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Ethylmalonic Encephalopathy

Synonym: ETHE1 Deficiency

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Summary

Clinical characteristics

Ethylmalonic encephalopathy (EE) is a severe, early-onset, progressive disorder characterized by developmental delay / mild-to-severe intellectual disability; generalized infantile hypotonia that evolves into hypertonia, spasticity, and (in some instances) dystonia; generalized tonic-clonic seizures; and generalized microvascular damage (diffuse and spontaneous relapsing petechial purpura, hemorrhagic suffusions of mucosal surfaces, and chronic hemorrhagic diarrhea). Infants sometimes have frequent vomiting and loss of social interaction. Speech is delayed and in some instances absent. Swallowing difficulties and failure to thrive are common. Children may be unable to walk without support and may be wheelchair bound. Neurologic deterioration accelerates following intercurrent infectious illness, and the majority of children die in the first decade.

Diagnosis/testing

The diagnosis of EE is suggested by clinical findings and the laboratory findings of increased blood lactate levels, C4- and C5-acylcarnitine esters, plasma thiosulphate, and urinary ethylmalonic acid.

The diagnosis is established by identification of biallelic pathogenic variants in *ETHE1* on molecular genetic testing.

Management

Treatment of manifestations: Multi-specialty care that includes child neurology, pediatrics, clinical genetics, nutrition, gastroenterology, pain management, and physical therapy can help with timely detection and treatment of the multiorgan dysfunction that characterizes EE. Treatment is primarily supportive including antispastic medications, muscle relaxants, and anti-seizure medication (ASM). Physical therapy early in the disease course can help prevent contractures. For severe diarrhea, it is important to maintain hydration and caloric intake. Tube feeding is often necessary.

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Prevention of secondary complications: Prevention of infections that could be fatal.

Surveillance: Recommendations based on individual patient findings can include: monitoring of feeding and electrolyte status particularly in those with severe diarrhea; monitoring of seizures and response to ASM.

Genetic counseling

EE is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. No individuals diagnosed with EE have been known to reproduce. Once the *ETHE1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Ethylmalonic encephalopathy (EE) **should be suspected** in an individual with the following clinical findings, preliminary laboratory findings, and brain MRI findings [Dionisi-Vici et al 2016].

Clinical findings

- Global neurologic impairment
  - Early-onset progressive psychomotor regression
  - Seizures
  - Dystonia
- Diffuse microvasculature injury
  - Petechiae and/or purpura
  - Orthostatic acrocyanosis
  - Hemorrhagic suffusions of mucosal surfaces
  - Chronic hemorrhagic diarrhea

Preliminary laboratory findings

- Increased blood lactate levels (normal range: 6-22 mg/dL)
- Increased blood C4-acylcarnitine esters (normal range: <0.9 µmol/L) [Merinero et al 2006, Zafeiriou et al 2007] *
- Increased blood C5-acylcarnitine esters (normal range: <0.3 µmol/L) [Merinero et al 2006, Zafeiriou et al 2007] *
- Increased plasma thiosulphate (normal range: <4 µmol/L)
- Increased urinary ethylmalonic acid (normal range: <10 µmol/mmol creatinine) evaluated on spot urine [Merinero et al 2006, Zafeiriou et al 2007]

* More data are needed to define the range of C4/C5 acylcarnitine elevation in individuals with molecularly proven EE.

Newborn screening (NBS). Tandem mass spectroscopy can identify C4 elevation in a NBS dried blood spot; however, NBS for EE is not available in the US as there is no definitive treatment (see Therapies Under Investigation). Note: (1) NBS may be performed elsewhere in the world. (2) C4 elevation can also be found in primary short-chain acyl-CoA dehydrogenase (SCAD) deficiency [McHugh et al 2011]; an algorithm (pdf) from the American College of Medical Genetics can be used to distinguish the two disorders.

Brain MRI

- Symmetric patchy T_2-weighted signals in the basal ganglia, periventricular white matter and dentate nuclei, brain stem, and cerebellar white matter. In some instances, cortical atrophy and diffuse leukoencephalopathy are present.
- Atypical neuroradiologic patterns were also reported [Grosso et al 2002, Heberle et al 2006].

Establishing the Diagnosis

The diagnosis of ethylmalonic encephalopathy **is established** in a proband with suggestive clinical and laboratory findings and biallelic pathogenic variants in *ETHE1* identified on molecular genetic testing (see Table 1).

Single-gene testing is the molecular genetic testing approach indicated. Sequence analysis of *ETHE1* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

Table 1. Molecular Genetic Testing Used in Ethylmalonic Encephalopathy

Gene [1]	Method	Proportion of Pathogenic Variants [2] in Probands Detectable by Method
ETHE1	Sequence analysis [3]	67/86 [4]
	Gene-targeted deletion/duplication analysis [5]	19/86 [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Tiranti et al [2006], Mineri et al [2008]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Deletion of exon 4 and deletion of exons 1 to 7 have been detected frequently [Tiranti et al 2006, Mineri et al 2008].

Clinical Characteristics

Clinical Description

Ethylmalonic encephalopathy (EE) is a severe, early-onset, progressive disorder, typically characterized by the following major manifestations: developmental delay, progressive neurologic involvement, seizures, and vascular damage. Findings usually appear in the first years of life, in some instances during metabolic stress such as infection or fever. Affected infants typically have severe neck, trunk, and limb hypotonia and loss of head control, sometimes associated with frequent vomiting and loss of social interaction. In addition, chronic diarrhea and failure to thrive are common.

Atypical findings have also been reported [Grosso et al 2002, Di Rocco et al 2006, Heberle et al 2006, Pigeon et al 2009].

Developmental delay, evident in early infancy, manifests later as intellectual disability that ranges from mild to severe. Speech difficulties are common; in some instances speech is absent.

Progressive neurologic involvement. Hypotonia evolves into spastic quadriparesis and eventually global neurologic impairment including pyramidal signs such as hypertonia and spasticity with increased deep tendon reflexes (in particular in the lower limbs) with paraparesis. Children may be unable to walk without support and in some instances are wheelchair bound. Difficulty in swallowing is common.

Dystonia, an extrapyramidal finding, generally involves the limbs and trunk.

Neurologic deterioration accelerates following intercurrent infectious illness, and the majority of patients die in the early years, although some are still alive in the second decade of life.

Generalized seizures. Generalized tonic-clonic seizures are characterized by spasms of the neck, trunk, and arms that could evolve into status epilepticus with decreased level of consciousness.

Microvasculature injury is common and is characterized by diffuse and spontaneous relapsing petechial purpura, especially in the trunk and associated with "cutis marmorata" of the extremities.

Distal orthostatic acrocyanosis with edema of the extremities is often visible.

Hemorrhagic suffusions of mucosal surfaces and chronic hemorrhagic diarrhea are common manifestations.

Individuals with Atypical Findings

Of two affected individuals reported by Grosso et al [2002], one had chronic very slow neuromotor deterioration, ataxia, and dysarthria, and the other had acute neonatal onset with severe neuromotor retardation, severe generalized hypotonia, and intractable seizures.

In one individual with a molecularly confirmed diagnosis, the clinical findings suggested a connective tissue disorder (vascular fragility, joint hyperextensibility, and delayed motor development with normal cognitive development); urinary excretion of ethylmalonic acid was not abnormally increased during intercritical phases [Di Rocco et al 2006].

One individual who had the typical findings of EE also had hydronephrosis, undescended testes, mild tricuspid regurgitation, and mild dilatation of the pulmonary artery [Heberle et al 2006].

Monochorial twins had severe axial hypotonia without petechiae, orthostatic acrocyanosis, or chronic diarrhea. Other clinical findings differed markedly: one twin had an episode of coma at age three years followed by spastic quadriparesis and loss of language; the other had pyramidal involvement (mainly limited to the lower extremities) and spoke two languages [Pigeon et al 2009].

MR spectroscopy showed a lactate peak in one patient [Grosso et al 2004].

Neuropathologic findings in the brain of an infant age nine months showed widespread luminal microthrombi, acute microhemorrhages, and focal perivascular hemosiderin-laden macrophages, the latter being consistent with previous bleeding. These findings were consistent with both acute and chronic ischemic damage and corresponded with abnormal signal intensity lesions observed on repeat MRI [Giordano et al 2012].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known to be associated with *ETHE1* biallelic pathogenic variants.

Prevalence

The prevalence of ethylmalonic encephalopathy is unknown. More than 80 individuals with features consistent with EE and a molecularly confirmed diagnosis have been reported [Tiranti et al 2004, Tiranti et al 2006, Mineri et al 2008].

To date, families with EE have been from (or could be traced to) different regions of the Mediterranean basin or the Arabian Peninsula; parental consanguinity is common.

Genetically Related (Allelic) Disorders

At present, no phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic *ETHE1* pathogenic variants.

Differential Diagnosis

Ethylmalonic acid is a dicarboxylic organic acid produced by the carboxylation of butyrate. Ethylmalonic encephalopathy (EE) should be included in the differential diagnosis of other forms of persistent ethylmalonic aciduria, including the following:

- Defects of beta-oxidation of fatty acids with similar clinical findings (e.g., vomiting, diarrhea, difficulty with feeding, and developmental delay) such as short-chain acyl-CoA dehydrogenase (SCAD) deficiency and 3-hydroxyacyl-CoA dehydrogenase (HADH) deficiency (OMIM 231530). Petechiae, purpura, and orthostatic acrocyanosis are specific to EE [Burlina et al 1994].
- Defects of the mitochondrial electron-transfer flavoprotein pathway or glutaric aciduria type II
- Some forms of respiratory chain deficiency

Of note, brain vascular lesions appear to be a specific neuropathologic feature of EE, not seen in other forms of ethylmalonic aciduria or in disorders caused by primary respiratory chain defects such as Leigh syndrome [Giordano et al 2012, Tiranti & Zeviani 2013].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ethylmalonic encephalopathy (EE), the recommended evaluations following diagnosis (if not performed as part of the evaluation that led to the diagnosis) are as summarized in Table 2.

Table 2. Recommended Evaluations Following Initial Diagnosis of Ethylmalonic Encephalopathy (EE)

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	Particularly if medications are being used to treat spasticity &/or extrapyramidal movement disorders (e.g., dystonia)
	Brain MRI	Indicated in any child w/EE w/seizures or spasticity who has not previously had a brain MRI
	EEG & video EEG	If seizures are suspected
Gastrointestinal	Feeding eval & nutrition assessment	Referral to appropriate feeding therapist &/or nutritionist as indicated
	Assessment for chronic diarrhea	Referral to gastroenterologist as needed
Musculoskeletal	Orthopedic eval	Referral to orthopedist as needed
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Multi-specialty care that includes child neurology, pediatrics, clinical genetics, nutrition, gastroenterology, orthopedic, pain management, and physical therapy can help with timely detection and treatment of the multiorgan dysfunction that characterizes ethylmalonic encephalopathy. Treatment is primarily supportive

including anti-spastic medications, muscle relaxants, and anti-seizure medication. Physical therapy early in the disease course can help prevent contractures.

Table 3. Treatment of Manifestations in Individuals with Ethylmalonic Encephalopathy

Manifestation/ Concern	Treatment	Considerations/ Other
Spasticity	Antispastic medications	
Dystonia	Muscle relaxants	
Contractures	Physical therapy	
Seizures	Anti-seizure medication	
Severe diarrhea	Maintain hydration & caloric intake	Tube feeding often necessary
Poor energy metabolism & oxidative stress	L-carnitine, riboflavin &/or coenzyme Q_{10} supplements (a cocktail of drugs generally used in mitochondrial disorders) & other vitamin therapies [1]	

1. Gorman et al [2016]

Off-label compassionate use of N-acetylcysteine (NAC) in combination with metronidazole may be considered as they are the only drugs known to slow disease progression and improve the metabolic abnormalities of EE [Viscomi et al 2010, Kılıç et al 2017].

- N-acetylcysteine (NAC), a cell-permeable precursor of glutathione, is abundant in mitochondria where it can act as one of the physiologic acceptors of the sulfur atom of hydrogen sulfide (H_2S), which has deficient clearance in persons with EE.
- Metronidazole is widely used to combat infections caused by anaerobic bacteria, and can reduce the sulfide-producing bacterial load in the large intestine.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies, and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures).
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function (e.g., feeding, grooming, dressing, writing).

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication) for individuals who have expressive language difficulties.

Prevention of Secondary Complications

All affected individuals should receive routine immunizations; as well as annual immunizations for influenza.

Physicians must pay particular attention to the prevention of infections that could be fatal.

Surveillance

Surveillance should be individualized based on symptoms and organs affected.

Table 4. Recommended Surveillance for Individuals with Ethylmalonic Encephalopathy

System/Concern	Evaluation/Action	Frequency
Growth	Assess growth & monitor for failure to thrive.	At each visit
Gastrointestinal	Monitor feeding & electrolyte status, particularly in those w/severe diarrhea.	
Neurologic	Monitor for epileptic crisis; modify therapy according to clinical presentation & EEG findings.	Routine

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

While clearance of circulating sulfide by a transplanted liver could be beneficial, to date only one instance of liver transplantation in EE has been reported [Dionisi-Vici et al 2016]. Although results were encouraging, follow up of this patient and experience with additional patients are necessary to determine therapeutic efficacy of liver

transplantation in EE and possible relevance for national or state-mandated newborn screening, particularly in populations with relatively high prevalence of pathogenic variants.

Possible future treatments include AAV-mediated gene therapy [Di Meo et al 2012] or liver transplantation [Dionisi-Vici et al 2016].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Ethylmalonic encephalopathy is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ETHE1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. No individuals diagnosed with ethylmalonic encephalopathy have been known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ETHE1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ETHE1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *ETHE1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**

  Ethylmalonic encephalopathy

- **Metabolic Support UK**

  United Kingdom

  Phone: 0845 241 2173

  metabolicsupportuk.org

- **Mitocon – Insieme per lo studio e la cura delle malattie mitocondriali Onlus**

  Mitocon is the reference association in Italy for patients suffering from mitochondrial diseases and their families and is the main link between patients and the scientific community.

  Italy

  Phone: 06 66991333/4

  Email: info@mitocon.it

  www.mitocon.it

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Ethylmalonic Encephalopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ETHE1	19q13.31	Persulfide dioxygenase ETHE1, mitochondrial	ETHE1 database	ETHE1	ETHE1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Ethylmalonic Encephalopathy (View All in OMIM)

602473	ENCEPHALOPATHY, ETHYLMALONIC; EE

Table B. continued from previous page.

608451	ETHE1 PERSULFIDE DIOXYGENASE; ETHE1

Gene structure. *ETHE1* comprises seven exons.

Pathogenic variants. To date several nonsense and missense pathogenic variants as well as single- and multiexon deletions have been described throughout the gene [Tiranti et al 2006, Mineri et al 2008, Tiranti & Zeviani 2013].

Deletion of exon 4 and deletion of the entire gene are the most frequent large deletions [Mineri et al 2008, Drousiotou et al 2011].

Table 5. Select *ETHE1* Pathogenic Variants

DNA Nucleotide Change (Alias)	Predicted Protein Change	Reference Sequences
c.-83_-79delCGCCC [1]	--	
	p.Met1Ile	NP_055112.2
	p.Gln12Ter	
	p.Ile23SerfsTer10	
	p.Tyr38Cys	
	p.Glu44ValfsTer62	
	p.Leu55Pro	
	p.Gln63Ter	
	p.Ala75SerfsTer32	
	p.Asn77IlefsTer68	
c.375+5G>A	--	NM_014297.3
c.406A>G	p.Thr136Ala	NM_014297.3 NP_055112.2
c.440_450del11	p.His147LeufsTer30	
c.455C>T	p.Thr152Ile	
c.482G>A	p.Cys161Tyr	
c.487C>G	p.Arg163Gly	
c.487C>T	p.Arg163Trp	
c.488G>A	p.Arg163Gln	
c.491C>A	p.Thr164Lys	
c.505+1G>T	--	NM_014297.3

Table 5. continued from previous page.

DNA Nucleotide Change (Alias)	Predicted Protein Change	Reference Sequences
c.554T>G	p.Leu185Arg	NM_014297.3 NP_055112.2
c.586G>A	p.Asp196Asn	
c.592dupC (592_593insC) [2]	p.His198fsProTer23	
c.604dupG (604_605insG) [2]	p.Val202GlyfsTer19	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. HGVS nomenclature: NG_008141.1:g.4985_4989delCGCCC, as c.-83_79delCGCCC is not encompassed in the RefSeq NM_014297.3.
2. Originally reported with designation that does not conform to current naming conventions

Normal gene product. ETHE1, a 30-kd polypeptide exclusively located in the mitochondrial matrix, is a homodimeric Fe-containing sulfur dioxygenase (SDO). It has a beta-lactamase domain that is involved in the catabolic oxidation of hydrogen sulfide (H_2S) to sulfate [Di Meo et al 2015].

Abnormal gene product. Impaired activity of ETHE1-SDO in ethylmalonic encephalopathy leads to the accumulation of H_2S in critical tissues (including colonic mucosa, liver, muscle, and brain) up to concentrations that inhibit short-chain acyl-CoA dehydrogenase (SCAD) and cytochrome *c* oxidase (COX) activities, thus inducing high plasma levels of C4- and C5-acylcarnitines, ethylmalonic acid, and lactate [Di Meo et al 2015].

Chapter Notes

Revision History

- 21 September 2017 (bp) Review posted live
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References

Literature Cited

Burlina AB, Dionisi-Vici C, Bennett MJ, Gibson KM, Servidei S, Bertini E, Hale DE, Schmidt-Sommerfeld E, Sabetta G, Zacchello F, et al. A new syndrome with ethylmalonic aciduria and normal fatty acid oxidation in fibroblasts. J Pediatr. 1994;124:79–86. PubMed PMID: 8283379.

Di Meo I, Auricchio A, Lamperti C, Burlina A, Viscomi C, Zeviani M. Effective AAV-mediated gene therapy in a mouse model of ethylmalonic encephalopathy. EMBO Mol Med. 2012;4:1008–14. PubMed PMID: 22903887.

Di Meo I, Lamperti C, Tiranti V. Mitochondrial diseases caused by toxic compound accumulation: from etiopathology to therapeutic approaches. EMBO Mol Med. 2015;7:1257–66. PubMed PMID: 26194912.

Dionisi-Vici C, Diodato D, Torre G, Picca S, Pariante R, Giuseppe Picardo S, Di Meo I, Rizzo C, Tiranti V, Zeviani M. De GoyetJde V. Liver transplant in ethylmalonic encephalopathy: a new treatment for an otherwise fatal disease. Brain. 2016;139:1045–51. PubMed PMID: 26917598.

Di Rocco M, Caruso U, Briem E, Rossi A, Allegri AE, Buzzi D, Tiranti V. A case of ethylmalonic encephalopathy with atypical clinical and biochemical presentation. Mol Genet Metab. 2006;89:395–7. PubMed PMID: 16828325.

Drousiotou A, DiMeo I, Mineri R, Georgiou T, Stylianidou G, Tiranti V. Ethylmalonic encephalopathy: application of improved biochemical and molecular diagnostic approaches. Clin Genet. 2011;79:385–90. PubMed PMID: 20528888.

Giordano C, Viscomi C, Orlandi M, Papoff P, Spalice A, Burlina A, Di Meo I, Tiranti V, Leuzzi V, d'Amati G, et al. Morphologic evidence of diffuse vascular damage in human and in the experimental model of ethylmalonic encephalopathy. J Inherit Metab Dis. 2012;35:451–8. PubMed PMID: 22020834.

Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, Suomalainen A, Thorburn DR, Zeviani M, Turnbull DM. Mitochondrial diseases. Nat Rev Dis Primers. 2016;2:16080. PubMed PMID: 27775730.

Grosso S, Mostardini R, Farnetani MA, Molinelli M, Berardi R, Dionisi-Vici C, Rizzo C, Morgese G, Balestri P. Ethylmalonic encephalopathy: further clinical and neuroradiological characterization. J Neurol. 2002;249:1446–50. PubMed PMID: 12382164.

Grosso S, Balestri P, Mostardini R, Federico A, De Stefano N. Brain mitochondrial impairment in ethylmalonic encephalopathy. J Neurol. 2004;251:755–6. PubMed PMID: 15311356.

Heberle LC, Al Tawari AA, Ramadan DG, Ibrahim JK. Ethylmalonic encephalopathy: report of two cases. Brain Dev. 2006;28:329–31. PubMed PMID: 16376514.

Kılıç M, Dedeoğlu Ö, Göçmen R, Kesici S, Yüksel D. Successful treatment of a patient with ethylmalonic encephalopathy by intravenous N-acetylcysteine. Metabolic Brain Disease. 2017;32:293–6. PubMed PMID: 27830356.

McHugh D, et al. Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: a worldwide collaborative project. Genet Med. 2011;13:230–54. PubMed PMID: 21325949.

Merinero B, Pérez-Cerdá C, Ruiz Sala P, Ferrer I, García MJ, Martínez Pardo M, Belanger-Quintana A, de la Mota JL, Martin-Hernández E, Vianey-Saban C, Bischoff C, Gregersen N, Ugarte M. Persistent increase of plasma butyryl/isobutyrylcarnitine concentrations as marker of SCAD defect and ethylmalonic encephalopathy. J Inherit Metab Dis. 2006;29:685. PubMed PMID: 16906473.

Mineri R, Rimoldi M, Burlina AB, Koskull S, Perletti C, Heese B, von Döbeln U, Mereghetti P, Di Meo I, Invernizzi F, Zeviani M, Uziel G, Tiranti V. Identification of new mutations in the ETHE1 gene in a cohort of 14 patients presenting with ethylmalonic encephalopathy. J Med Genet. 2008;45:473–8. PubMed PMID: 18593870.

Pigeon N, Campeau PM, Cyr D, Lemieux B, Clarke JT. Clinical heterogeneity in ethylmalonic encephalopathy. J Child Neurol. 2009;24:991–6. PubMed PMID: 19289697.

Tiranti V, Briem E, Lamantea E, Mineri R, Papaleo E, De Gioia L, Forlani F, Rinaldo P, Dickson P, Abu-Libdeh B, Cindro-Heberle L, Owaidha M, Jack RM, Christensen E, Burlina A, Zeviani M. ETHE1 mutations are specific to ethylmalonic encephalopathy. J Med Genet. 2006;43:340–6. PubMed PMID: 16183799.

Tiranti V, D'Adamo P, Briem E, Ferrari G, Mineri R, Lamantea E, et al. Ethylmalonic encephalopathy is caused by mutations in ETHE1, a gene encoding a mitochondrial matrix protein. Am J Hum Genet. 2004;74:239–52. PubMed PMID: 14732903.

Tiranti V, Zeviani M. Altered sulfide (H(2)S) metabolism in ethylmalonic encephalopathy. Cold Spring Harb Perspect Biol. 2013;5:a011437. PubMed PMID: 23284046.

Viscomi C, Burlina AB, Dweikat I, Savoiardo M, Lamperti C, Hildebrandt T, Tiranti V, Zeviani M. Combined treatment with oral metronidazole and N-ace-tylcysteine is effective in ethylmalonic encephalopathy. Nat Med. 2010;16:869–71. PubMed PMID: 20657580.

Zafeiriou DI, Augoustides-Savvopoulou P, Haas D, Smet J, Triantafyllou P, Vargiami E, Tamiolaki M, Gombakis N, van Coster R, Sewell AC, Vianey-Saban C, Gregersen N. Ethylmalonic encephalopathy: clinical and biochemical observations. Neuropediatrics. 2007;38:78–82. PubMed PMID: 17712735.

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