

2.1 Introduction

This chapter will focus on primary disorders of serotonin and catecholamine (biogenic amine) metabolism and the defect affecting the glycine receptor (hyperekplexia). Secondary disorders of biogenic amine metabolism are described elsewhere (disorders 1.2, 1.3, 1.4, 1.5, 1.6, 21.4, 31.2).

■ Disorders of Serotonin and Catecholamine Metabolism

Described defects in biogenic amine metabolism include deficiencies of tyrosine hydroxylase (TH) (EC 1.14.16.2) [1, 2], aromatic L-amino acid decarboxylase (AADC) (EC 4.1.1.28) [3], dopamine β -hydroxylase (D β H) (EC 1.14.17.1) [4, 5] and monoamine oxidase (MAO) (EC 1.4.3.4). MAO deficiency has been described as an isolated defect of MAO-A [6] and as a deficiency of either MAO-A or MAO-B, or both, in association with Norrie disease [7]. Inheritance in all of these disorders is thought to be autosomal recessive.

There is clear biochemical and clinical heterogeneity between these conditions, but the small number of reported cases precludes an accurate ascertainment of intra-disease heterogeneity. Lack of TH leads to a specific deficit of the catecholamines (dopamine, norepinephrine and adrenaline). AADC is required for the synthesis of the catecholamines and serotonin. Lack of this enzyme therefore causes a global deficiency of all of these neurotransmitters as is found in the abnormalities of tetrahydrobiopterin metabolism (Chap. 1). The clinical symptoms are also similar, including developmental delay, central and peripheral hypotonia, temperature instability, chorea, ptosis and oculogyric crises. The two conditions are in general distinguishable as hyperphenylalaninemia is not present in AADC deficiency. However, certain forms of tetrahydrobiopterin deficiency also do not present with hyperphenylalaninemia.

Deficiency of D β H results in an inability to synthesize norepinephrine from dopamine. The disease has only been described in adults and the characteristic finding is a disabling orthostatic hypotension. Retrospective case histories have reported ptosis and episodic hypothermia, hypoglyce-

mia and hypotension in the neonatal period [8]. The disorder has never been recognized in infancy and it is possible, therefore, that many infants succumb to this disorder undiagnosed.

MAO-A and MAO-B are required for the catabolism of serotonin and the catecholamines.

A large kindred with a point mutation in the structural gene for MAO-A has been studied. The disease is X linked and affected males have borderline mental retardation and exhibit abnormal behavior, including disturbed regulation of impulsive aggression [6]. Five patients with X chromosomal deletions, including MAO-A and MAO-B as well as the Norrie disease gene, had severe mental retardation [7], whilst two brothers with a complex deletion involving the Norrie disease gene and part of the MAO-B structural gene but with an intact MAO-A gene had no psychiatric symptoms or mental retardation [9]. The involvement of deletions of the X chromosome in areas other than the structural genes for MAO-A and MAO-B make interpretation of the clinical data in these patients difficult and to date a specific defect affecting only MAO-B has not been described, therefore, only the MAO-A patient will be referred to in the following review.

These diseases are not detected via conventional screening methodology (i.e. organic acids, amino acids etc.), therefore diagnosis relies on the analysis of neurotransmitters and their metabolites in CSF, urine or plasma. In general, TH deficiency leads to low levels of catecholamines and their metabolites, AADC deficiency leads to decreased concentrations of catecholamines, serotonin and their metabolites. In AADC deficiency there is also an accumulation of neurotransmitter precursors, namely 5-hydroxytryptophan, levodopa and its methylated derivative, 3-O-methyldopa. D β H deficiency leads to decreased norepinephrine and an increase in dopamine, and MAO-A deficiency to an increase in the biogenic amines and their O-methylated catabolites, and to a decrease in concentration of their deaminated catabolites.

Therapy in the deficiencies of TH, AADC and D β H is aimed at correcting the neurotransmitter abnormalities. Bypassing the metabolic block using levodopa/carbidopa together with dopamine agonists has led to improvement in TH deficiency [10]. Monoamine oxidase inhibitors, in conjunction with dopamine agonists and vitamin B6 (cofactor for AADC) ameliorated symptoms in AADC deficiency [3] and dihydroxyphenylserine (DOPS – decarboxylated to form norepinephrine) has corrected the norepinephrine deficiency in D β H deficiency [8]. Currently a therapy for MAO-A deficiency has not been described.

■ Glycine Receptor Defects (Hyperekplexia)

Hyperekplexia (or familial startle disease) is characterized by extreme generalized stiffness after birth (stiff baby syndrome), exaggerated startle response, continuing hypertonia during infancy and a transient increase in tone following startle attacks [11]. In some families the disease is associated with spastic paraparesis. Many cases of hyperekplexia are caused by mutations in the α_1 subunit of the glycine receptor (GLRA1) gene [12]. There are likely also to be other causes as cases have been described where mutations in the GLRA1 gene have not been found [13]. The disease can be inherited in either an autosomal dominant or recessive manner.

As all biochemical testing is generally negative, diagnosis has to be initially made on clinical grounds. In the severe neonatal form of hyperekplexia, 'stiff baby syndrome' abrupt stimuli leads to a dramatic startle reflex followed by a sustained tonic spasm. Apnoea may occur leading to sudden infant death syndrome (SIDS). Hyperekplexia should be considered where there is hyperexcitability, episodes of muscle rigidity, apnoea, aspiration pneumonia or near miss SIDS. In later life, the mainstay in diagnosis is the observation of an episode following abrupt stimuli. An episode consists of startle, followed by hands dropping to the sides and unprotected falling. Consciousness is preserved (unless there is head trauma) and there is usually no evidence for EEG abnormality. Definitive diagnosis is accomplished by the finding of mutations in the GLRA1 gene. Treatment at all ages is with clonazepam.

2.2 Nomenclature

No.	Disorder-affected component	Tissue distribution	Chromosomal localisation	McKusick
2.1	Tyrosine hydroxylase deficiency	Brain, kidney	11p15.5	191290
2.2	Aromatic L-amino acid decarboxylase (AADC) deficiency	Brain, liver, kidney, peripheral neurons	7p12.1–p12.3	107930
2.3	Dopamine β -hydroxylase (D β H) deficiency	Brain, peripheral neurons	9q34	223360
2.4	Monoamine oxidase (MAO)-A deficiency	Ubiquitous	Xp11–p21 region	307850
2.5	Hyperekplexia, glycine receptor defect	Brain	5q33–q35	149400

2.3 Metabolic Pathway

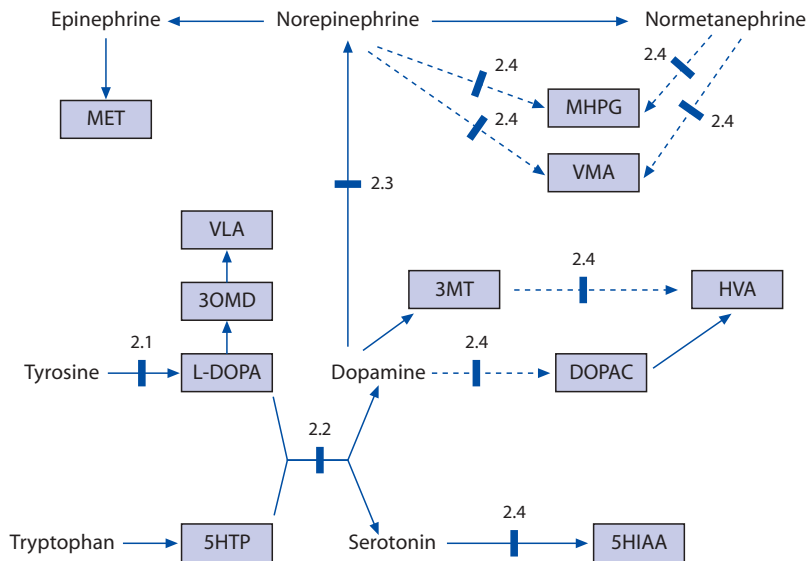


Fig. 2.1. Metabolism of serotonin and the catecholamines. 2.1=tyrosine hydroxylase; 2.2=aromatic L-amino acid decarboxylase; 2.3=dopamine β -hydroxylase; 2.4=monoamine oxidase. VLA=vanillactic acid; 3OMD=3-O-methyldopa; 5HTP=5-hydroxytryptophan; 5HIAA=5-hydroxyindoleacetic acid; DOPAC=dihydroxyphenylacetic acid; HVA=homovanillic acid; VMA=vanillylmandelic acid; MHPG=3-methoxy-4-hydroxyphenylglycol; MET=metanephrine; 3MT=3-methoxytyramine. - - > represents several steps involved. Pathological metabolites used as markers in the differential diagnosis are shown within boxes

2.4 Signs and Symptoms

Table 2.1. Tyrosine hydroxylase deficiency [10]

System	Symptoms/ markers	Neonatal	Infancy	Childhood
Characteristic clinical findings	Truncal hypotonia		+	+
	Chorea/athetosis		+	+
	Ptosis of eyelids		+	+
	Parkinsonian symptoms		+	+
	Tremor		+	+
	Hypokinesia		+	+
Routine laboratory	Glucose ↓	±	±	±
Special laboratory	MRI/CT		n or cerebral/ cortical atrophy	n or cerebral/ cortical atrophy
	Prolactin (P)		↑	↑
	Norepinephrine (U)		↓-n	↓-n
	Dopamine (U)		↓-n	↓-n
	VMA (U)		↓-n	↓-n
	HVA (U)		↓-n	↓-n
	HVA (CSF)		↓↓	↓↓
	MHPG (CSF)		↓↓	↓↓
	Oculogyric crises		±	±
	Ptosis		+	+
GI	Feeding difficulties		±	±
	Gastroesophageal reflux		±	±
	Hypersalivation		+	+
	Swallowing difficulties		±	±
CNS	Chorea/athetosis		±	±
	irritability		+	+
	MR/DD		±	±
	Truncal hypotonia		+	+
	Developmental delay		+	+
	Dystonia		±	±
	Tremor		±	±
	Hypokinesia		±	±
	Limb hypertonia		+	+
	Seizures		±	±
Temperature	Unstable		±	±
Dermatological	Excessive sweating		±	±

HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxy-phenylglycol; VMA, vanillylmandelic acid.

Table 2.2. Aromatic L-amino acid decarboxylase (AADC) deficiency [15]

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence
Characteristic clinical findings	Oculogyric crises		+	+	+
	Hypotonia	+	+	+	+
	Sweating		+	+	+
	Retardation		+	+	+
	Temperature instability	+	+		
	Chorea		+	+	+
Special laboratory	Ptosis of eyelids	+	+	+	+
	MRI/CAT		± cerebral atrophy		
	Prolactin		↑		
	Norepinephrine (P)		↓	↓	
	Epinephrine (P)		↓	↓	
	L-Dopa (P, U, CSF)		↑	↑	
	3OMD (P, U, CSF)		↑↑↑	↑↑↑	
	5HTP (P, U, CSF)		↑	↑	
	Serotonin (BL)		↓↓	↓↓	
	L-Dopa decarboxylase (P)		↓↓↓	↓↓↓	
	HVA (CSF)		↓↓↓	↓↓↓	
	5HIAA (CSF)		↓↓↓	↓↓↓	
	Organic acids (U)		↑		
	(vanillactic acid)				
Eye	Oculogyric crises		+	+	+
	Ptosis	+	+	+	+
	Miosis	+	+		
GI	Reverse Argyll Robertson pupil		±		
	Feeding difficulties	+	±	±	±
	Hypersalivation		+	+	+
CNS	Gastroesophageal reflux		±	±	±
	Chorea/athetosis		+	+	+
	Torticollis		±		
	Dystonia		±	±	±
	Irritability	+	+		
	MR		+	+	+
	Truncal hypotonia	+	+	+	+
Temperature	Limb hypertonia		+	+	+
	Developmental delay		+	+	+
	Unstable	+	+		
Dermatological	Pallor		+		
	Excess sweating		+	+	+
Other	Diurnal variation		±	±	±

3OMD, 3-O-methyldopa; 5HTP, 5-hydroxytryptophan; HVA, homovanillic acid; 5HIAA, 5-hydroxyindoleacetic acid.

Table 2.3. Dopamine β -hydroxylase (D β H) deficiency [5]

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Delay in opening eyes	±				
	Ptosis of eyelids	±	±	±	±	±
	Hypoglycemia	±	±			
	Hypothermia	±	±			
	Orthostatic hypotension				+	+
	Seizures ^a				+	+
Special ^b laboratory	Norepinephrine (P, U, CSF)				↓↓↓	↓↓↓
	Dopamine (P)				↑↑	↑↑
	Epinephrine (P)				↓↓	↓↓
	L-Dopa (P, CSF)				↑	↑
	3OMD (P)				↑-n	↑-n
	D β H (P) ^c				↓↓↓	↓↓↓
	HVA (U, CSF)				↑	↑
	MHPG (CSF)				↓	↓
	VMA (U)				↓	↓
					↓	↓
Eye	Ptosis	±	±	±	±	±
Cardiac	ECG				±	±
CNS	Hypotonia	±			±	±

^a When present, seizures have been secondary to hypotension and EEG has been normal.

^b Metabolite values have not been reported in children but a similar pattern is predicted.

^c Plasma D β H activity can be low to undetectable in normal individuals, therefore a low value is not diagnostic by itself. 3OMD, 3-*O*-methyldopa; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxy-phenylglycol; VMA, vanillylmandelic acid.

Table 2.4. Monoamine oxidase A (MAO-A) deficiency (one family)

System	Symptoms/markers	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Aggressive/violent behavior		+	+
	Mild mental retardation	+	+	+
	Stereotyped hand movements		±	±
Special laboratory	Normetanephrine (U)		↑↑	↑↑
	3-methoxytyramine (U)		↑↑	↑↑
	Serotonin (U)		↑↑	↑↑
	Tyramine (U)		↑↑	↑↑
	VMA (U)		↓	↓
	HVA (U)		↓	↓
	MHPG (U)		↓-n	↓-n
	5HIAA (U)		↓-n	↓-n
	MAO-B (PLT)		n	n
	MAO-A (FB)		↓↓	↓↓
CNS	MR/DD		±	±

VMA, Vanillylmandelic acid; HVA, Homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; 5HIAA, 5-hydroxyindoleacetic acid.

Table 2.5. Glycine receptor defect (hyperekplexia)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings CNS	Hypertonia	++	++	++	++	++
	Exaggerated startle response	++	++	++	++	++
	Nocturnal myoclonus	+	+	+	+	+
	Seizures	±	±	±	±	±
	Delayed motor development	+	+			
Other	Dislocation of the hips	±				
	'Insecure gait'			±	±	±
	Hernias	±	±	±	±	±

2.5 Reference Values

■ Enzyme Analyses

Age	Plasma l-dopa decarboxylase (pmol/min/ml)	Liver L-Dopa de-carboxylase (pmol/min/mg protein)	Fibroblast MAO-A (pmol/min/mg protein)	Plasma DβH (nmol/min/ml)
Fetal	–	720–2590	–	–
<3 y	36–129	125–695	–	–
Adult	24–43	–	10–350 ^a	0–100 ^b

^a After stimulation with dexamethasone [14].

^b Plasma dopamine-β-hydroxylase: Approximately 5% of the normal population have undetectable plasma DβH. The diagnosis of DβH deficiency, therefore, cannot be made solely on the basis of undetectable plasma DβH. On the other hand its presence rules out the diagnosis.

■ CSF Neurotransmitters and Metabolites (nmol/l) (HPLC, electrochemical (EC) or fluorescence (F) detection)

Age	3OMD (EC)	L-Dopa (F)	5HTP (F)	5HIAA (EC)	HVA (EC)	MHPG (EC)	NE (EC)	DA (EC)
<0.5 y	100–300	<25	<10	189–1380	324–1379	98–168		
0.5–1 y	<100	<25	<10	152–462	302–845	51–112		
1–2 y	<50	<25	<10	97–367	236–867	47–81		
2–5 y	<50	<25	<10	89–341	231–840	39–73		
5–10 y	<50	<25	<10	68–220	137–582	39–73		
10–16 y	<50	<25	<10	68–115	148–434	28–60		
Adult	<50	<25	<10	45–135	98–450	28–60	0.3–1.2	0–0.2

3OMD, 3-O-methyldopa; 5HTP, 5-hydroxytryptophan; 5HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; NE, norepinephrine; DA, dopamine.

■ Blood and Plasma Neurotransmitters and Metabolites (nmol/l)
(HPLC, Electrochemical (EC) or Fluorescence (F) Detection)

Age	3OMD (F)	L-Dopa (F)	5HTP (F)	NE ^a (EC)	DA ^a (EC)	Whole blood serotonin (F)
<3	<80	<25	<20	–		550–1780
Adult	<80	<25	<20	0.5–3.1	0–0.7	450–980

^a Plasma catecholamines: Age-specific lower limits of plasma norepinephrine and dopamine have not been determined. Plasma norepinephrine varies with posture, activity, volume status and dietary salt, but should be present in plasma even during resting conditions at concentrations of at least 0.3 nmol/l.

3OMD, 3-O-methyldopa; 5HTP, 5-hydroxytryptophan; NE, norepinephrine; DA, dopamine.

■ Urine Neurotransmitters and Metabolites (nmol/mmol Creatinine)
(HPLC, Electrochemical (EC) or Fluorescence (F) Detection)

Age (yrs)	3OMD ^a (F)	L-Dopa ^a (F)	5HTP ^a (F)	5HIAA ^a (F)	HVA ^a (F)	NE ^a (EC)	E ^a (EC)	DA ^a (EC)	NMN ^a (EC)	3MT ^a (EC)	VMA ^a (EC)	5HTa (F)	VLAa (EC)
<3	152–378			5500–7300	7000–8500	22–140	2.5–26	76–1350	5–143	45–480	500–2500	130–170	<150
Adult	90–225	12–42	<5	300–5100	1000–2800	10–53	2–11	60–225	55–200	60–145	800–2200	11–68	<80

^a Unconjugated.

3OMD, 3-O-methyldopa; 5HTP, 5-hydroxytryptophan; NE, norepinephrine; E, epinephrine; DA, dopamine; NMN, normetanephrine; 3MT, 3-methoxytyramine; VMA, vanillylmandelic acid; 5HT, serotonin; HVA, homovanillic acid; 5HIAA, 5-hydroxyindoleacetic acid; VLA, vanillactic acid.

2.6 Pathological Values/Differential Diagnosis

Condi- tion	3OMD (P) (U) & CSF	L-Dopa (P)(U) & CSF	5HTP (P)(U) & CSF	5HIAA (CSF)	HVA (CSF)	MHPG (U) & CSF	DO- PAC (P)(U)	NE (P)(U)	E (P)(U)	DA (P)(U)	NMN (U)	3MT (U)	VMA (U)	5HT (BL)	VLA (U)
2.1 TH	n			n	↓↓	↓↓				↓-n			↓-n		
2.2 AADC	↑↑↑	↑↑	↑↑	↓↓	↓↓ (CSF) ↑(U)		↑(U)	↓↓↓	↓	↑-n (U)		↑(U)		↓↓	↑
2.3 DβH	↑-n	↑(P) (CSF)			↑(U)	↓↓	↑↑(P)	↓↓↓	↓	↑↑↑			↓		
2.4 MAO-A				↓-n (U)	↓-n(U)					↑↑	↑↑	↓-n	↑(U)		

It is likely that the disease-specific patterns are found in CSF, plasma and urine, but in many cases the levels of metabolites have not been measured in each compartment.

2.7 Loading Tests

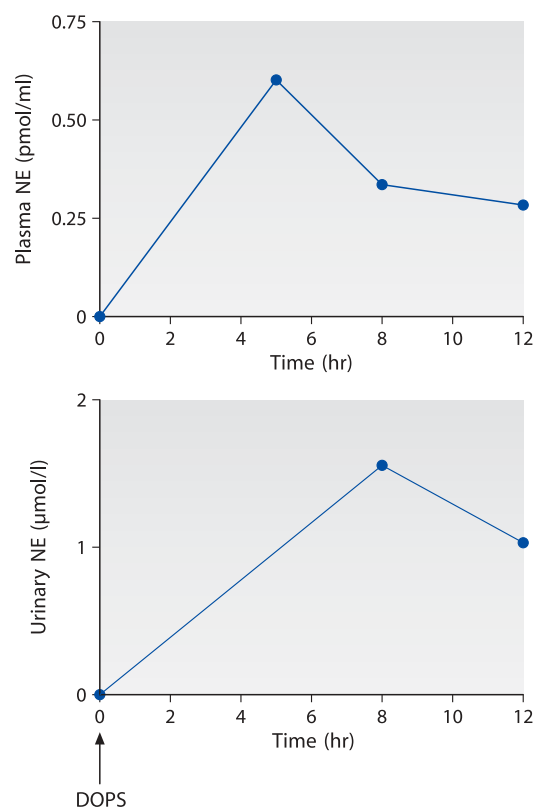


Fig. 2.2. The effect of oral dihydroxyphenylserine (*d,l*-DOPS – 4 mg/kg) on plasma and urinary norepinephrine (NE) in an adult $D\beta H$ -deficient patient

2.8 Diagnostic Flow-Chart

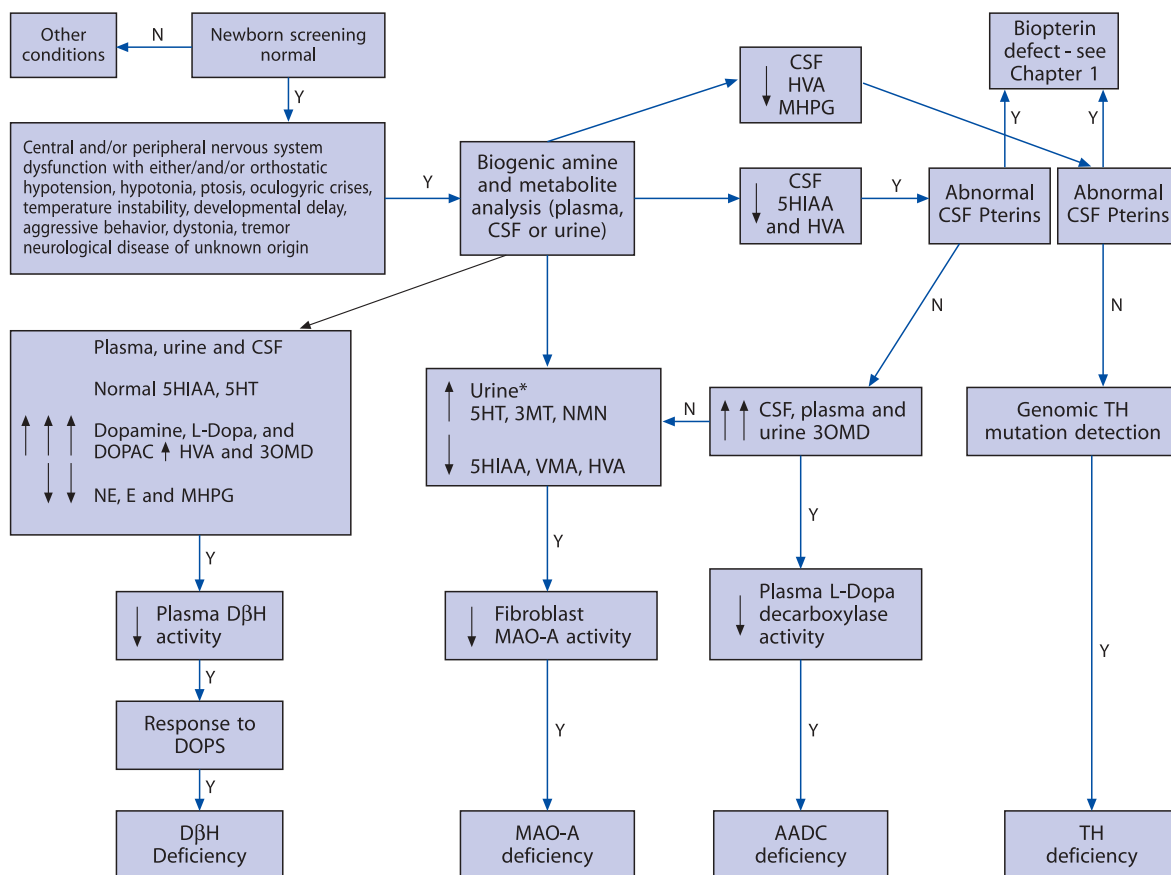


Fig. 2.3. Diagnostic flow-chart in the differentiation of defects of biogenic amine neurotransmitter metabolism. The correct differential diagnosis depends on the pattern of amines and their metabolites in either urine, CSF or plasma. ↑ represents increased values, ↓ represents lowered values. 5HIAA: 5-hydroxyindoleacetic acid; HVA: homovanillic acid; 5HT: serotonin; 3OMD: 3-*O*-methyldopa; DOPAC: dihydroxyphenylacetic acid; 3MT: 3-methoxytyramine; NMN: normetanephrine; VMA: vanillylmandelic acid; DOPS: dihydroxyphenylserine; MHPG: 3-methoxy-4-hydroxyphenylglycol; Y: yes; N: no. * Plasma and CSF levels have not been analysed but they probably reflect those seen in urine. For interpretation of quantitative results see pathological values.

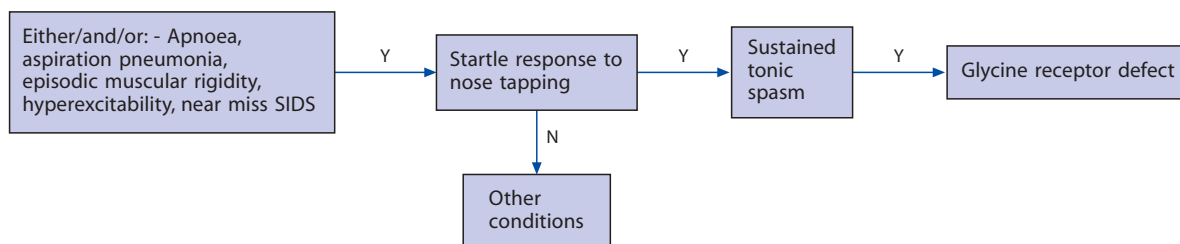
The full spectrum of the clinical signs of TH, AADC, DβH and MAO-A deficiency in the neonatal and infant periods are unknown. It is likely, therefore, that many cases are not recognised. Analysis of biogenic amine metabolites in CSF from neonates and infants with neurological disease of unknown origin would likely be informative if these diseases are present. Levels of HVA and MHPG are decreased in TH deficiency, HVA and 5HIAA are greatly decreased in AADC deficiency. It is expected that CSF HVA and 5HIAA will also be decreased in MAO-A deficiency, with normal 5HIAA

and increased HVA in D β H deficiency. However, CSF values in MAO-A deficiency and D β H deficiency have not been reported.

If CSF is not available, highly elevated plasma and urine levels of 3OMD point to AADC deficiency. More modest elevations are found in D β H deficiency. Measurement of plasma dopamine and norepinephrine will distinguish between these two conditions.

Studies on MAO-A deficiency are limited to one family and only urine has been analysed. It is probable that elevated whole blood serotonin and plasma catecholamines would also point to this condition.

Neonatal/infantile hyperekplexia



Post infantile hyperekplexia

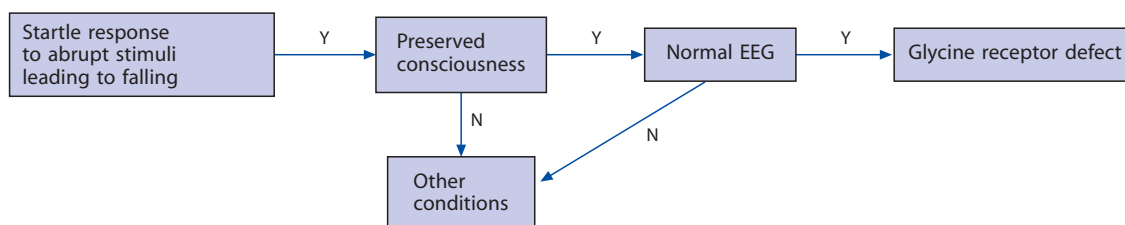


Fig. 2.4. Diagnostic flow-chart for the differential diagnosis of glycine receptor defects. No biochemical tests are available. Differential diagnosis therefore relies on clinical signs and symptoms. SIDS: sudden infant death syndrome

2.9 Specimen-Collection

Test	Preconditions	Material	Handling	Pitfalls
5HIAA, 3OMD, L-Dopa HVA, MHPG L-Dopa decarboxylase	Before medication	CSF Plasma Liver (for prenatal diagnosis)	First 0.5 ml drawn, store at -70°C 1 ml, heparin tube, store at -70°C Snap frozen, store at -70°C	Unstable in blood contaminated samples
5HT, 3MT, 3OMD, NMN, 5HIAA, VMA, HVA, DA, E, MHPG, NE 5HT	Diet free of biogenic amine-containing foodstuffs	urine whole blood	24 h urine collected into 6 M HCl, store at -20°C 2 ml, EDTA tubes containing 6 mg ascorbic acid store at -20°C	Many foods, e.g. bananas, dates, contain biogenic amines and metabolites
D β H		plasma	1 ml, heparin tube, store at -70°C	
MAO-A Catecholamines, and metabolites		fibroblast plasma	Room temp. 1 ml, in EDTA tube, store at -70°C	
Vanillic acid		random urine	10 ml, store at -20°C	

2.10 Prenatal Diagnosis

Disorder	Material	Timing-trimester
2.1	CCVS (if mutations are known)	I
2.2	CCVS (if mutations are known), liver for enzyme analysis	I II

2.11 DNA Analysis

Disorder	Tissue	Methodology
2.1	Genomic DNA	PCR/RFLP/SSCP/sequencing
2.2	Genomic DNA	PCR/RFLP/sequencing
2.4	Cultured fibroblasts	PCR/sequencing
2.5	Genomic DNA	PCR/sequencing

PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSCP, single-strand conformation polymorphism

2.12 Initial Treatment (Management While Awaiting Results)

■ General Intervention

Supportive.

■ Specific Intervention

● *Control of Hypoglycemia in TH Deficiency*

D β H deficiency in the neonatal and infant period would probably require correction of hypoglycemia.

In the first year of life in hyperekplexia there is risk of death from apnoea and aspiration pneumonia.

2.13 Summary/Comments

The primary disorders of serotonin and catecholamine metabolism have only recently been recognized and full details of the early clinical picture remain uncertain. Disorders of D β H and MAO-A have been recognized in later life and it is unclear whether these represent the 'worst case scenario' or whether they are mild forms of the disease. Unfortunately none of these conditions can be detected using normal screening procedures (organic acids, amino acids etc.), although an increase in urinary vanillic acid may point to AADC deficiency. A systematic investigation of biogenic amine metabolism in neonates and infants with non-specific neurological disease of unknown origin is therefore required to allow the true incidence of these abnormalities to be established. Recognition of more cases at an earlier age would allow a clear picture of the clinical features to be established. Such recognition is important as all the data to date suggests that the neurological features associated with TH, AADC and D β H deficiencies can be ameliorated with treatment.

Hyperekplexia relates to an abnormal startle response due to dominant or recessive inheritance of glycine receptor mutations. Recognition in early life is important due to the possibility of death following apnoea or aspiration pneumonia. Although so far all molecular confirmations have involved mutations in the gene for the ligand binding α_1 subunit of the glycine receptor, it is highly likely that mutations in the structural β subunits may also be disease causing as a mouse mutant with mutations in this subunit has a phenotype that resembles hyperekplexia [15].

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