Treatable inborn errors of metabolism presenting as cerebral palsy mimics: Systematic literature review

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Supplementary Data

Table S1. Overview of all 50 treatable IEMs presenting as CP mimics identified through systematic literature review. The IEMs are grouped according to the biochemical phenotype as presented in standard textbooks, and alphabetically.

Biochemical category	Disease name	OMIM#	Gene(s)	Treatment	Effect	Level of Evidence	CP symptoms	CP mimic reference
Amnio acids	Hartnup disease	234500	*SLC6A19 (AR)*	High protein diet	stabilizing/ preventative treatment	IV	Dystonia	[30]
	Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome	238970	*SLC25A15 (AR)*	Dietary protein restriction, ornithine supplement, sodium benzoate, phenylacetate	stabilizing/ preventative treatment	IV	Spasticity	[31, 32]
	Late onset non-ketotic hyperglycinemia	605899	*AMT/GLDC/ GCSH (AR)*	Glycine restriction, +/- sodium benzoate, NMDA receptor antagonists, other neuromodulating agents	stabilizing/ preventative treatment	IV	Spastic diplegia	[33]
	Phenylketonuria (PKU)	261600	*PAH (AR)*	Dietary phenylalanine restriction +/- amino acid supplements (BH(4) supplement)	stabilizing/ preventative treatment	II	Spastic diplegia	[34, 35]
	PHGDH deficiency (Serine deficiency)	601815	*PHGDH (AR)*	L-serine & +/- glycine supplements	primary / targeting underlying pathophysiology	IV	Spastic diplegia/ tetraparesis	[36, 37]
Cerebral glucose transport	Blood brain-barrier glucose-transporter (GLUT1) defect	606777	*SLC2A1 (AR)*	Ketogenic diet	primary / targeting underlying pathophysiology	IV	Spasticity, dystonia, ataxia	[38]
Creatine	GAMT deficiency	612736	*GAMT (AR)*	Arginine restriction, creatine & ornithine supplements	primary / targeting underlying pathophysiology	IV	Movement disorder: extrapyramidal signs, athetosis, & ataxia	[39, 40]
Fatty acid oxidation	Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency	201450	*ACADM (AR)*	Sick day formula, L-carnitine, avoid fasting	stabilizing/preventative treatment	III	CP symptoms	[41]
	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	201470	*ACADS (AR)*	Sick day formula, L-carnitine	stabilizing/preventative treatment	III	Spastic diplegia	[42]

Biochemical category	Disease name	OMIM#	Gene(s)	Treatment	Effect	Level of Evidence	CP symptoms	CP mimic reference
Hyperhomo-cysteinemia	Homocystinuria due to Cystathionine -synthase deficiency	236200	*CBS (AR)*	Methionine restriction, +/- pyridoxine, +/- betaine	stabilizing/preventative treatment	III	Dystonia	[43, 44]
	MTHFR Deficiency	236250	MTHFR (AR)	Betaine supplements, +/- folate, carnitine, methionine supplements	stabilizing/preventative treatment	IV	Ataxic gait, hypotonia, extrapyramidal movements, upper motor neuron signs	[45]
Lysosomal	Fucosidosis	230000	*FUCA1 (AR)*	Haematopoietic stem cell transplant	stabilizing/preventative treatment	IV	Severe spasticity; spastic paresis, generalized dystonia	[46, 47]
	Krabbe disease	245200	*GALC (AR)*	Haematopoietic stem cell transplant	stabilizing/preventative treatment	III	Progressive spasticity	[48]
	Metachromatic leucodystrophy (MLD)	250100	*ARSA (AR)*	Haematopoietic stem cell transplant	stabilizing/preventative treatment	IV	Loss of all gross motor function measured by CP scale	[49]
	Neimann-Pick, type C	257220	*NPC1, NPC2*	Miglustat	stabilizing/preventative treatment	I	Axial hypotonia, spastic diparesis, dystonic posturing of the hands	[50]
Metals	Menkes Disease	309400	*ATP7A*	Copper histidine	stabilizing/preventative treatment	IV	Progressive spasticity, hypotonia	[51]
	Wilson Disease	277900	*ATP7B*	Zinc & tetrathiomolybdate; oxcarbazepine	stabilizing/preventative treatment	III	Neurological symptoms, dystonia	[52]

Biochemical category	Disease name	OMIM#	Gene(s)	Treatment	Effect	Level of Evidence	CP symptoms	CP mimic reference
Mitochondria	Coenzyme Q10 deficiency	607426	*COQ2, APTX, PDSS1, PDSS2, CABC1, COQ9 (most AR)*	CoQ supplements	primary / targeting underlying pathophysiology	IV	Spastic paresis; progressive ataxia and dystonia	[53, 54]
	MELAS	540000	*mtDNA 8993 (NARP)*	Arginine supplements	stabilizing/preventative treatment	IV	dx. CP	[55]
	Pyruvate dehydrogenase deficiency	312170, 245348	*PDHA1 (X-linked recessive), DLAT (AR), PDHX (AR)*	Ketogenic diet & thiamine	primary / targeting underlying pathophysiology	IV	Spastic quadriplegia; dystonia	[56, 57, 58]
Neurotransmission	Aromatic-L-amino-acid decarboxylase deficiency	608643	*DDC (AR)*	MAO inhibitors, B6, anti-cholinergics, dopa agonists)	primary / targeting underlying pathophysiology	IV	Limb dystonia, athetoid movement	[59, 60]
	DHPR deficiency (biopterin deficiency)	261630	*QDPR (AR)*	BH4,diet, amine replacement, folinic acid	primary / targeting underlying pathophysiology	IV	Ataxia, gait disorder, peripheral spasticity	[61]
	Dopamine transporter deficiency syndrome	126455	*SLC6A3*	Dopamine antagonist (Ropinirole)	primary / targeting underlying pathophysiology	IV	dx. CP	[62]
	GTPCH1-deficient dopa-responsive dystonia	233910	*GCH1 (AR)*	BH4, amine replacement	primary / targeting underlying pathophysiology	IV	dx. CP; spastic diplegia	[63, 64]
	PTPS deficiency (biopterin PTS PTSP deficiency	261640	*PTS (AR)*	BH4, diet, amine replacement	primary / targeting underlying pathophysiology	IV	Dystonia; spastic extremities; generalized dystonia, choreoathetoid arm movements & axial hypotonia	[65, 66, 67]

Biochemical category	Disease name	OMIM#	Gene(s)	Treatment	Effect	Level of Evidence	CP symptoms	CP mimic reference
Neurotransmission	Sepiapterin reductase deficiency	612716	*SPR (AR)*	Amine replacement	primary / targeting underlying pathophysiology	IV	Limb spasticity, dystonic signs; ‘‘hypotonic cerebral palsy’’; dystonia, axial hypotonia; misdx. CP	[68, 69, 70]
	Succinic semialdehyde dehydrogenase deficiency (SSADH)	271980	*ALDH5A1 (AR)*	Vigabatrin	stabilizing/preventative treatment	IV	Hypotonia, ataxia; gait clumsiness, dystonia	[71, 72]
	Tyrosine hydroxylase deficiency	605407	*TH (AR)*	L-dopa substitution	primary / targeting underlying pathophysiology	IV	Spastic paraplegia /tetraparesis	[73, 74]
	Vesicular monoamine transporter 2 (VMAT2)	193001	*SLC18A2*	Dopamine aginist	primary / targeting underlying pathophysiology	IV	Dystonia	[75]
Organic acids	-Ketothiolase deficiency	203750	*ACAT1 (AR)*	Avoid fasting, sickday management, protein restriction	stabilizing/preventative treatment	IV	Ataxia, diplegia, hypotonia	[76, 77]
	2-Methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency	300438	*HSD17B10 (X-linked)*	Avoid fasting, sick daymanagement, isoleucine restricted diet	stabilizing/preventative treatment	IV	Ataxia, dystonia, choreoathetosis, spastic di-/tetra-plegia, hypotonia	[78]
	3-Methylcrotonyl-CoA carboxylase (MCC) deficiency	210200; 210210	*MCC1/MCC2 (AR)*	Dietary protein restriction; carnitine, glycine, biotin supplements; avoid fasting; sick day management	stabilizing/preventative treatment	IV	dx. CP	[79]
	3-Methylglutaconic aciduria type 1	250950	*AUH (AR)*	Carnitine supplements, avoid fasting, sick day management	stabilizing/preventative treatment	IV	dx. CP	[80, 81]
	Ethylmalonic encephalopathy	602473	*ETHE1 (AR)*	N-acetylcysteine, oral metronidazol	stabilizing/preventative treatment	IV	CNS malformations, episodic ataxia; pyramidal tract signs	[82, 83]

Biochemical category	Disease name	OMIM#	Gene(s)	Treatment	Effect	Level of Evidence	CP symptoms	CP mimic reference
Organic acids	Glutaric aciduria type I (GA1) aka glutaryl-CoA dehydrogenase deficiency	231670	*GCDH (AR)*	Lysine restriction, carnitine supplements	stabilizing/preventative treatment	III	Generalized spasticity, dystonia with athethosis; dx. CP; dyskinesia, dystonic tetraparesis	[84, 85, 86, 87, 88, 89]
	Isovaleric acidemia	243500	*IVD (AR)*	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management	stabilizing/preventative treatment	III	Hypotonia, paresis	[90, 91]
	Multiple acyl-CoA-dehydrogenase deficiency (MADD) (aka Glutaric aciduria type II)	231680	*ETFA , ETFB, ETFDH (AR)*	Carnitine, riboflavin, -hydroxybutyrate supplements; sick day management	primary / targeting underlying pathophysiology	IV	Encephalopathy	[92]
	Maple syrup urine disease	248600	*DBT, BCKDHB, BCKDHA (AR)*	Dietary restriction, branched amino-acids, avoid fasting, (liver transplantation)	stabilizing/preventative treatment (liver tx= primary treatment)	IV	Spastic diplegic CP ; paroxysmal dystonia	[93, 94]
	Methylmalonic acidemia (mutase deficiency)	251000	*MUT (AR)*	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management	stabilizing/preventative treatment	III	Total body dystonia	[95]
	Lesch-Nyhan syndrome	300322	*HPRT1 (X-linked)*	Haematopoietic stem cell transplant	primary / targeting underlying pathophysiology	IV	dx. Athetotic/ dyskinetic CP; dystonia	[96, 97, 98, 99]
	Propionic acidemia	606054	*PCCA, PCCB (AR)*	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management	primary / targeting underlying pathophysiology	III	Dystonia, hypotonia	[100, 101]
Urea cycle	Argininemia	207800	*ARG1 (AR)*	Dietary protein restriction, arginine supplement, sodium benzoate, phenylbutyrate (Liver transplantation)	stabilizing/preventative treatment (liver tx= primary treatment)	III	Spastic diplegia, ataxia, dx. CP	[102, 103, 104, 105]
	Citrullinemia, type II	605814	*SLC25A13 (AR)*	Dietary protein restriction, arginine supplement, sodium benzoate, phenylbutyrate (Liver transplantation)	stabilizing/preventative treatment (liver tx= primary treatment)	III	dx. CP; spastic quadriplegia	[106]

Biochemical category	Disease name	OMIM#	Gene(s)	Treatment	Effect	Level of Evidence	CP symptoms	CP mimic reference
Urea cycle	Ornithine transcarbamylase deficiency	311250	*OTC (X-linked)*	Dietary protein restriction, citrulline supplements, sodium benzoate/ phenylbutyrate (Liver transplantation)	stabilizing/preventative treatment (liver tx= primary treatment)	III	Hemiplegia; ataxia	[107, 108]
Vitamins/ Co-factors	Biotinidase deficiency	253276 0	*BTD (AR)*	Biotin supplement	primary / targeting underlying pathophysiology	III	Spastic tetraparesis	[109]
	Biotin-thiamine-responsive basal ganglia disease	607483	SLC19A3 (AR)	Biotin supplement	primary / targeting underlying pathophysiology	IV	Ataxia, dystonia	[110, 111]
	Cerebral folate deficiency syndrome	613068	FOLR1 (AR)	Folinic acid	primary / targeting underlying pathophysiology	IV	spastic paraplegia	[112]
	Holocarboxylase synthetase deficiency	253270	HLCS (AR)	Biotin supplement	primary / targeting underlying pathophysiology	IV	dx. CP	[113]
	Molybdenum cofactor deficiency	252150	MOCS1, MOCS2, (AR)	Precursor Z/cPMP	primary / targeting underlying pathophysiology	IV	Spastic quadriplegia dx. CP	[114]
	Pyridoxamine 5'-phosphate oxidase deficiency	610090	PNPO (AR)	Pyridoxal 5'-phosphate	stabilizing/preventative treatment	IV	Spastic quadriplegia	[115, 116]

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