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The International Working Group on Neurotransmitter related Disorders (iNTD): A worldwide research project focused on primary and secondary neurotransmitter disorders

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ABSTRACT

Introduction: Neurotransmitters are chemical messengers that enable communication between the neurons in the synaptic cleft. Inborn errors of neurotransmitter biosynthesis, breakdown and transport are a group of very rare neurometabolic diseases resulting in neurological impairment at any age from newborn to adulthood.
Methods and results: The International Working Group on Neurotransmitter related Disorders (iNTD) is the first international network focusing on the study of primary and secondary neurotransmitter disorders. It was founded with the aim to foster exchange and improve knowledge in the field of these rare diseases. The newly established iNTD patient registry for neurotransmitter related diseases collects longitudinal data on the natural disease course, approach to diagnosis, therapeutic strategies, and quality of life of affected patients. The registry forms the evidence base for the development of consensus guidelines for patients with neurotransmitter related disorders.
Conclusion: The iNTD network and registry will improve knowledge and strengthen research capacities in the field of inborn neurotransmitter disorders. The evidence-based guidelines will facilitate standardized diagnostic procedures and treatment approaches.

Abbreviations: AADC, aromatic L-amino acid decarboxylase; AR/ADGTPCH, autosomal recessive/dominant GTP-cyclohydrolase deficiency; BH_4, tetrahydrobiopterin; DAT, dopamine transporter; DβH, dopamine β-hydroxylase; DHFR, dihydrofolate reductase deficiency; DHPR, dihydropteridine reductase; FOLR1, folate receptor alpha; GABA, gamma aminobutyric acid; MAOA, monoamine oxidase A; 5-MTHF, 5-methyltetrahydrofolate; NKH, nonketotic hyperglycinemia; NOS, nitric oxide synthase; PAH, phenylalanine hydroxylase; 3-PGDH, 3-phosphoglycerat dehydrogenase; 3-PGH, 3-phosphoglycerat dehydrogenase; PSAT, phosphoserine aminotransferase; 3-PSP, 3-phosphoserine phosphatase; PTPS, 6-pyruvoyl-tetrahydropterin synthase; SR, sepiapterin reductase; SSADH, succinic semialdehyde dehydrogenase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; VMAT, vesicular monoamine transporter.

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1. Introduction

Neurotransmitters are a group of chemical messengers that enable communication between the neurons in the synaptic cleft. With regard to chemical properties, neurotransmitters can be grouped into amino acids (including glutamate, glycine, serine and gamma aminobutyric acid), peptides, purines, and monoamines or biogenic amines (including acetylcholine, epinephrine, norepinephrine, dopamine and serotonin). Most neurotransmitters have either excitatory or inhibitory effects, but only a few can exert both depending upon the type of receptors that are present [13]. After biosynthesis neurotransmitters are stored within synaptic vesicles and secreted in response to the appropriate nerve impulse [13]. Peptides have higher molecular weight than biogenic amines and amino acids, and are produced and released by neurons through the regulated secretory route. Interestingly, many peptides exhibit neurotransmitter activity as well as possess hormonal function.

Inborn errors of neurotransmitter biosynthesis, breakdown or transport are a group of very rare neurometabolic diseases. The incidence of the combined neurotransmitter diseases can only be estimated, but so far around 1500 patients have been published worldwide [3,12,19,21,28]. Clinical symptoms can appear at any age from newborn to adulthood. In the following the different groups of neurotransmitter disorders and their main features are described:

Disorders of monoamines and tetrahydrobiopterin metabolism.

Tetrahydrobiopterin (BH_4) is known to be the natural cofactor for phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), and tryptophan hydroxylase (TPH) as well as all three isoforms of nitric oxide synthase (NOS) [27]. The BH_4 dependent enzymes TH and TPH are together with the aromatic amino acid decarboxylase (AADC) the key enzymes in the biosynthesis of the neurotransmitters dopamine and serotonin [1]. Accordingly, disorders of BH_4 metabolism result in deficiency of biogenic amines. In addition to enzyme deficiencies, two transporter defects are known to cause disorders of biogenic amine metabolism [16,23]. The relevant enzymes and transporters are listed in Table 1. The clinical presentation is determined by the type and severity of the underlying disorder [18] and ranges from intermittent focal dystonia and dystonia-parkinsonism to severe, lethal infantile encephalopathies. In adulthood these diseases may cause behavioral and mood disorders [11,20,25]. Patients with disorders of BH_4 metabolism can with two exceptions be identified by detection of hyperphenylalaninemia on newborn screening (PKU), thereby allowing early diagnosis and initiation of treatment in asymptomatic individuals.

Table 1
Overview on inborn errors of neurotransmitter metabolism included in the iNTD patient registry, including acronym and OMIM number (Online Mendelian Inheritance in Man).

Disease name	Acronym	*Gene name*	OMIM#
Aromatic L-amino acid decarboxylase deficiency	AADCD	*DDC*	#608643
Tyrosine hydroxylase deficiency	THD	*TH*	#191290
Dopamine β-hydroxylase deficiency	DβHD	*DβH*	#223360
Monoamine oxidase A deficiency	MOAAD	*MAO-A*	# 309850
Dopamine transporter deficiency	DATD	*SLC6A3*	#126455
Vesicular monoamine transporter deficiency	VMATD	*SLC18A2*	#193001
Autosomal recessive GTP-cyclohydrolase deficiency	ARGTPCHD	*GCH1*	#233910
Autosomal dominant GTP-cyclohydrolase deficiency	ADGTPCHD	*GCH1*	#600225
6-Pyruvoyl-tetrahydropterin synthase deficiency	PTPSD	*PTS*	#261640
Dihydropteridine reductase deficiency	DHPRD	*QDPR*	#261630
Sepiapterin reductase deficiency	SRD	*SPR*	#182125
Folate receptor alpha deficiency	FOLR1D	*FOLR1*	# 613068
Dihydrofolate reductase deficiency	DHFRD	*DHFR*	# 613839
3-Phosphoglycerat dehydrogenase deficiency	3-PGDHD	*PHGDH*	#606879
3-Phosphoserine phosphatase deficiency	3-PSPD	*PSPH*	#172480
Phosphoserine aminotransferase deficiency	PSATD	*PSAT1*	#610936
Nonketotic hyperglycinemia	NKH	*AMT* *GLDC* *GCSH*	*T#238310* *P#238300* *H#238330*
GABA-transaminase deficiency	GABATD	*ABAT*	#137150
Succinate semialdehyde dehydroxylase deficiency	SSADHD	*ALDH5A1*	#271980

1.1. Folates

Folates play an essential role in central one-carbon methyl transfer reactions, mediating several biological processes including synthesis of neurotransmitters. 5-MTHF is the widely distributed form in the bloodstream. The autosomal recessive inherited folate receptor alpha (FOLR1) deficiency leads to impaired transport of folate to the CNS resulting in psychomotor decline, progressive movement disturbance, white matter disease, and epilepsy [5,24]. Patients with dihydrofolate reductase deficiency (DHFR) present with megaloblastic anemia, cerebral folate deficiency and a variety of neurological manifestations, which respond at least partly to treatment with folinic acid [6].

1.2. Disorders of GABA metabolism

Two disorders of GABA catabolism are known: Succinic semialdehyde dehydrogenase (SSADH) and GABA-transaminase deficiency. Most patients with SSADH deficiency develop symptoms in the first 2 years of life and present with prominent deficits in expressive language, motor delay, hypotonia, non-progressive ataxia, epilepsy and neuropsychiatric symptoms [10,22]. Two families with GABA-transaminase deficiency have been reported displaying developmental delay and hypotonia in early childhood and severe expressive language impairment and obsessive-compulsive disorder in adolescence and adulthood as well as ataxia and hyporeflexia [14,26].

1.3. Disorders of serine metabolism

Defects of serine metabolism encompass phosphoglycerate dehydrogenase deficiency, phosphoserine aminotransferase deficiency, and 3-phosphoserine phosphatase deficiency. Patients with phosphoglycerate dehydrogenase or phosphoserine aminotransferase manifest with severe intellectual disability, spastic tetraparesis, severe microcephaly and epilepsy [8]. A deficiency of 3-phosphoserine phosphatase was identified in one patient with moderate intellectual disability who also had Williams's syndrome [15] and in another patient with intrauterine growth restriction, intellectual disability, childhood onset epilepsy, and borderline microcephaly who developed progressive lower extremity hypertonia, axonal neuropathy, and hand contractures in adulthood [4].

1.4. Disorders of glycine breakdown

A deficiency of the activity of the glycine cleavage enzyme system leads to nonketotic hyperglycinemia (NKH) due to an accumulation of glycine in tissues and the central nervous system. Based on the amount of residual activity resulting from the particular mutation, clinical presentation of NKH ranges from severe neonatal hypotonia, failure to thrive and burst suppression pattern on EEG in the severe form, to mild mental retardation, learning disabilities or even normal intelligence in the mild from [7,12].

All neurotransmitter related disorders are rare, and consequently, patients are scattered around the world and frequently do not have access to medical care at centers of expertise. Furthermore, evidence base of current diagnostic and therapeutic approaches is extremely limited and current diagnostic and treatment strategies vary enormously between centers, resulting in sub-optimal care for individual patients. It can be expected that these inequalities have a negative