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Misdiagnoses in Children With Dopa-responsive Dystonia

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Dystonia is a state of continuous contraction of groups of agonist and antagonist muscles resulting in a sustained abnormal posture. Dopa-responsive dystonia was first described in 1976 by Segawa. Patients typically have diurnal variation of their symptoms with worsening at the end of the day and a dramatic response to low-dose L-dopa. This report presents five consecutive children with dopa-responsive dystonia who were misdiagnosed initially as spastic diplegic cerebral palsy, intractable epilepsy, hereditary spastic paraplegia, or a neurodegenerative disorder. There were two males and three females aged 3-13 years (mean 8.6 years). They were monitored for up to 2 years (mean 14.8 months). One had focal, one axial, one segmental, and two generalized dystonia. The dystonia was paroxysmal in two (tiptoe walking and opisthotonus), and all had a progressive course. All children responded dramatically to L-dopa (mean 200 mg/day), including three who were wheelchair-bound for several years. The difficulties in early diagnosis, variability of clinical presentation, and dramatic response to L-dopa will be illustrated. To conclude, dopa-responsive dystonia should be considered in any child who presents with paroxysmal or progressive hypertonia of unknown etiology, because it responds so dramatically to L-dopa. **© 2004 by Elsevier Inc. All rights reserved.**

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Introduction

Dystonia is defined as a state of continuous contraction of groups of agonist and antagonist muscles resulting in a sustained abnormal posture, which is frequently twisting in nature [1]. Muscle tone typically fluctuates, varying from normal to extreme hypertonia [2]. Oppenheim first described dystonia in 1911; however, the phenomenology, pathophysiology, and management have become much better understood over the last decade [3]. To organize the clinical and etiologic heterogeneity of dystonia, different classifications have been proposed [4]. Clinically, dystonia can be classified according to the age of onset as early (<21 years) or late (>21 years), or according to the distribution of affected body regions as summarized in Table 1 [5]. Dystonic movements usually occur spontaneously. They can be precipitated or worsened by attempts to move and can vary with alterations in emotional state and fatigue. However, dystonia typically diminishes or disappears with distraction or sleep. Dystonia can be subclassified as action induced or posture induced, although secondary dystonia in children is typically present at rest and is increased by action (Table 1). There are many diverse causes of dystonia (Table 2) [6]. It can be primary (idiopathic) or secondary (symptomatic) to neurodegenerative disorders or other lesions of the brain (Table 2). However, with the recent mapping of genes for idiopathic dystonias, the term *primary* is becoming outdated [7]. Table 3 summarizes an updated genetic classification and highlights recently mapped genes of various inherited dystonias [8].

Dopa-responsive dystonia was first described in 1976 by Segawa [9]. It is a rare inherited primary dystonia plus syndrome (Table 2). Typically, the patient has a diurnal variation with symptoms that are worse by the end of the day [2]. Dopa-responsive dystonia begins at 1-12 years of age (median 6.5), most often with progressive dystonia in a foot and associated alterations in gait [10]. It should be considered in any child who presents with dystonia of unknown etiology because it responds so dramatically to L-dopa. The aim of this article is to provide an updated overview of childhood dystonias with emphasis on dopa-responsive dystonia. Five cases representing my experience with this interesting syndrome are presented. All patients were evaluated and monitored by the author at

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Table 1. Clinical classification of childhood dystonia*

Clinical Classification	Description
A. By distribution	
1. Focal	Eyelids (blepharospasm), mouth (oromandibular dystonia), larynx (spasmodic dysphonia), neck (spasmodic torticollis), hand (writer's cramp)
2. Segmental	Cranial, axial, brachial (arms), or crural (legs)
3. Multifocal	Involve two or more noncontiguous body parts
4. Hemidystonia	Involve ipsilateral arm and leg
5. Generalized	Both legs plus one or more other body part
B. Activation characteristics	
1. Task-specific	Only during certain tasks in one region (writer's cramp)
2. Action	Only during moving the involved region
3. Overflow	Also induced by moving other uninvolved body parts
4. Fixed	Present at rest
5. Paradoxical	Improves by talking or other voluntary movements

* Adapted from Uc and Rodnitzky, 2003 [5].

King Faisal Specialist Hospital and Research Center or King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. All patients were referred for further evaluation of their diagnoses and management, and all had initial misdiagnoses (Table 4). These cases will illustrate the difficulties in early diagnosis, variability of clinical presentation, and dramatic response to L-dopa. The following is a concise summary of the most relevant clinical findings in each of these patients.

Table 2. Etiologic classification of childhood dystonia*

I. Primary (idiopathic)
  1. Primary torsion dystonia (dystonia musculorum deformans)
  2. Segmental (cervical/cranial) dystonia
  3. Sporadic focal dystonia
II. Dystonia plus syndromes
  1. Dystonia with parkinsonism
    a. Dopa-responsive dystonia
    b. Dopamine agonist responsive dystonia
    c. Rapid onset dystonia-parkinsonism
  2. Myoclonus-dystonia syndrome
III. Secondary dystonia
  1. Congenital malformations
  2. Trauma (physical, electric, shock)
  3. Perinatal cerebral injury (anoxia, kernicterus, trauma)
  4. Drug-induced (neuroleptics, antiepileptics, levodopa, cocaine)
  5. Toxic (manganese, cyanide, carbon monoxide, wasp sting)
  6. Infection (encephalitis, HIV, subacute sclerosing panencephalitis)
  7. Endocrine (hypoparathyroidism)
IV. Inherited degenerative disorders
  1. Autosomal dominant (Juvenile Parkinson's disease, Huntington's disease)
  2. Autosomal recessive (Wilson's disease, Hallervorden-Spatz syndrome, Neuronal ceroid lipofuscinosis, Gangliosidosis, Lesch-Nyhan syndrome, Homocystinuria)
  3. X-linked dominant (Rett syndrome)
  4. X-linked recessive (Dystonia-parkinsonism)
  5. Mitochondrial (Leigh's disease, Leber's disease)
V. Psychogenic dystonia

* Adapted from Langlois, Richer, and Chouinard, 2003 [6].

Case Reports

Patient 1

A 3-year-old male was referred because of "tiptoe walking". He was the product of a term uncomplicated pregnancy and spontaneous vaginal delivery. His early development was appropriate with sitting unsupported at 7 months, standing at 12 months, and walking independently at 14 months. Around the age of 18 months, the mother noticed the intermittent tiptoe walking involving particularly the left foot. He was observed by a number of physicians and evaluated by a physiotherapist. Brain computerized tomographic scan was obtained and was normal. The referral diagnosis was mild spastic diplegic cerebral palsy. During our interview, it was evident that his symptoms were episodic and more prominent toward the end of the day. They generally developed midday and lasted for several hours. These episodes occurred 2-3 times per week; the child seemed normal between the episodes. In fact, his examination in the morning clinic revealed minimal residual hypertonia of the left leg. However, the mother was concerned about his episodic limping. Sinemet 110 mg (equivalent to 100 mg levodopa with 10 mg carbidopa) was initiated in two divided doses per day. His symptoms completely disappeared within 1 week. He was monitored for 6 months with no further recurrence of his complaints.

Patient 2

A 4-year-old male was referred because of intractable epilepsy. He was the product of a term uncomplicated pregnancy and spontaneous vaginal delivery. His early development was appropriate, and he had no prior history of head injury, meningitis, encephalitis, or febrile seizures. Around the age of 2 1/2 years he developed intermittent episodes of opisthotonus without associated vomiting or feeding difficulties. His head and neck would arch backward, and he would lose mobility for 2-3 hours, then gradually improve over the next hour. Although he looks uncomfortable, he remains alert and interactive. The parents photographed one of these opisthotonic episodes. He was observed by a number of physicians, and several electroencephalograms, cranial computed tomography, and magnetic resonance imaging were always normal. He was placed on a number of antiepileptic drug trials including phenobarbital, phenytoin, carbamazepine, and valproic acid with no benefit. On assessment, it was clear that epilepsy was unlikely and paroxysmal dystonia was suspected.

Table 3. Updated genetic classification of dystonia*

Class	Clinical Phenotype	Inheritance	Locus	Gene
DYT1	Primary torsion dystonia	Autosomal dominant	9q34	Torsin A
DYT2	Primary torsion dystonia	Autosomal recessive	NM	NM
DYT3	Dystonia-parkinsonism	X-linked recessive	Xq13.1	NM
DYT4	Whispering dysphonia	Autosomal dominant	NM	NM
DYT5	Dopa-responsive dystonia	Autosomal dominant	14q22.1	GTPCH-1
		Autosomal recessive	11p15.5	TH
DYT6	Torsion dystonia, in adults	Autosomal dominant	8p21	NM
DYT7	Familial cervical dystonia	Autosomal dominant	18p	NM
DYT8	Paroxysmal dystonic choreoathetosis	Autosomal dominant	2q33	NM
DYT9	Paroxysmal dyskinesia with spasticity	Autosomal dominant	1p21	NM
DYT10	Paroxysmal kinesigenic dyskinesia	Autosomal dominant	16p11-12	NM
DYT11	Myoclonus-dystonia	Autosomal dominant	7q21	ε-sarcoglycan
DYT12	Dystonia-parkinsonism	Autosomal dominant	19q13	NM
DYT13	Cranial-cervical-brachial	Autosomal dominant	1p36	NM
DYT14	Dopa-responsive dystonia	Autosomal dominant	14q13	NM
DYT15	Myoclonus-dystonia	Autosomal dominant	18p11	NM

*Adapted from Langlois, Richer, and Chouinard, 2003 [6].

Abbreviations:
GTPCH-1 = Guanosine-5-triphosphate cyclohydrolase-1
NM = Not mapped
TH = Tyrosine hydroxylase

His episodes generally occurred toward the end of the day and were becoming more frequent, sometimes more than once per day. Neurologic examination revealed minimal axial hypertonia. Sinemet 110 mg daily was initiated with remarkable reduction in the frequency of these episodes. The dose was gradually increased to 110 mg three times per day, and concurrent antiepileptic drugs were withdrawn. He was monitored for 1 year with occasional mild episodes.

Patient 3

An 11-year-old female was referred because of progressive spastic diplegia. Hereditary spastic paraplegia was suspected; however, there was no family history of consanguinity or similar illness. Her perinatal history was unremarkable. She developed well until the age of 5 years when an abnormal gait was observed. She progressed slowly and became wheelchair-bound over the previous 3 years. Clinically she manifested dystonia of both lower limbs with hyperreflexia, clonus, and normal plantar responses. She was able to walk with great difficulty. Brain and lumbosacral magnetic resonance imaging were normal. She received physiotherapy and Baclofen with no benefit. Minimal fluctuations of her symptoms were observed with mild worsening toward the end of the day. Sinemet 110 mg was initiated in two divided doses per day. Ten days later she was able to walk unassisted. When the dose was doubled, she developed tremor, so she remains on 55 mg b.i.d. Her symptoms were continuing to improve on last follow-up 8 months later.

Patient 4

A 12-year-old female was referred because of an undiagnosed progressive neurodegenerative disorder. Her perinatal history was complicated by jaundice resulting from blood group incompatibility, which only required phototherapy. She developed well until the age of 6 years when an abnormal gait was observed. She manifested generalized progressive motor and speech deterioration, diffuse hypertonia, and walking difficulties with no clear diurnal variation. Her parents were second-degree relatives. No similar cases were described in the family. She progressed slowly and became wheelchair-bound over the prior 4 years. On examination, she manifested diffuse limb and truncal dystonia, dysarthria, masked faces, and hyperreflexia. She had a negative detailed evaluation including metabolic testing and testing for Wilson's disease. Repeated brain magnetic resonance imaging revealed mild nonspecific atrophy, but her head circumference remained normal. She received physiotherapy and multiple antispasticity medications with no benefit. Sinemet 110 mg was initiated and increased to 220 mg/day in two divided doses. After 2 weeks she was able to ambulate with assistance. Shortly after, she was able to walk independently with remarkable

Table 4. Summaries of the five illustrated cases with dopa-responsive dystonia

Case	Age	Sex	Type	Clinical Presentation	Referral Diagnosis
1	3 years	Male	Focal	Episodic tiptoe walking	Mild spastic diplegic cerebral palsy
2	4 years	Male	Axial	Episodic opisthotonus	Intractable epilepsy
3	11 years	Female	Segmental	Progressive spastic diplegia, in a wheelchair for 3 years	Hereditary spastic paraplegia
4	12 years	Female	Generalized	Progressive motor and speech deterioration, diffuse hypertonia, walking difficulties, in a wheelchair for 4 years	Undiagnosed neurodegenerative disorder
5	13 years	Female	Generalized	Progressive motor and speech deterioration, diffuse hypertonia, inability to walk, in a wheelchair for 6 years	Undiagnosed neurodegenerative disorder

improvement of her speech. Last follow-up was 2 years later with ongoing improvement.

Patient 5

A 13-year-old female was referred because of an undiagnosed progressive neurodegenerative disorder. Her perinatal history was unremarkable. She developed well until the age of 7 years when an abnormal gait was observed. She manifested generalized progressive motor and speech deterioration, diffuse hypertonia, and difficulty in walking with no clear diurnal variation. Her parents were not consanguineous. There were no similar cases in the family. She progressed slowly and became wheelchair-bound over the prior 6 years. On examination she manifested diffuse limb and truncal dystonia, rigidity, dysarthria, masked faces, and hyperreflexia. She had a negative detailed evaluation including metabolic testing, skin fibroblast culture, and testing for Wilson's disease. Repeated brain magnetic resonance imaging scans were normal. She received physiotherapy and multiple antispasticity medications with no benefit. She developed bilateral foot deformities that necessitated corrective orthopedic surgery 1 year before our assessment. Sinemet 110 mg was administered twice per day. After 2 1/2 weeks she was able to ambulate with assistance. The dose was increased slowly on follow-up to 440 mg/day in two divided doses. Last follow-up was 2 years later when she was able to walk independently and never required the wheelchair. There was remarkable improvement of her speech and facial expressions.

Discussion

These five cases illustrate the difficulties in early diagnosis, variability of clinical presentation, and dramatic response to L-dopa in dopa-responsive dystonia. Since the initial description of this syndrome by Segawa in 1976, many cases have been reported worldwide [11-13]. Dopa-responsive dystonia is a genetic disorder with autosomal dominant inheritance (Table 3). Occasional recessive inheritance and sporadic cases have also been observed. The penetrance in dominant families has been estimated to be 30-40% with a female to male ratio of 2-3:1 [6]. The female predominance was found to be much higher in a recent study [14]. The causative gene has been mapped to chromosome 14q22.1, which codes for the enzyme guanosine-5-triphosphate cyclohydrolase-1 [15]. Approximately 85 different mutations have been reported in patients with dopa-responsive dystonia worldwide; however, approximately 40-50% of patients have no known mutations [16-18]. This finding suggests that the disorder is genetically complex, as different families may have different mutations. Guanosine-5-triphosphate cyclohydrolase-1 is responsible for catalyzing the formation of tetrahydrobiopterin, an essential cofactor of tyrosine hydrolase, which in turn is the rate-limiting step for dopamine biosynthesis (Fig 1) [19]. Therefore heterogenous mutation in this gene in patients with dopa-responsive dystonia leads to a decrease in the activity of tetrahydrobiopterin and a decrease in striatal dopamine levels to less than 20% of the normal values. This observation is consistent with the reduction of the levels of neopterin and biopterin in the cerebrospinal fluid and reduction of the activities of guanosine-5-triphosphate cyclohydrolase-1 in mononuclear blood cells and in cultured lymphocytes of these patients [15,20,21]. Some patients with dopa-responsive dystonia have homozygous mutations in other enzymes involved in dopamine synthesis, including tyrosine hydroxylase and 6-pyruvoyltetrahydropterin synthase [22-24]. These autosomal recessive conditions present in a more severe clinical picture with additional features, such as hypotonia, bradykinesia, ptosis, or progressive spastic paraplegia.

The important clinical features of dopa-responsive dystonia are: (1) onset of dystonia is usually at 4-8 years of age and usually commences in the lower limbs, causing an abnormal gait; (2) diurnal fluctuation of signs and symptoms, with worsening later in the day observed frequently, but not invariably; and (3) other associated features such as hyperreflexia and extensor plantar reflexes (in 25%), parkinsonian signs (such as mask faces), or tremor. The clinical manifestations are variable [14,25], as is illustrated well in our five patients. Dopa-responsive dystonia can masquerade as disorders such as spastic diplegia or progressive paraparesis. Some patients may not manifest the diurnal variation, as documented in two of the patients (Patients 4 and 5) [11]. Others may present late, such as Patients 4 and 5, with contractures and foot deformities [19]. The course of the latter two patients is similar to the three patients described by Harwood et al. [26]. Their three patients progressed to severe disability and parkinsonian rigidity. After administration of small doses of L-dopa, they manifested rapid improvement from being wheelchair-bound to being ambulatory over a few weeks [26].

All major symptoms of dopa-responsive dystonia are linked to striatal dopamine deficiency and may begin in infancy, resembling cerebral palsy. In fact, it is misdiagnosed relatively often [5]. It is not uncommon for a child to be referred with the diagnosis of spasticity, when in fact the child has undiagnosed dystonia [2,10]. In one series, up to 24% of patients with dopa-responsive dystonia had been misdiagnosed as cerebral palsy [10]. Dystonic movements do not usually cause the wasting, contractures, and deformities that develop in spasticity [2]. Patients usually have a good muscle bulk because of the repeated dystonic contractions. The clue to the diagnosis of dopa-responsive dystonia is the diurnal fluctuation and lower limb onset. However, it is not uncommon for these patients to have hyperreflexia and ankle clonus, but plantar responses are usually normal [6,14]. Interestingly, dorsiflexion of the big toe "striatal toe sign" can be observed spontaneously or induced by exercise [27]. Dopa-responsive dystonia can usually be distinguished from juvenile parkinsonism clinically by the diurnal variation, benign course, and sustained responsiveness to low doses of L-dopa without emergence of motor fluctuations or other neurologic manifestations [28]. It is important to differentiate the two disorders because the administration of L-dopa in juvenile parkinsonism can result in tardive dyskinesia, which can be prevented by the initial use of dopa agonists [14,28]. In dopa-responsive dystonia, both fluorodopa positron emis-

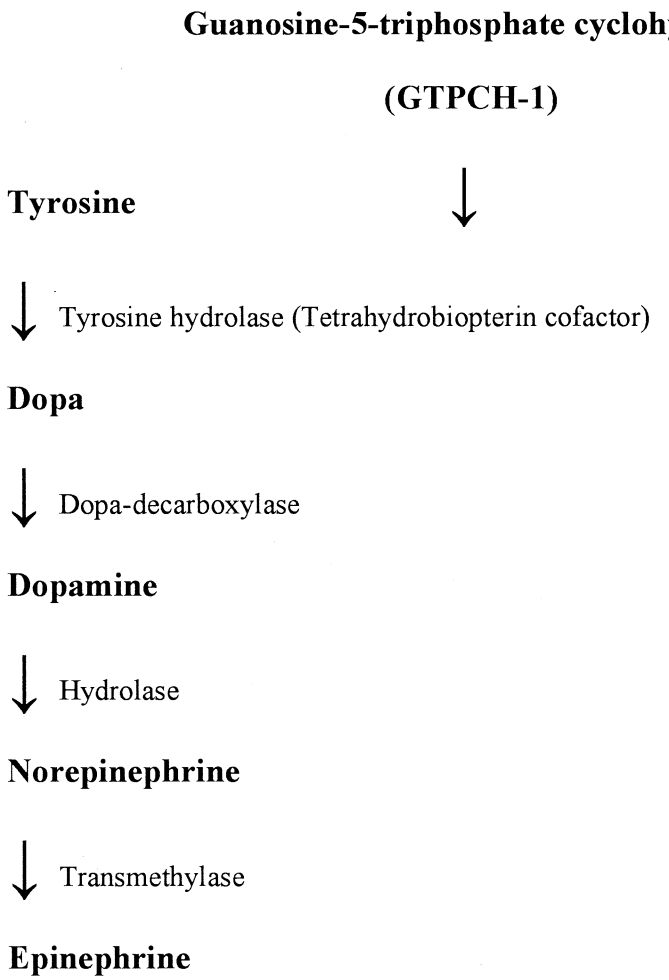

Figure 1. Metabolic pathway of dopamine synthesis in the brain [19].

sion tomography and single-photon emission computerized tomography scans are normal, in contrast to the findings in parkinsonism [28]. As well, studies on molecular genetics indicate that the nigrostriatal dopamine deficiency in dopa-responsive dystonia is not associated with neuronal death in contrast to what is observed in parkinsonism [17].

Genetic and biochemical studies are of diagnostic assistance but may not be available in all centers. Moreover, not all possible mutations of the responsible gene are known. Low homovanillic acid level in the cerebrospinal fluid is a pathognomonic finding; however, the most reliable diagnostic tests are decreased (<30%) guanosine-5-triphosphate cyclohydrolase-1 activity in peripheral mononuclear blood cells and reduced levels of biopterin in the cerebrospinal fluid [27]. Abnormally elevated phenylalanine/tyrosine ratio in the phenylalanine loading test may help differentiate guanosine-5-triphosphate cyclohydrolase-1 deficiency from tyrosine hydroxylase deficiency [29]. These genetic and biochemical tests were not available to our patients. Therefore it is possible that the more severely involved children (Patients 3, 4, and 5) are compound heterozygote or have the autosomal recessive tyrosine hydroxylase deficiency, which may manifest features of spastic paraplegia depending on the loci of gene mutation. In practice, the diagnosis of dopa-responsive dystonia depends on the clinical suspicion and a dramatic and sustained response to low doses of L-dopa, usually less than 300 mg/day [30]. Another report suggested an optimal dose of 20 mg/kg/day of L-dopa, which is equivalent to 4-5 mg/kg/day of carbidopa [31]. Patients with excellent response have enjoyed long-term clinical stability on chronic L-dopa treatment for many years [14,31]. They have not developed fluctuations in response, increased dose requirements, or long-term adverse effects such as the "on-off" phenomenon [10]. Occasionally, compound heterozygotes and adult onset cases may require more substantial doses [32]. A good response to anticholinergic drugs has also been reported [33]. After the initiation of L-dopa, spontaneous remission has been rarely reported [34]. After 1-2 years of treatment, slow withdrawal of L-dopa may be suggested, to assess the need for longer-term treatment. The five patients reported here remained stable for up to 2 years of follow-up while on treatment, and none of the parents agreed to taper the low-dose L-dopa treatment to this point.

Conclusions

Dopa-responsive dystonia (Segawa disease) is a rare but treatable cause of childhood onset dystonia. The diagnosis should be considered in any child who presents with paroxysmal or progressive course of unexplained foot twisting, unexplained gait difficulties, or hypertonia of unknown etiology because it responds so dramatically to L-dopa. Treatment of these patients is one of the most satisfying experiences in pediatric neurology.

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