Dopa-responsive dystonia

HANS RANDBY

Department of Paediatric Medicine, Vestfold Hospital Trust
He contributed to the study concept and design, article searches and review/reading, and to the preparation and drafting of the manuscript.
Hans Randby, senior consultant.
The author has completed the ICMJE form and reports no conflicts of interest.

CATHRIN LYTOMT SALVADOR

Department of Medical Biochemistry
Oslo University Hospital
She contributed to the review of selected articles, proposed references, and helped with the design and drafting of the manuscript.
Cathrin Lytomt Salvador, senior consultant and PhD candidate.
The author has completed the ICMJE form and reports no conflicts of interest.

MARI OPPEBØEN

Division of Paediatric and Adolescent Medicine
Oslo University Hospital
She contributed to the review of selected articles, proposed references, and helped with the design and drafting of the manuscript.
Mari Oppebøen, specialty registrar in paediatric medicine with a particular interest in neurotransmitter disorders.
The author has completed the ICMJE form and reports no conflicts of interest.

INGER MARIE SKOGSEID

Department of Neurology
Oslo University Hospital
She contributed to the review of selected articles, proposed references, and helped with the design and drafting of the manuscript.
Inger Marie Skogseid, PhD, researcher and senior consultant.
The author has completed the ICMJE form and reports the following conflicts of interest: She has received lecture fees from Medtronic and Desitin/Merz Pharma for lectures at scientific meetings.

JEANETTE KOHT

E-mail: jeanette.koht@medisin.uio.no
Department of Neurology
Drammen Hospital
Vestre Viken Health Trust
and
Institute of Clinical Medicine
University of Oslo
She contributed to the study concept and design, article searches and review/reading, and to the preparation and drafting of the manuscript.
Jeanette Koht, PhD, senior consultant and associate professor.
The author has completed the ICMJE form and reports no conflicts of interest.

BACKGROUND

Dopa-response dystonia is the collective term for a group of highly treatable disorders that are characterised by altered neurotransmitter levels. Increased insight into the underlying pathophysiology has improved understanding of these disorders.

METHOD

This article is based on 39 articles identified through a systematic search of the Medline database, two websites and a textbook.

RESULTS

Dopa-responsive dystonia usually has onset in childhood or adolescence and gives rise to motor, cognitive, psychiatric and/or autonomic symptoms and findings. These may be non-specific and are easily misinterpreted as reflecting other neurological disorders. Dopa-responsive dystonia is caused by monogenic mutations and shows autosomal recessive or dominant inheritance. Pathogenic variants have been identified in three genes: *guanosine triphosphate (GTP) cyclohydrolase 1*, *sepiapterin reductase* and *tyrosine hydroxylase*. The pathogenic variants lead to enzyme deficiencies and give rise to early-onset dystonia, which responds well to levodopa. A precise diagnosis is made by determining levels of pterins, biogenic monoamines and their metabolites in the cerebrospinal fluid, and by genetic testing.

INTERPRETATION

Current knowledge is based on case reports and small patient datasets, which show that this patient population benefits greatly from levodopa. Diagnosis has become easier in recent years due to modern biochemical and molecular genetic analyses. The current scientific literature gives reason to believe that there may be undiagnosed patients in Norway with dopa-responsive dystonia.

Dystonia is a movement disorder characterised by persistent and intermittent muscle contractions that cause involuntary repetitive movements, and that can lead to abnormal posture in affected parts of the body (1). Classic dopa-responsive dystonia typically begins in childhood or adolescence, most often with walking difficulties. Symptoms worsen towards the evening and improve in the morning after sleep, and show a highly positive and sustained response to levodopa (2–4).

The aim of this article is to provide general practitioners, neurologists, paediatricians and other interested parties with a basic knowledge of this diagnostic group, with an emphasis on clinical aspects.

Method

We searched the Ovid database (Medline) for the period 1 January 1946–2 December 2016 with the following search strings: ((dopa* or levodopa* or hereditary) adj3 (respon* or progressive*) adj (parkinson* or dystoni* or extrapyramid*)).tw or (segawa* adj5 (disease or dystoni* or syndrome)).tw or (dystoni* and ((infantile or juvenile or young)) adj2 parkinson*).mp or (GTP adj (Cyclohydrolase or CH) adj3 deficien*).tw or (sepiapterin reductase adj3 deficien*).mp or sr deficien*.mp or (tyrosine hydroxylase adj3 deficien*).mp.

We included only those articles that were written in English or a Scandinavian language and that related to humans.

The database search yielded 812 hits, and we identified an additional four references from our own archive. A total of 747 articles were excluded on the basis of the title and abstract or

because they were duplicates, while 65 publications were considered in full text. Only original articles describing two or more patients, and describing diagnosis and treatment, were included. We also included all individual case reports based on Norwegian patients. Older review articles that had been superseded by newer reviews were excluded. A total of 39 articles were included in the current review, one of which was a review article from our own literature archive (5). A textbook (6) and the websites 'Gene Reviews' (7) and 'OMIM' (8) were also included. The search strategy is shown in Figure 1.
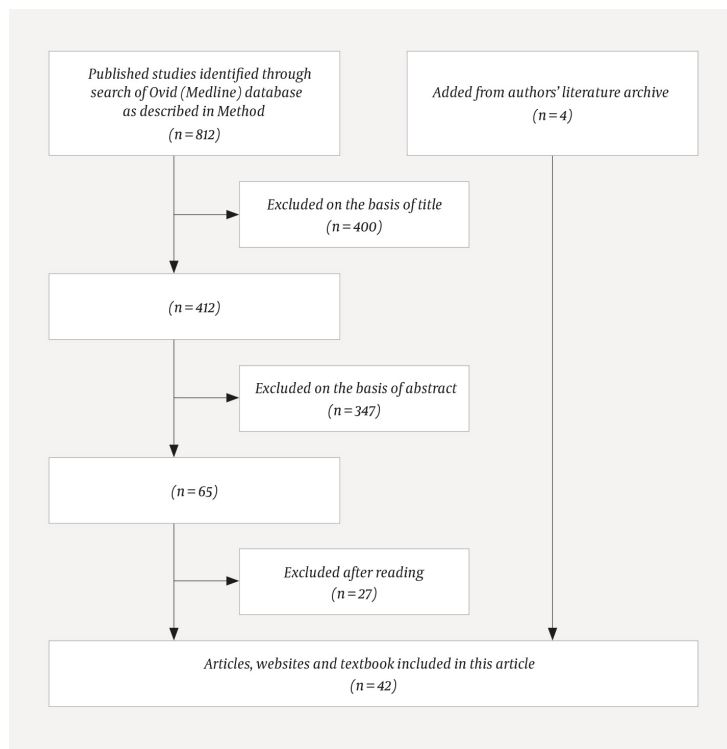

Figure 1 *Flowchart summarising the article search*

Background

Segawa *et al.* published the first patient dataset with nine patients in 1976 (9). The disorder has been referred to by several names: Segawa's disease, hereditary progressive dystonia/diurnal dystonia and infantile parkinsonism. The term 'dopa-responsive dystonia' was introduced by Nygaard in 1988 (10) and is now the most widely used.

From the 1990s onwards, studies have been conducted to characterise the underlying genetic causes and associated biochemical deficiencies and pathophysiology. This has led to changes in the names of the disorders and has formed the basis for a more targeted clinical approach. To date, patients have been shown to have pathogenic variants in one of three genes: *guanosine triphosphate (GTP) cyclohydrolase 1*, *sepiapterin reductase*, and *tyrosine hydroxylase* (3, 11, 12). There is a lack of high quality epidemiological data on the disorders, and underdiagnosis is likely (6, 12, 13). A prevalence in the general population of 0.5 per million is often reported in the literature (12, 13). Only a few articles based on Norwegian data have been published (14–16).

Pathophysiology and inheritance

Dopamine, noradrenaline and serotonin are monoamine transmitters that play a crucial role in motor control, sleep, emotions, and in cognitive and autonomic functions (6). GTP cyclohydrolase 1 and sepiapterin reductase are key enzymes in the formation of tetrahydrobiopterin, an essential cofactor for tyrosine, tryptophan and phenylalanine hydroxylase. Tyrosine and tryptophan hydroxylase are rate-limiting enzymes in the formation of dopamine and serotonin, respectively (6) (Figure 2). Impaired phenylalanine hydroxylase function gives rise to Følling's disease/phenylalaninaemia, a better known

disorder that may be detected during neonatal screening. Dopa-responsive dystonia with pathogenic variants in the genes *GTP cyclohydrolase 1*, *sepiapterin reductase* or *tyrosine hydroxylase* generally goes undetected in neonatal screening, as patients usually have normal levels of phenylalanine in the blood (6). Phenylalanine hydroxylase, like tyrosine hydroxylase, is dependent on the cofactor tetrahydrobiopterin.
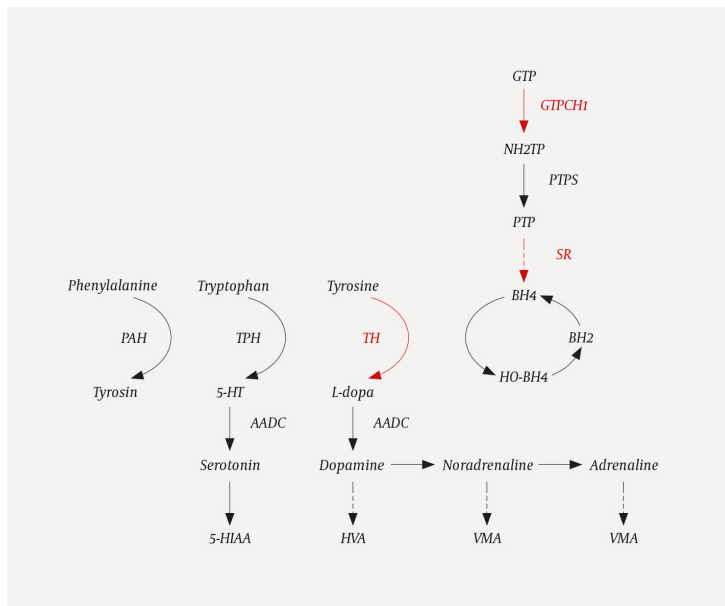

Figure 2 *The figure shows the pathways by which dopamine and serotonin are synthesised, and the various enzymes and metabolites involved. Most of the intermediates and end products can be measured in the cerebrospinal fluid, providing information on which enzyme has reduced activity. Phenylalanine, tryptophan and tyrosine are all dependent on BH_4 as a cofactor. The arrows/enzymes in red are the enzymes affected in cases of dopa-responsive dystonia. Dashed lines indicate that there are multiple steps in the reaction path. AADC = aromatic L-amino acid decarboxylase, BH_2 = dihydrobiopterin, BH_4 = tetrahydrobiopterin, GTP = guanosine triphosphate, GTPCH1 = GTP cyclohydrolase 1, HO-BH_4 = hydroxy-BH_4, 5-HIAA = 5-hydroxyindoleacetic acid, 5-HT = 5-hydroxytryptophan, HVA = homovanillic acid, NH_2TP = dihydroneopterin triphosphate, PAH = phenylalanine hydroxylase, PTP = 6-pyruvoyltetrahydropterin, PTPS = PTP synthase, SR = sepiapterin reductase, TH = tyrosine hydroxylase, TPH = tryptophan hydroxylase, VMA = vanillylmandelic acid.*

Dopa-responsive dystonia may show autosomal recessive or dominant inheritance. However, many patients are the only family member to be affected, as *de novo* mutations, reduced penetrance and variable expressivity are common (3, 6).

Clinical presentation

Dopa-responsive dystonia is primarily described as a motor disorder (6, 11, 12). Nevertheless, many patients have cognitive and psychiatric symptoms (17–19), and variation in the clinical picture has been reported (7, 12, 20–22).

School-age children and adolescents with dystonia or increased tonus in their legs that shows diurnal variation must always be assessed for the condition (12). Infants and young children with dystonia or other movement disorders, possibly accompanied by other neurological symptoms such as hypotonia, hypersomnia and/or autonomic dysfunction, should also be assessed for dopa-responsive dystonia. Oculogyric crises, which are episodes of dystonic, bilateral movements of the eyes, should raise suspicion of these disorders (2, 3, 6, 12, 23, 24).

The term 'dopa-responsive dystonia-plus' is used to refer to patients with earlier disease onset, more severe motor symptoms and more prominent non-motor symptoms compared to the classic form (6, 11, 25).

Patients often experience a delay between symptom onset and a correct diagnosis; Box 1 lists common misdiagnoses received by patients (3, 6, 13, 19, 22, 26–28).

Box 1 Misdiagnoses commonly received by patients with dopa-responsive dystonia (3, 6, 13, 19, 22, 26–28)

Cerebral palsy
Hereditary spastic paraplegia
Idiopathic dystonia/isolated dystonia
Juvenile Parkinson's disease
Muscular dystrophy
Psychosomatic disorder
Neurodegenerative disease
Congenital metabolic disease of unknown origin

Subgroups

AUTOSOMAL DOMINANT GTP CYCLOHYDROLASE 1 DEFICIENCY

This is the most common form of dopa-responsive dystonia (25). The typical patient is a previously healthy child who, at the age of 6–12 years, begins to show asymmetric gait abnormalities (see video). Parents often report worsening of symptoms in the afternoon and evening. Physical activity typically exacerbates symptoms, while symptoms may fully resolve at rest. The dystonia progresses over time if left untreated, and gradually spreads asymmetrically to other extremities and the trunk. It can easily be mistaken for increased tonus with alternative aetiology. A number of patients develop parkinsonian symptoms with bradykinesia, rigidity, postural tremor or postural instability (9, 13, 18, 19, 26, 29). Clinical examination typically reveals lively deep tendon reflexes. Many patients have a so-called 'striatal toe'; i.e. a dystonic extension of the big toe. Autosomal dominant GTP cyclohydrolase 1 deficiency may also have onset in adulthood with dystonia, tremor and/or parkinsonism (3, 29).

AUTOSOMAL RECESSIVE GTP CYCLOHYDROLASE 1 DEFICIENCY

This disease gives rise to complex and severe neurological symptoms, and is sometimes diagnosed following the discovery of hyperphenylalaninaemia during neonatal screening (23, 30). Symptoms usually begin during the first few months of life and may be present from birth.

Prominent signs are severe psychomotor retardation, bradykinesia, truncal hypotonia, autonomic dysfunction and often epilepsy (23, 28, 31).

AUTOSOMAL RECESSIVE TYROSINE HYDROXYLASE DEFICIENCY

This disease is associated with a broad clinical picture consistent with catecholamine deficiency (32). The enzyme deficiency can give rise to classic dopa-responsive dystonia, hypokinesia, rigidity and severe progressive encephalopathy (33). Willemsen *et al.* described 36 patients with the disorder and divided them into two main clinical groups (32). Type A has onset in the first year of life with a progressive hypokinetic-rigid syndrome (infantile parkinsonism) and dystonia, with cognitive function usually within the normal range. These patients respond well to levodopa. Type B is described as a severe encephalopathy with neonatal onset. Type B typically features truncal hypotonia, possibly combined with extremity hypertonia, and vegetative symptoms with episodes of sweating and drooling, as well as periods of irritability.

AUTOSOMAL RECESSIVE SEPIAPTERIN REDUCTASE DEFICIENCY

This is described as a 'dopa-responsive dystonia-plus' disease, and patients present with symptoms of both dopamine and serotonin deficiency (14, 22, 34). The most common

symptoms are psychomotor development retardation, axial hypotonia, dystonia, muscle weakness and oculogyric crises. In addition, many patients have behavioural disorders, autonomic dysfunction and sleep disorders (22, 35).

OTHER CONDITIONS

Up to 20 % of patients with dopa-responsive dystonia test negative for pathogenic variants in the three known genes (25). Other genes are also likely to be involved in the pathogenesis of this disease group (5, 6, 25). Pathogenic variants in other known genes can give rise to a similar clinical picture, with a partial response to levodopa (5, 25). There are reports of patients with hereditary ataxias or spastic paraplegias, or with early-onset familial Parkinson's disease/infantile parkinsonism with dystonia/increased tonus, responding to levodopa (5, 25). Based on their clinical presentation and treatment response, the latter diseases have not typically been regarded as dopa-responsive dystonia (2, 3, 6, 11).

Assessment

Given the good therapeutic response and broad clinical picture of dopa-responsive dystonia, it is important that patients are thoroughly assessed (3, 6, 24). Many patients first undergo a negative round of testing in the form of brain magnetic resonance imaging, electroencephalography and routine cerebrospinal fluid analyses (cells, protein, glucose, amino acid quantification, lactate) as well as metabolic screening of urine and blood.

After this preliminary testing, several publications recommend attempting treatment with levodopa as part of the diagnostic work-up (2, 3, 6, 12). Treatment should be continued for at least one month. It is important to emphasise that dystonia is not always the main symptom in these patients and an immediate treatment response is not always achieved. In other words, the term 'dopa-responsive dystonia' must not limit the diagnostic testing of these patients (2).

It is recommended that treatment should be continued for a minimum of 2–3 months in patients with oculogyric crises, focal or generalised dystonia, parkinsonism and encephalopathy, as time to treatment response is expected to be longer in this group (3, 6, 24). Quantification of pterins, biogenic monoamines and their metabolites (often referred to simply as neurotransmitter substances) in the cerebrospinal fluid is a key part of the work-up, along with molecular genetic testing (6). Biochemical changes in the cerebrospinal fluid in the various disorders are shown in Table 1 (36). It should be noted that ongoing treatment with levodopa may affect the results. Lumbar puncture should thus be performed prior to treatment initiation and the sample frozen for later analysis (6, 12). In most patients, genetic testing will confirm the precise diagnosis (12, 25).

Table 1

Biochemical changes in cerebrospinal fluid in the various dopa-responsive dystonias. N = normal, ↓ = values lower than reference range, ↓↓ = values much lower than reference range, ↑ = values higher than reference range. Reference ranges are age-dependent. GTPCH1 = guanosine triphosphate cyclohydrolase 1, TH = tyrosine hydroxylase, SR = sepiapterin reductase.

Biochemical marker in cerebrospinal fluid	GTPCH1 deficiency[1]	SR deficiency	TH deficiency
Total neopterin	↓	N/↑	N
Total biopterin	↓	↑	N
Tetrahydrobiopterin (BH$_4$)	↓	N	N
Dihydrobiopterin (BH$_2$)	N	↑	N

Biochemical marker in cerebrospinal fluid	GTPCH1 deficiency[1]	SR deficiency	TH deficiency
Sepiapterin	N	↑	N
Homovanillic acid (HVA)	↓	↓	↓/↓↓
5-hydroxyindoleacetic acid (5-HIAA)	N/↓	↓	N
HVA/5-HIAA-ratio	-	-	↓/↓↓

[1]Both autosomal recessive and dominant forms

Dopamine transporter scintigraphy (DaTSCAN) usually shows normal results in the various conditions, but may reveal pathology in cases of early-onset familial Parkinson's disease/juvenile parkinsonism, a neurodegenerative disorder with a distinct genetic aetiology (3).

The serum concentration of prolactin may be elevated in cases of sepiapterin reductase or tyrosine hydroxylase deficiency owing to a lack of dopaminergic inhibition (6, 14, 37), while prolactin levels are usually normal in cases of autosomal dominant GTP cyclohydrolase 1 deficiency (38).

Although dopa-responsive dystonia does not usually give rise to hyperphenylalaninaemia, a bolus dose of phenylalanine followed by serum concentration measurements after one and two hours often reveals an elevated phenylalanine/tyrosine ratio in patients with pathogenic variants of the genes *GTP cyclohydrolase 1* and *sepiapterin reductase* (6, 36, 39). This is due to a lack of tetrahydrobiopterin. The test will yield normal results in cases of tyrosine hydroxylase deficiency.

Treatment

Levodopa is the cornerstone of the treatment of dopa-responsive dystonia. However, the dosage, regimen, expected response and need for additional treatment depend on the underlying aetiology, disease severity, and adverse effects (2, 6, 28, 40).

Treatment must be tailored to the individual in collaboration with a doctor with experience in the field. The recommended starting dose of levodopa is 0.5–1 mg/kg/day (2, 6, 24, 28, 32, 35). If no response is seen but the diagnosis is still suspected, the dose should be gradually increased. In addition, tablets containing 5-hydroxytryptophan and/or tetrahydrobiopterin may be appropriate for patients with 'dopa-responsive dystonia-plus' (6, 24). The response to levodopa treatment is not always satisfactory in complex forms of tyrosine hydroxylase deficiency (33, 41).

Discussion

'Dopa-response dystonia' was named in line with the symptoms shown by most patients and the treatment to which they respond. However, the term encompasses various genetic disorders, with varying clinical presentation and therapeutic requirements, in addition to patients for whom no genetic diagnosis has been established. Identifying the underlying enzyme deficiency and precise genetic diagnosis is advantageous both in the clinic and in research (3).

Several different assessment strategies have been proposed in the literature (6, 12). The optimal order of testing will depend on clinical findings, the results of previous tests, the response to attempted treatment and the availability of the various tests.

Molecular genetic testing is becoming increasingly important in neurological diseases. Gene panels are now available for neurological diseases with motor symptoms and for metabolic disorders; such panels include the genes implicated in dopa-responsive dystonia (42). Nevertheless, it is important to also take advantage of the information offered by concentrations of pterins, biogenic monoamines and their metabolites in cerebrospinal fluid. This information can be of assistance in reaching an exact diagnosis, revealing the

significance of a genetic variant and selecting drugs as adjuvants to levodopa. Cerebrospinal fluid analysis will often be indicated as part of the initial work-up for movement disorders as well as in cases of dopa-responsive dystonia.

It must be emphasised that even if the exact diagnosis cannot be confirmed biochemically and/or genetically, this should not preclude a diagnosis of dopa-responsive dystonia or treatment attempts on the basis of clinical indication.

International networks and increased expertise will be essential for gathering and disseminating information about this patient population (43).

MAIN MESSAGE

Dopa-responsive dystonia often begins in early childhood with gait abnormalities

The disease progresses over time without treatment

Patients can make a full recovery following initiation of levodopa therapy

REFERENCES:

1. Albanese A, Bhatia K, Bressman SB et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013; 28: 863 - 73. [PubMed][CrossRef]

2. Friedman JR. What is not in the name? Doparesponsive dystonia may respond to more than l-dopa. Pediatr Neurol 2016; 59: 76 - 80. [PubMed][CrossRef]

3. Wijemanne S, Jankovic J. Dopa-responsive dystonia–clinical and genetic heterogeneity. Nat Rev Neurol 2015; 11: 414 - 24. [PubMed][CrossRef]

4. Furukawa Y, Rajput AH, Tong J et al. A marked contrast between serotonergic and dopaminergic changes in dopa-responsive dystonia. Neurology 2016; 87: 1060 - 1. [PubMed][CrossRef]

5. Ng J, Papandreou A, Heales SJ et al. Monoamine neurotransmitter disorders–clinical advances and future perspectives. Nat Rev Neurol 2015; 11: 567 - 84. [PubMed][CrossRef]

6. Blau NH, Georg F. red. Congenital Neurotransmitter Disorders – A Clinical Approach. US, New York, NY: Nova Science Publishers Inc, 2015.

7. Furukawa Y. GTP cyclohydrolase 1-deficient doparesponsive dystonia. Seattle, WA: Gene Reviews, NCBI, 2015. https://www.ncbi.nlm.nih.gov/books/NBK1508/ (31.8.2018).

8. Dystonia, doparesponsive; DRD. OMIM – Online Mendelian Inheritance in Man. http://www.omim.org/entry/128230 (31.8.2018).

9. Segawa M, Hosaka A, Miyagawa F et al. Hereditary progressive dystonia with marked diurnal fluctuation. Adv Neurol 1976; 14: 215 - 33. [PubMed]

10. Nygaard TG, Marsden CD, Duvoisin RC. Dopa-responsive dystonia. Adv Neurol 1988; 50: 377 - 84. [PubMed]

11. Lee WW, Jeon BS. Clinical spectrum of dopa-responsive dystonia and related disorders. Curr Neurol Neurosci Rep 2014; 14: 461. [PubMed][CrossRef]

12. Malek N, Fletcher N, Newman E. Diagnosing dopamine-responsive dystonias. Pract Neurol 2015; 15: 340 - 5. [PubMed][CrossRef]

13. Nygaard TG. Dopa-responsive dystonia. Curr Opin Neurol 1995; 8: 310 - 3. [PubMed][CrossRef]

14. Koht J, Rengmark A, Opladen T et al. Clinical and genetic studies in a family with a novel mutation in the sepiapterin reductase gene. Acta Neurol Scand Suppl 2014; 129: 7 - 12. [PubMed][CrossRef]

15. Haugarvoll K, Bindoff LA. A novel compound heterozygous tyrosine hydroxylase mutation (p.R441P) with complex phenotype. J Parkinsons Dis 2011; 1: 119 - 22. [PubMed]

16. Farbu E, Bindoff LA. Doparesponsiv dystoni–en arvelig dystoni som er lett å behandle. Tidsskr Nor Laegeforen 2002; 122: 379 - 81. [PubMed]

17. Brüggemann N, Stiller S, Tadic V et al. Non-motor phenotype of dopa-responsive dystonia and quality of life assessment. Parkinsonism Relat Disord 2014; 20: 428 - 31. [PubMed][CrossRef]

18. López-Laso E, Sánchez-Raya A, Moriana JA et al. Neuropsychiatric symptoms and intelligence quotient in autosomal dominant Segawa disease. J Neurol 2011; 258: 2155 - 62. [PubMed][CrossRef]

19. Tadic V, Kasten M, Brüggemann N et al. Dopa-responsive dystonia revisited: diagnostic delay, residual signs, and nonmotor signs. Arch Neurol 2012; 69: 1558 - 62. [PubMed][CrossRef]

20. Naiya T, Misra AK, Biswas A et al. Occurrence of GCH1 gene mutations in a group of Indian dystonia patients. J Neural Transm (Vienna) 2012; 119: 1343 - 50. [PubMed][CrossRef]

21. Uncini A, De Angelis MV, Di Fulvio P et al. Wide expressivity variation and high but no gender-related penetrance in two dopa-responsive dystonia families with a novel GCH-I mutation. Mov Disord 2004; 19: 1139 - 45. [PubMed][CrossRef]

22. Friedman J, Roze E, Abdenur JE et al. Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. Ann Neurol 2012; 71: 520 - 30. [PubMed][CrossRef]

23. Opladen T, Hoffmann G, Hörster F et al. Clinical and biochemical characterization of patients with early infantile onset of autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia. Mov Disord 2011; 26: 157 - 61. [PubMed][CrossRef]

24. Pearl PL, Hartka TR, Taylor J. Diagnosis and treatment of neurotransmitter disorders. Curr Treat Options Neurol 2006; 8: 441 - 50. [PubMed][CrossRef]

25. Clot F, Grabli D, Cazeneuve C et al. Exhaustive analysis of BH4 and dopamine biosynthesis genes in patients with Dopa-responsive dystonia. Brain 2009; 132: 1753 - 63. [PubMed][CrossRef]

26. Trender-Gerhard I, Sweeney MG, Schwingenschuh P et al. Autosomal-dominant GTPCH1-deficient DRD: clinical characteristics and long-term outcome of 34 patients. J Neurol Neurosurg Psychiatry 2009; 80: 839 - 45. [PubMed][CrossRef]

27. Low K, Harding T, Jardine P. Dopa responsive dystonia. BMJ 2010; 340: c668. [PubMed][CrossRef]

28. Ng J, Heales SJ, Kurian MA. Clinical features and pharmacotherapy of childhood monoamine neurotransmitter disorders. Paediatr Drugs 2014; 16: 275 - 91. [PubMed][CrossRef]

29. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol 2003; 54 (suppl 6): S32 - 45. [PubMed][CrossRef]

30. Horvath GA, Stockler-Ipsiroglu SG, Salvarinova-Zivkovic R et al. Autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia: evidence of a phenotypic continuum between dominant and recessive forms. Mol Genet Metab 2008; 94: 127 - 31. [PubMed][CrossRef]

31. Nardocci N, Zorzi G, Blau N et al. Neonatal dopa-responsive extrapyramidal syndrome in twins with recessive GTPCH deficiency. Neurology 2003; 60: 335 - 7. [PubMed][CrossRef]

32. Willemsen MA, Verbeek MM, Kamsteeg EJ et al. Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. Brain 2010; 133: 1810 - 22. [PubMed][CrossRef]

33. Hoffmann GF, Assmann B, Bräutigam C et al. Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. Ann Neurol 2003; 54 (suppl 6): S56 - 65. [PubMed][CrossRef]

34. Bonafé L, Thöny B, Penzien JM et al. Mutations in the sepiapterin reductase gene cause a novel tetrahydrobiopterin-dependent monoamine-neurotransmitter deficiency without hyperphenylalaninemia. Am J Hum Genet 2001; 69: 269 - 77. [PubMed][CrossRef]

35. Echenne B, Roubertie A, Assmann B et al. Sepiapterin reductase deficiency: clinical presentation and evaluation of long-term therapy. Pediatr Neurol 2006; 35: 308 - 13. [PubMed][CrossRef]

36. Opladen T, Okun JG, Burgard P et al. Phenylalanine loading in pediatric patients with dopa-responsive dystonia: revised test protocol and pediatric cutoff values. J Inherit Metab Dis 2010; 33: 697 - 703. [PubMed][CrossRef]

37. Yeung WL, Wong VC, Chan KY et al. Expanding phenotype and clinical analysis of tyrosine hydroxylase deficiency. J Child Neurol 2011; 26: 179 - 87. [PubMed][CrossRef]

38. Furukawa Y, Guttman M, Wong H et al. Serum prolactin in symptomatic and asymptomatic dopa-responsive dystonia due to a GCH1 mutation. Neurology 2003; 61: 269 - 70. [PubMed][CrossRef]

39. Opladen T, Hoffmann GF, Kühn AA et al. Pitfalls in phenylalanine loading test in the diagnosis of dopa-responsive dystonia. Mol Genet Metab 2013; 108: 195 - 7. [PubMed][CrossRef]

40. Opladen T, Hoffmann GF, Blau N. An international survey of patients with tetrahydrobiopterin deficiencies presenting with hyperphenylalaninaemia. J Inherit Metab Dis 2012; 35: 963 - 73. [PubMed][CrossRef]

41. Chi CS, Lee HF, Tsai CR. Tyrosine hydroxylase deficiency in Taiwanese infants. Pediatr Neurol 2012; 46: 77 - 82. [PubMed][CrossRef]

42. Senter for Medisinsk genetikk og Molekylærmedisin HU. Norsk portal for medisinsk genetisk-genetiske analyser. https://www.genetikkportalen.no/ (31.8.2018).

43. Opladen T, Cortès-Saladelafont E, Mastrangelo M et al. The International Working Group on Neurotransmitter related Disorders (iNTD): A worldwide research project focused on primary and secondary neurotransmitter disorders. Mol Genet Metab Rep 2016; 9: 61 - 6. [PubMed][CrossRef]