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REVIEW ARTICLE

# Update in pediatric neurometabolic disorders: folate and polyamine metabolism

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## Abstract

More widespread use of exome and genome sequencing combined with improved data sharing platforms have led to the characterization of "new" neurometabolic disorders. This review provides an overview of the folate and polyamine metabolic pathways, summarizes the established disorders, and highlights two recently described disorders of folate and polyamine metabolism. 5,10-methenyltetrahydrofolate synthetase (MTHFS) deficiency is an emerging disorder of folate metabolism that manifests with neurodevelopmental abnormalities, epilepsy, spasticity, short stature, microcephaly, cerebral hypomyelination, and cerebellar atrophy. Cerebrospinal fluid 5-MTHF levels are reduced, with normal peripheral folate levels. MTHFS deficiency may be amenable to treatment with 5-methyltetrahydrofolate, whereas folinic acid, used in other forms of cerebral folate deficiency, may be contraindicated. There are two inborn errors of polyamine metabolism in humans described to date, including the neurodevelopmental disorder Snyder-Robinson syndrome and the recently described ODC1 disorder. ODC1 disorder is associated with a recognizable phenotype, including neurodevelopmental and behavioral abnormalities, macrocephaly, alopecia, craniofacial dysmorphisms, and MRI abnormalities. The pathogenic variants in this gene described to date appear to confer a gain-of-function effect. It is yet to be determined if there is an effective targeted treatment for ODC1 disorder.

**Keywords:** cerebral folate deficiency, folate metabolism, 5,10-methenyltetrahydrofolate synthetase (MTHFS) deficiency, polyamine metabolism, ornithine decarboxylase 1 (ODC1) deficiency.





## Introduction

Inborn errors of metabolism are genetic disorders that disrupt biochemical processes in the human body by impairing enzymes, transporters, or mitochondrial bioenergetics. More than 500 individual disorders are described to date, and while they are individually rare, they have a collective incidence between 1/800 to 1/2500 [1]. In recent years, the more widespread use of exome and genome sequencing and improved data sharing platforms have led to the discovery of several "new" neurometabolic disorders. These disorders do not have diagnostic metabolic profiles on routine metabolic testing and require more specialized testing (e.g., metabolomics analysis) or genetic testing for diagnosis. Fortunately, many of these disorders have distinctive, recognizable clinical features. This review highlights two recently characterized disorders of folate metabolism and polyamine metabolism and provides a review of the relevant metabolic pathways and differential diagnoses.

## Part 1: Folate Metabolism

### *Background*

Folate serves a number of vital functions in humans. Folate is required to re-methylate the amino acid homocysteine to methionine, which is a prerequisite for the over 100 methylation reactions in the human body [2]. Folate is also involved in 2 reactions in *de novo* purine synthesis and one in *de novo* pyrimidine (thymidine) synthesis, impacting cell growth. In addition, folate is involved in the *de novo* synthesis of the amino acid glycine [2]. Finally, folate is required for intra-mitochondrial translation [2].

### *Folate metabolism*

The folate metabolic pathway is summarized in figure 1. Folic acid from the diet is metabolically inactive. To perform its various metabolic roles, it must be reduced and one carbon loaded to an active folate vitamer. The folate vitamer 5,10-methylene tetrahydrofolate participates in *de novo* thymidine synthesis. It can also be reduced to 5-methyltetrahydrofolate (5-MTHF), which participates in the re-methylation of homocysteine to methionine. The folate vitamer 5,10-methenyltetrahydrofolate participates in purine synthesis. Most folate is transported in the body in the form of 5-methyltetrahydrofolate [3, 4].

There are various folate transporters. The proton-coupled folate transporter (PCFT) functions optimally at low pH and is the primary transporter in the gastrointestinal tract [5]. The reduced folate carrier (RFC) is ubiquitously expressed. It preferentially transports reduced forms of folate. The FOLR1 transporter is expressed on the luminal surface of polarized epithelial cells and plays an important role in folate transport across the blood-CSF barrier [5]. The FOLR1 transporter functions via receptor-mediated endocytosis and is ATP-dependent [5].

### *Disorders of folate metabolism:*

There are numerous acquired and genetic disorders of folate metabolism. General symptoms of disordered folate metabolism may include neurological manifestations such as dementia, psychiatric abnormalities, seizures, upper motor neuron signs, decelerating head growth, and peripheral neuropathy. Neuroimaging abnormalities may include leukoencephalopathy, cerebral atrophy, and cerebral calcification [4]. Non-neurological features may include macrocytic anemia, thrombophilia, and immunodeficiency [4].

Acquired disorders of folate metabolism include dietary deficiency (e.g., severe malnutrition, malabsorption, or a highly restrictive diet); medication effects (e.g., methotrexate, valproic acid); and auto-antibodies against the FOLR1 transporter [4]. The latter has been postulated to result from cross-reactive antibodies directed against epitopes found in cow's milk [6].

Genetic defects in almost every step of folate metabolism have been described. These can be divided into disorders with low folate in blood and those with isolated cerebrospinal fluid (CSF) deficiency. The latter is termed *cerebral folate deficiency* [4]. Genetic disorders of folate metabolism may be related to enzymes involved in the reduction or one-carbon loading of folic acid or may affect folate transporters [4]. Inheritance is autosomal recessive for all of the primary disorders of folate metabolism [4]. Distinguishing clinical features in these genetic disorders of folate metabolism are summarized in table 1 [2, 4, 7]. In addition to primary genetic disorders of folate metabolism, secondary cerebral folate deficiency can be seen in a number of other genetic and metabolic disorders, including mitochondrial disorders, neurotransmitter (biogenic amine) disorders, and serine deficiency syndromes, amongst others [4].

Special note should be made that there is a severe form of methylenetetrahydrofolate reductase (MTHFR) deficiency and a hypomorphic form associated with only mildly reduced enzyme activity caused by polymorphisms in the gene. The polymorphism p.A222V (c.677 C>T) is called the *thermolabile* variant and is found in homozygosity in more than 25% of Hispanics and 10-15% of North American Caucasians [8]. Homozygosity for the thermolabile variant only slightly increased the absolute risk of venous thromboembolism, recurrent miscarriage, and neural tube defects [7]. In contrast, the severe form of MTHFR deficiency, if untreated, may present with severe neurodevelopmental abnormalities, hypotonia, progressive microcephaly, spasticity, epilepsy, and thrombosis [9].

Management of most forms of cerebral folate deficiency is typically with folinic acid (5-formyltetrahydrofolate), a metabolically active folate vitamer [4]. Treatment with folic acid is contraindicated since it is an inactive form of folate, it competes with 5-methyltetrahydrofolate (5-MTHF) for transport across the blood-CSF barrier, and the enzymes that reduce and one carbon load folate are expressed at low levels in the central nervous system [4]. Treatment with folic acid may worsen cerebral folate deficiency in these individuals. In certain instances, treatment with 5-methyltetrahydrofolate (5-MTHF), another active folate vitamer, may be superior to folinic acid. In a previous case series, 5-MTHF could normalize CSF 5-MTHF levels in individuals with severe MTHFR deficiency, whereas folinic acid could not achieve this [10].

### *5,10-Methenyltetrahydrofolate synthetase (MTHFS) deficiency*

One additional disorder of folate metabolism was recently characterized as resulting from deficiency of the enzyme 5,10-methenyltetrahydrofolate synthetase (MTHFS) [2]. The condition has autosomal recessive inheritance [2]. Three affected individuals have been described in the peer-reviewed literature with a consistent and unique clinical phenotype [2, 11]. Clinical features include global developmental delay/intellectual disability, epilepsy, spastic diplegia, microcephaly, and growth restriction [2, 11]. One individual was reported to have macrocytic anemia [11]. Brain MRI demonstrates hypomyelination, thinning of the corpus callosum, and mild cerebellar atrophy [2]. Biochemical features include reduced CSF 5-MTHF, normal plasma folate, plasma and CSF amino acids, homocysteine, urine purines/pyrimidines, and lactate [2]. Molecular diagnosis was made through clinical whole-exome sequencing [2]. Research-based enzymology in fibroblasts of affected individuals demonstrates an absence of MTHFS enzyme activity relative to normal enzyme activity in controls. Fibroblasts of affected individuals also demonstrate selective elevation of folinic acid (5-formyltetrahydrofolate) with normal levels of other folate vitamers [2].

Folinic acid can be obtained exogenously from the diet or endogenously synthesized from 5,10-methenyltetrahydrofolate. The MTHFS enzyme is responsible for converting folinic acid to 5,10-methenyltetrahydrofolate. With a deficiency of the MTHFS enzyme, folinic acid accumulates in body tissues and likely exerts a toxic effect. The precise mechanism for this toxicity is yet to be elucidated. It has been previously demonstrated that folinic acid inhibits the enzyme serine hydroxymethyltransferase, which is involved in the one-carbon loading of tetrahydrofolate by serine; this may explain the reduced CSF 5-MTHF levels seen in this disorder [2, 12]. In addition, folinic acid is believed to inhibit the enzyme AICAR formyltransferase, a critical enzyme in *de novo* purine synthesis [12]. A possible reduction in purine nucleotides and/or accumulation of the metabolite AICAR in some cellular compartments may also account for part of the phenotype seen in this disorder, although abnormalities in purine metabolites have yet to be demonstrated [2].

**Table 1.** Disorders of folate metabolism.

| Disorder | Neurological | Anemia | Immune deficiency | Thrombosis |
|---|---|---|---|---|
| **Enzyme defects** | | | | |
| Dihydrofolate reductase (DHFR) deficiency | GDD, Sz, microcephaly | Yes | No | No |
| 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency | GDD, Sz, microcephaly | **No** | No | **Yes** |
| Glutamate formiminotransferase-cyclodeaminase deficiency | GDD | Yes | No | No |
| Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) deficiency | GDD | Yes | **Yes** | No |
| 5,10-methenyltetrahydrofolate synthetase (MTHFS) deficiency | GDD, Sz, microcephaly | ? (1/3 cases) | No | No |
| **Transporter defects** | | | | |
| Proton coupled folate transporter (PCFT) deficiency | GDD, Sz | Yes | **Yes** | No |
| FOLR1 transporter deficiency | GDD, Sz | **No** | No | No |



The optimal management of this disorder has yet to be determined. Based on the current understanding of this disorder, treatment with folinic acid is likely contraindicated and may worsen the clinical course [2]. Likewise, folic acid is likely to worsen cerebral folate deficiency. 5-MTHF supplementation and methylcobalamin IM injections were trialed in one of the cases, resulting in sustained normalization of CSF 5-MTHF levels and subjective clinical improvement in alertness [2].

## Part 2: Polyamine metabolism

### *Background*

Polyamines are organic compounds that contain more than two amine groups. They include putrescine, spermidine, and spermine. The polyamines serve a number of crucial functions in humans, including regulation of cell proliferation, intracellular signaling, GABA synthesis, and modulation of ion channels such as the NMDA receptor [13]. Polyamine levels are tightly regulated in humans through endogenous synthesis, inter-conversion, and transport [13].

### *Polyamine Metabolism*

The polyamine metabolic pathway is summarized in figure 2. *De novo* polyamine synthesis occurs with the conversion of the amino acid ornithine into putrescine. Putrescine can be acetylated and converted into GABA or the polyamine spermidine. Spermidine can be converted into spermine. The spermine can be converted back to spermidine and spermidine back to putrescine via sequential acetylation and oxidation reactions. Polyamines can also derive from the diet (e.g., dairy/cheese) or from synthesized by gastrointestinal flora [13].

### *Disorders of Polyamine Metabolism*

Polyamine metabolism has been thoroughly studied in the field of oncology. Elevated polyamine levels from upregulation of de novo polyamine synthesis are found in various cancers, including breast, lung, prostate, colon, and skin [14]. Further, the polyamine pathway appears to be a target for various oncogenes, including Myc and Ras [14].

Until recently, only one genetic disorder of polyamine metabolism called Snyder-Robinson syndrome (SRS) was known, first described in 1969 [15]. It is a syndromic neurodevelopmental disorder resulting from hemizygous pathogenic variants in the x-linked SMS gene. The SMS gene encodes the enzyme spermine synthase, which converts the polyamine spermidine into spermine. Clinical features include global developmental delay, moderate to severe intellectual disability, hypotonia, epilepsy, asthenia, osteoporosis, proportionate short stature, kyphoscoliosis, facial dysmorphisms, nephrocalcinosis, renal cysts, genital anomalies, and rarely brain calcifications. Management is supportive [16].

Diagnosis of SRS is generally made with broad genetic tests for intellectual disability, such as gene panels or whole-exome sequencing. Enzymology for spermine synthase and quantitative measurements of spermidine and spermine and spermidine/spermine ratio can be performed on a research basis.

The pathophysiology of SRS is believed to relate to an imbalance in polyamine levels, such that spermidine is increased and spermine is decreased. Increased spermidine results in excess toxic aldehydes and hydrogen peroxide production, increasing oxidative stress [17]. There is also evidence of secondary lysosomal and mitochondrial dysfunction in SRS [17].

### *Ornithine Decarboxylase 1 (ODC1) disorder*

A second disorder of polyamine metabolism was recently described in association with the ornithine decarboxylase 1 (ODC1) gene. This disorder has an autosomal dominant inheritance. Five affected individuals (including one fetal case) have been reported in the peer-reviewed literature [13, 18]. Clinical features include neurodevelopmental abnormalities; behavioral difficulties (ADHD, aggression); hypotonia; macrocephaly; alopecia involving eyebrows, eyelashes, and variably involving scalp hair; facial dysmorphisms; hypoplastic nails; and cryptorchidism. A prenatal history of polyhydramnios is common. MRI features include prominent perivascular spaces, periventricular cysts, abnormal white matter, and corpus callosum abnormalities. Polymicrogyria and calcifications were also reported in one individual [13]. Biochemical features in one individual include elevated levels of plasma N-acetylputrescine on clinical metabolomics [14]. Research testing has also demonstrated elevated putrescine and ODC1 protein levels in patient red blood cells [18].

ODC1 encodes the enzyme ornithine decarboxylase 1, the first and rate-limiting enzyme of *de novo* polyamine synthesis. It converts the amino acid ornithine to putrescine. ODC1 is ubiquitously expressed. Its activity is highly regulated at the transcriptional and protein level. It has a very short half-life of approximately 10 minutes.

It functions in its active form as a homodimer. For its degradation, the ODC1 monomer binds non-covalently to ODC antizyme protein. This inactivates the ODC1 enzyme and triggers a conformational change that exposes a c-terminal 37 amino acid destabilization region. The ODC1 enzyme is then degraded by the proteasome in an ubiquitin-independent manner [13, 18].

All individuals with ODC1 disorder reported to date have truncating variants in the final exon of the ODC1 gene that abolish the protein's C-terminal 37-amino acid destabilization region [13, 18]. This is predicted to result in a mutant protein that escapes non-sense mediated decay and has reduced degradation compared to wild type, causing a gain-of-function of ODC1 enzyme activity. This is supported by the biochemical findings in the reported affected individuals [13, 18].

There is a transgenic mouse model that possesses a C-terminal deletion in ODC1 that confers decreased ODC1 degradation and increased ODC1 enzyme activity – the same genetic mechanism that is seen in the reported human cases. The mice develop alopecia, dermal follicular cysts, progressive skin wrinkling, and a high rate of spontaneous skin tumors [13, 18]. The mice do not display any known neurological manifestations in distinction to the human disease. Interestingly, treating the mice with oral difluoromethylornithine (DFMO) prevents hair loss and/or regrows hair [13, 18].

The pathophysiology of the ODC1 disorder in humans has yet to be fully elucidated. It is likely that chronically elevated putrescine has a toxic effect and may directly cause the alopecia, as recapitulated in the mouse model [13, 18]. As a growth factor, it may also cause the observed macrocephaly [13]. It is yet to be determined what other downstream metabolic and neuromodulatory pathways may be perturbed [13]. Putrescine is a precursor for the synthesis of GABA and may also play a role in modulating the NMDA receptor [13]. It is also conceivable that there is increased oxidative stress, as is seen in Snyder-Robinson syndrome.

The optimal management of ODC1 disorder is yet to be determined. Further, based on currently available data, there is no evidence for any progression/deterioration of symptoms, and so even if metabolic treatment is available, it is not clear how this may affect disease outcome. In terms of possible targeted therapies, the medication DFMO has been considered [13, 18]. DFMO is a synthetic ODC1 inhibitor. It is FDA-approved for treating African trypanosomiasis and as a topical treatment for hirsutism.

Further, ongoing clinical trials are investigating its use in colon cancer and neuroblastoma [13]. It is a generally well-tolerated medication, with possible side effects including myelosuppression, seizures, and hearing loss [13]. One group recently treated fibroblasts of a patient with ODC1 gene disorder with DFMO [19]. DFMO reduced ODC activity and putrescine to control levels without adversely affecting cell morphology or viability [19]. The *in vivo* effects of DFMO in individuals with ODC1 gene disorder are yet to be studied.

Additional potential therapies requiring further investigation include natural ODC1 inhibitors, such as the arginine metabolite agmatine or turmeric/curcumin [13]. Intermittent courses of an antibiotic (e.g., metronidazole) aimed at decreasing putrescine production by GI flora, a putrescine-restricted diet (low in dairy/cheese), or antioxidants are other possibilities that require further investigation [13].

Another unanswered question concerning the ODC1 disorder is the role for cancer surveillance, particularly for skin cancers, given the findings in the murine model. At this time, it is reasonable to advocate for skin sun protection and frequent skin checks [13].

## Conclusion

There are both genetic and acquired disorders of folate metabolism. Isolated folate deficiency in the CNS is termed cerebral folate deficiency. MTHFS deficiency is a recently described form of cerebral folate deficiency associated with neurodevelopmental abnormalities, epilepsy, spasticity, short stature, mi-

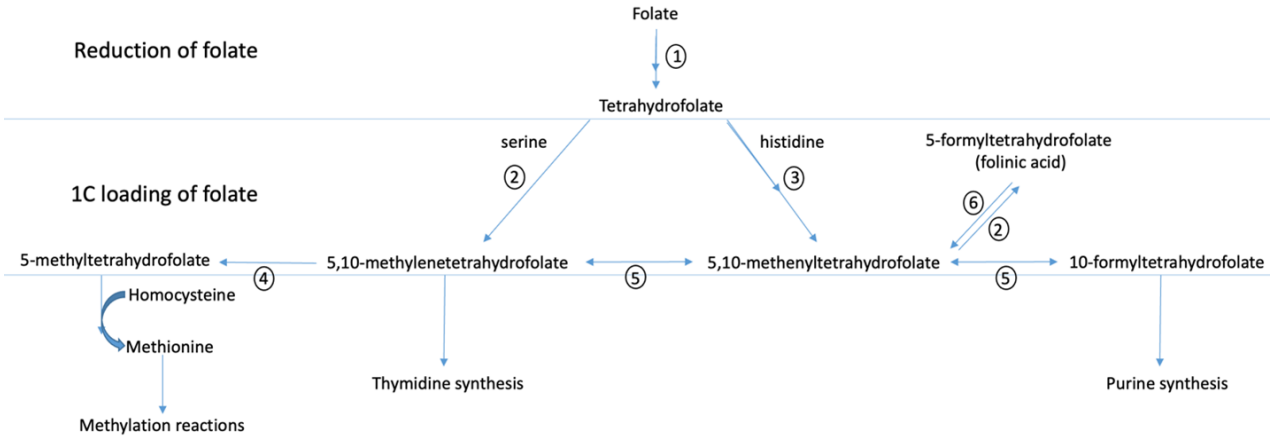


**Figure 1.** Folate metabolic pathway.
Figure legend:
1. Dihydrofolate reductase
2. Serine hydroxymethyltransferase
3. Glutamate formiminotransferase-cyclodeaminase deficiency
4. 5,10-methylenetetrahydrofolate reductase
5. Methylenetetrahydrofolate dehydrogenase 1
6. 5,10-methenyltetrahydrofolate synthetase deficiency

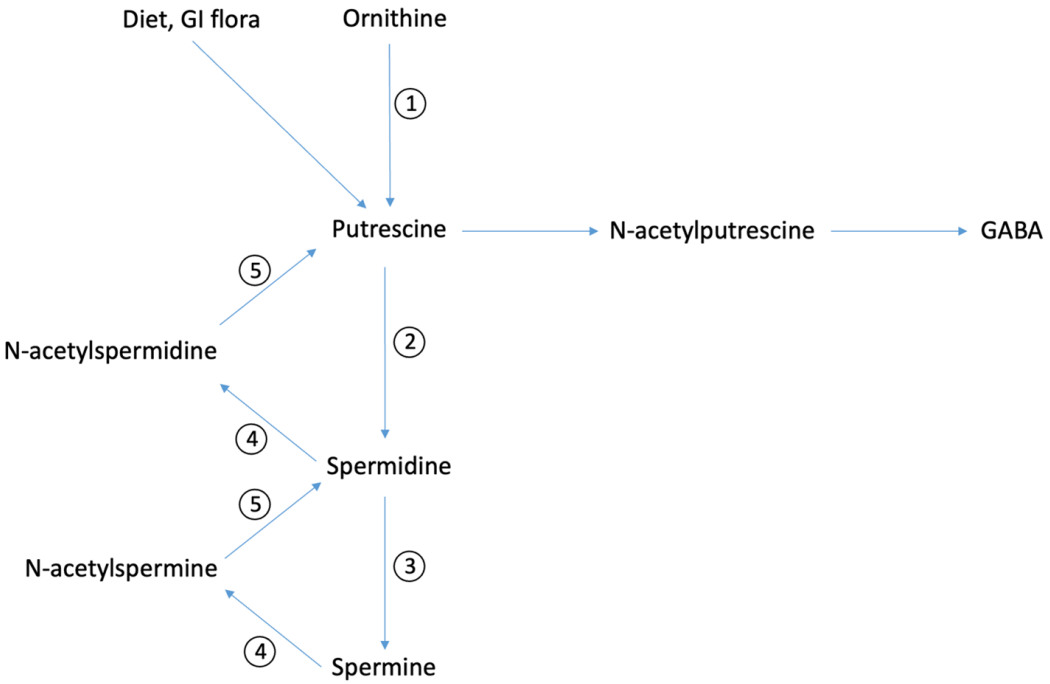


**Figure 2.** Polyamine metabolic pathway.
Figure legend:
1) Ornithine decarboxylase 1
2) Spermidine synthase
3) Spermine synthase
4) Acetyl-CoA:spermidine/spermine N-acetyltransferase
5) Polyamine oxidase

crocephaly, cerebral hypomyelination with cerebellar atrophy. Standard treatment of cerebral folate deficiency is with folinic acid, but 5-methyltetrahydrofolate appears to be the treatment of choice for MTHFS deficiency and may be preferable in severe MTHFR deficiency. There are two inborn errors of polyamine metabolism in humans described to date, including Snyder-

Robinson syndrome and *ODC1* disorder. *ODC1* disorder is associated with a recognizable phenotype, including neurodevelopmental and behavioral abnormalities, macrocephaly, alopecia, craniofacial dysmorphisms, and MRI abnormalities. It is yet to be determined if there is an effective targeted treatment for *ODC1* disorder (e.g., DFMO).

## Competing interests

The author declares that they have no competing interests.

## Author contributions

Lance Rodan has conceived, designed, drafted and revised the manuscript critically for important intellectual content, and have given final approval for the version to be published.



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