time showed abnormal low-amplitude spikes in her brain, consistent with her seizures. Initially, her focal seizures were well controlled with valproate; however, her tremor worsened, leading to a switch to levetiracetam. At this point, pyridoxine was also added to her regimen.

By 9 years and 5 months, she began experiencing increasingly difficult behavioral problems. Levetiracetam was stopped, and oxcarbazepine was started. Following this medication change, she gained a significant amount of weight. At 10 years and 4 months, brivaracetam was added with the intention of gradually reducing her oxcarbazepine dose, primarily due to her weight gain and persistent challenging behavior. Over the next three months, her behavior took a sharp turn for the worse. She became severely aggressive, even though her seizures were under control. Given this alarming decline in behavior, brivaracetam was stopped one month before her admission, and she continued on a lower dose of oxcarbazepine, with clobazam added.

She was admitted urgently at 10 years and 8 months of age in a severe acute state, experiencing aggression, extreme agitation, and disturbing auditory and visual hallucinations. This sudden psychiatric crisis prompted us to consider a broader metabolic evaluation to find an underlying diagnosis for her complex symptoms.

A repeat MRI of her brain during this admission (Figure 4a) revealed noticeable loss of brain volume (generalized supratentorial white matter and gray matter volume loss) when compared to previous scans, indicating a progression of brain shrinkage. Magnetic Resonance Spectroscopy (MRS), which looks at brain chemistry, was normal. Her EEG was markedly abnormal, showing a slow and disorganized background, though without clear seizure activity at that moment. A comprehensive metabolic investigation was then performed. This revealed a strikingly high total homocysteine in her blood (330,mumol/L), with a prominent mixed disulfide peak, and an elevated free homocystine of 36,mumol/L. Crucially, her methionine level was profoundly low at 7,mumol/L. Her urine tests and dried blood spot analysis were normal, and her full blood count showed no signs of macrocytosis, which strongly pointed toward MTHFR deficiency rather than an internal vitamin B12-related disorder [3, 4]. Additional spinal fluid (CSF) tests confirmed undetectable methionine and very low 5-methyltetrahydrofolate (MTHF) levels (less than 10,nmol/L; normal range 46–160,nmol/L). Her serum folate was also reduced at 3.1,mug/L.

Genetic testing definitively confirmed the diagnosis, showing a homozygous pathogenic change, c.386C>T (p.Thr129Ile), in her MTHFR gene. We immediately started her on a comprehensive treatment plan including pyridoxine (50,mg once daily), vitamin B2 (10,mg once daily), betaine (3,g twice daily), methylfolate (15,mg once daily), and vitamin B12 (1,mg intramuscularly once a month). Following this targeted metabolic treatment, her behavior dramatically improved, with a significant reduction in aggression, agitation, and the complete resolution of her hallucinations. Her clinical progress was very encouraging, and a follow-up MRI of her brain seven months after starting treatment (Figure 4b) showed remarkable resolution of both the brain shrinkage and the widening of brain spaces, demonstrating that some neurological changes can indeed be reversed with early and appropriate intervention [21]. This case powerfully illustrates the critical need to consider metabolic disorders when children present with acute psychiatric symptoms, especially if they also have a history of neurological issues and progressive intellectual difficulties.

DISCUSSION

The cases we've shared here strongly support the idea that severe methylenetetrahydrofolate reductase (MTHFR) deficiency in children has a much broader range of symptoms than we previously thought. These observations reinforce that the ways this rare metabolic disorder can appear are incredibly varied and complex. It's not just about the classic brain-related problems like developmental delays, a small head size, or seizures [1, 4, 13]. Our findings really emphasize that MTHFR deficiency can present with highly diverse and sometimes unusual symptoms, making early diagnosis a significant clinical puzzle, but a puzzle we absolutely must solve to achieve the best possible outcomes for these children [1, 21].

Our first case, an infant experiencing a rapid decline in brain function and severe muscle weakness, is a clear example of the most severe end of this condition's spectrum. This kind of presentation aligns with previous descriptions of profound brain-related forms of MTHFR deficiency [1, 13]. Even though we acted quickly and aggressively with treatment, her long-term progress, despite good biochemical control and impressive improvements seen on brain scans, was slow, with

ongoing significant motor and developmental challenges. This highlights a crucial point: while early treatment can halt or even reverse some aspects of brain damage, it might not fully undo damage that has already occurred. This underscores the absolute necessity of diagnosing this condition even before symptoms appear (pre-symptomatic diagnosis) and starting treatment as early as possible to prevent irreversible harm [10, 21]. The fact that she also had a chronic, hard-to-treat eczematous rash further broadened her symptom profile, hinting at a body-wide inflammatory response or skin vulnerability tied to her metabolic imbalance—a less common, but documented, manifestation [6]. The subtle findings of low spinal fluid 5-hydroxyindoleacetic acid and the possibility of impaired serotonin production also point to the complex chemical disruptions in the brain caused by MTHFR deficiency, which can contribute to intricate neurological and behavioral problems [7].

The second case, a boy who first came to our attention because of a bone fracture from a minor fall, represents a truly unique and surprising initial symptom of severe MTHFR deficiency. As far as we know, a pathological fracture as the primary reason for diagnosis hasn't been widely described in the context of MTHFR deficiency before. While this patient also had several nutritional deficiencies (vitamin D, folate, B12, iron), which no doubt played a role in his weak bones, the underlying MTHFR deficiency likely made him more prone to this type of injury. This is supported by scientific literature showing a complex link between homocysteine metabolism and bone strength. High homocysteine levels are known to interfere with how collagen, a vital building block of bone, forms cross-links. This disruption can weaken the bone matrix, potentially leading to lower bone mineral density (BMD) and an increased risk of fractures [15, 16, 17]. Some studies have even found that specific genetic variations in the MTHFR gene can be linked to lower BMD and a slightly higher fracture risk, suggesting that individuals with two copies of these variations might be more vulnerable [15, 16]. This case powerfully illustrates how MTHFR deficiency can affect multiple body systems and underlines how important it is to perform a thorough metabolic evaluation in children with unexplained bone problems, especially when they also have subtle signs like poor growth or appetite issues that might hint at an underlying metabolic condition. The significant improvement in his body mass index and his return to normal physical activities after treatment really highlight the profound positive impact of targeted metabolic therapy on a child's overall health and growth.

Our third case, a girl who developed severe and sudden psychiatric symptoms like aggression, agitation, and hallucinations, on top of existing learning difficulties and a history of focal seizures, is another example of how challenging MTHFR deficiency can be to diagnose in older children. While psychiatric issues, including psychosis that can be triggered by infections, have been reported in MTHFR deficiency [14], the severity and sudden onset of her symptoms strongly point to the critical need for metabolic screening during pediatric psychiatric emergencies. The impressive improvement in her behavior and the remarkable resolution of brain shrinkage seen on follow-up MRI after treatment strongly suggest that some brain changes can indeed be reversible with the right metabolic intervention [21]. This finding supports the understanding that a healthy brain relies heavily on enough SAM and proper methylation processes, which are disrupted in MTHFR deficiency [7, 10]. We also considered the complex interaction between her previous anti-epileptic medications and the sudden worsening of her behavior, recognizing that drug-metabolism interactions can occur in genetically vulnerable individuals, although the main problem seemed to be the underlying metabolic imbalance. This case strongly argues for a comprehensive, holistic approach in evaluating children and teenagers with complex neurodevelopmental and psychiatric issues, especially when standard diagnostic tests don't provide answers.

Taken together, these cases make it clear that the specific symptoms and their severity in MTHFR deficiency are influenced by many factors. These include the exact genetic changes in the MTHFR gene, which determine how much enzyme activity is left, and possibly environmental and nutritional factors that can modify how the disease unfolds [5, 8]. The link between genetic makeup and symptoms can be very complex; even patients with severe biochemical problems might initially present with milder, unusual, or slowly worsening symptoms [5, 13].

The role of newborn screening (NBS) programs is incredibly important for finding inherited metabolic errors early. However, how consistently homocystinuria and related metabolic disorders are included in routine screening varies greatly across different countries [18, 20]. In the Republic of Ireland, for example, newborn blood spot screening has successfully included classical homocystinuria (identified by high methionine) since 1971 [18, 19]. But detecting severe MTHFR deficiency specifically, which often involves low methionine, can be tricky unless specific tests for homocysteine are routinely used [20]. There's a strong case to be made for expanding and standardizing newborn screening to specifically look for severe MTHFR deficiency. Why? Because starting treatment before symptoms appear, or very early on, has been shown to significantly improve long-term outcomes, including survival and brain development [12, 21]. Based on the three confirmed cases in our national center [22], we estimate the approximate prevalence in the Republic of Ireland to be 0.08 cases per 100,000. While rare, this suggests it's a condition that warrants proactive screening efforts.

From a treatment perspective, the cornerstone of care for MTHFR deficiency is early identification and the swift initiation of a multi-pronged treatment approach. This typically involves betaine, high doses of folic acid (or 5-MTHF), and vitamin B12 [9, 11, 12, 21]. Betaine acts like a

bypass, helping the body remethylate homocysteine directly into methionine, which lowers homocysteine levels and increases methionine and SAM [4, 9]. Folic acid (or 5-MTHF) provides the necessary building block for the MTHFR enzyme if it has any residual activity, and vitamin B12 is essential for another enzyme crucial in methionine synthesis [4]. While our cases show that even with good biochemical responses, clinical improvement can vary, especially when there's already significant brain damage, the overall trend is towards stabilization and improvement, particularly if treatment starts before or very early in the symptom phase [12, 21]. It's also crucial to remember to specifically request a "total plasma homocysteine" concentration when doing metabolic workups, especially in children with developmental delays or other suggestive symptoms. This is because it's often not included in routine amino acid panels and can degrade quickly in blood samples [4, 6].

CONCLUSION

In summary, methylenetetrahydrofolate reductase deficiency is a complex metabolic condition with an incredibly diverse array of symptoms in childhood. The cases we've presented here emphasize how important it is for doctors from various specialties to maintain a high level of suspicion. A thorough metabolic evaluation, including specific blood tests for total plasma homocysteine and spinal fluid tests for folate, is vital for a quick and accurate diagnosis, especially for children who present with unusual neurological, skin, psychiatric, or bone problems that might otherwise be missed. Increasing clinical awareness of this broad spectrum of symptoms isn't just an academic exercise; it's fundamental to improving diagnosis rates and, consequently, enabling earlier treatment. This early intervention is the best way to prevent irreversible complications, slow down disease progression, and ultimately improve the long-term quality of life for children affected by MTHFR deficiency. Moving forward, research should focus on refining how we diagnose these unusual presentations, finding the best treatment plans tailored to each patient's response, and digging deeper into the exact ways MTHFR deficiency affects the body at a molecular and cellular level.

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