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Review

The Neurobiology of the Opsoclonus-Myoclonus Syndrome

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Summary: Opsoclonus-myoclonus is a pervasive neurological syndrome of children and adults. Although rare, it raises important clinical and neurobiological issues. This article provides an overview of the clinical and laboratory features, differential diagnosis, treatment, and outcome of opsoclonus-myoclonus. It pursues immunologic, genetic, electrophysiologic, neurochemical, and other clues to a pharmacologic model. Key questions include how and where the brain is injured, reversibility of the injury, possible targets for pharmacologic intervention, and which new studies are needed. **Key Words:** Myoclonus—Opsoclonus—Paraneoplastic—Neuroblastoma—ACTH.

The association of the ocular and somatic dyskinesias, opsoclonus and myoclonus, continues to tantalize pediatricians, oncologists, neuro-ophthalmologists, neurologists, movement disorder specialists, immunobiologists, molecular geneticists, and pharmacologists. Now more than 80 years since the original description of opsoclonus and its co-occurrence with myoclonus by Orzechowski (1,2), the syndrome of opsoclonus-myoclonus is internationally recognized as a neurologic manifestation of remote cancers and toxic, metabolic, infectious, structural, and degenerative disorders. Nearly 200 cases have been reported in children and adults. It has been variously named myoclonic encephalopathy (3–10) of infants (7,11–15) or childhood (16,17), dancing eyes (18,19), dancing feet (20), infantile polymyoclonia (21–23) or polymyoclonus syndrome (20,24–26), opsoclonus syndrome (27,28), acute cerebellar encephalopathy (29–32), encephalitis (33), or ataxia (34), syndrome of rapid irregular movements of eyes and limbs in childhood (35), oculocerebellomyoclonic syndrome (36–38), Kinsbourne syndrome (9,39–41), opsoclonus, body tremulousness, and benign encephalitis (42–43), syndrome of ocular oscillations and truncal myoclonus (44), encephalopathy associated with

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occult neuroblastoma (45), opsomyoclonus (46–48), or opsoclonus-myoclonus (49–55), opsoclonic cerebellopathy (56,57), or simply opsoclonus (58–60). The description opsoclonus, myoclonus, ataxia, (61) and encephalopathy (62) may be the most complete, but opsoclonus-myoclonus will be used here. There have been several large reviews of this syndrome (54,62–65), but none from the point of view of the movement disorder pharmacologist. A pharmacologic approach may be useful in identifying new hypotheses for study and potential new pharmacologic therapies.

CLINICAL FEATURES

Opsoclonus

Opsoclonus refers to conjugate or semiconjugate, chaotic, rapid, randomly directed eye movements, also called "saccadomania" (66). Although rare, opsoclonus may be dramatic. Orzechowski (1,2) said "the ocular globes are in a state of continuous agitation, being shaken and increasingly displaced by very rapid and unequal movements, which generally take place in the horizontal plane." Despite confusing terminology (67), the term opsoclonus is used by neuro-ophthalmologists in distinction from other ocular dyskinesias such as ocular myoclonus ("lightning eye movements") (68–70), ocular dysmetria (71), ocular flutter (71), and macrosaccadic oscillations (72). The relatedness of these movements is suggested by the occurrence of opsoclonus, ocular dysmetria, and ocular flutter in a pattern of temporal regression in the same patient (73). Orzechowski made the association of opsoclonus with ataxia and myoclonus. While opsoclonus is only one of several eye movement disturbances associated with myoclonus (74), myoclonus is the dyskinesia most often associated with opsoclonus. Opsoclonus may occur in "spells or bursts" (44,75–78). It persists with eyelids open or closed (77,79), but diminished (51). In sleep, opsoclonus may persist (11,12,76,80–82), though diminished (7,51), or may disappear (18–20). It is increased by saccadic movements (79) or fixation (12,44,51,72,76,78,81,83,84) and seldom decreased by fixation (43). Opsoclonus is increased by startle (12,81) or stimulation (78,85). Some patients prefer keeping one or both eyes closed (72,78,86), but for others, opsoclonus increases with eye closure (80). Oscillopsia has been reported (42,87, 88), but diplopia is absent (77,86).

Electronystagmyography (52,67) or electrooculography (35,87,89,90) has shown bursts of back-to-back saccades without saccadic interval in horizontal and vertical planes and dysconjugate features (78).

Opsoclonus may onset before the myoclonus (11,20,44,75). Opsoclonus may occur in the absence of myoclonus (91). In cases of coma, opsoclonus may persist (92). Occasionally, rotatory features have been noted (12,51,83,93) and what is described as opsoclonus is frequently called nystagmus (29,46,94). Opsoclonus may be increased by doll's-eye manuevers. Ice water calorics transiently interrupt (95), increase (81), superimpose deviation (11), or have no effect (44,77) on opsoclonus. Optokinetic nystagmus may be present (42,44,85) or absent (11,81).

Myoclonus

Although myoclonus has seldom been thoroughly described in any one report, it is possible to gain a collective impression from case reports (Table 1). The distribution of myoclonus may include the face (5,12,20,77,94,96,97), head and neck (5,12,27,75,78), limbs (18,20,27,35,51,62,77,78,85,98,99), fingers and hands (5,7,12,58,89), and the trunk (12,18,20,44,62,77,78) in truncal torsion jerks (11). Some authors comment that myoclonus was present in eyelids (12,18,100), or that there was eyelid fluttering or blinking (3,11,20,81,83,86,96). Some use the term "blepharospasm" (101,102). Palatal myoclonus is absent (53,77,100) except rarely (83). Respiratory impairment by myoclonus (12) or myoclonus of the diaphragm (83) is unusual. Unilateral myoclonus is also rare (94).

Myoclonus may occur spontaneously (12,51,103), but not always (53). It may be evoked by action (65,104) or intention (12,51,53). Other stimuli which induce myoclonus include noise, light, visual threat, and pinprick (11,12,35,53,77). Myoclonus is exacerbated by crying, excitement, or stress (12,18,20,27,65). Some cases are not stimulus-sensitive (86). The descriptions "asynchronous" or "irregular" have sometimes been applied (18,20,43,95,105–107). The term "minipolymyoclonus" (21,22,24,25,27,28) has been used to describe the small jerks that often involve only the fingers in opsoclonus-myoclonus, but implies primary generalized epileptic myoclonus (108). Not all jerks result in movement of a joint. There may be "attacks" of myoclonus (18). The severity of myoclonus is vari-

TABLE 1. *Clinical description of myoclonus*

Feature	Apparent incidence[a]	Reference
Distribution		
Face	+ + + +	5, 12, 20, 77, 94, 96, 97
Eyelids	+ + +	12, 18, 100
Palate	−/+	83
Head and Neck	+ + +	5, 12, 27, 75, 78
Limbs	+ + + +	18, 20, 27, 35, 51, 62, 77, 78, 85, 98, 99
Fingers or Hands	+ + +	5, 7, 12, 58, 89
Trunk	+ + + +	12, 18, 20, 44, 62, 77, 78
Diaphragm	−/+	83
Type		
Spontaneous	+	12, 51, 103
Action-induced	+ + +	65, 104
Intention-induced	+ +	12, 51, 53
Sensory-induced	+ + +	11, 12, 35, 53, 77
Light	+	
Sound	+ +	
Pinprick	+	
Emotion-exacerbated	+ + +	12, 18, 20, 27, 65
Functional Impairment		
Sitting	+ + + +	5, 11, 12, 18, 20, 29, 44, 51, 75, 77, 78, 83, 86, 98, 100, 101
Standing	+ + + +	5, 11, 20, 29, 42, 44, 51, 65, 77, 101, 104, 110, 111
Speech	+/−	5, 11, 12, 18, 29, 65, 71, 86, 110, 134
Feeding	+/−	11, 12, 137
Respirations	−/+	12

[a] −/+ indicates rare occurrence; +/− indicates infrequent occurrence.

able, ranging from violent (11,20,51,104) to occasional (80). There is no temporal association of myoclonus with opsoclonus (11,18,20,35,77,86). Myoclonus may onset before (18,77,103), or without opsoclonus (109). Myoclonus persists in sleep at slower rates (3,12).

The functional impact of myoclonus is typically severe. Standing and walking is usually compromised or refused (5,11,20,29,42,44,51,65,77,101,104,110,111). Involuntary kicking may occur when feet are placed on the ground (51). Patients are typically unable to sit (5,11,12,18,20,29,44,51,75,77,78,83,86,98,100,101) and revert to crawling (from walking) (11,12,40). Often, the patients "prefer lying down" (12,44,94), or "lying on back" (12), but may be unable to lie on back. One author comments the child cried when held upright (7).

Ataxia

The term "ataxia" has been used to mean apparently different things in the opsoclonus-myoclonus syndrome. Orzechowski (77) states that "among this entire picture of disease, we can always find a few symptoms of cerebellar disease . . ." Specific reference to "cerebellar ataxia" has been made (87,97,99, 108,112–115). Some patients were apparently ataxic enough to be discharged with a diagnosis of "acute cerebellar ataxia" (18,35,58,116), and "severe" ataxia has been described (5,7,44,51,62). There are reports of "titubation" of head or trunk (5,6,12,29,83), "truncal ataxia" (6,83,100,101,117,118), and limb dysmetria (29,65).

However, it has also been suggested that the "ataxia" is unlike cerebellar ataxia but is instead due to myoclonic jerks (20). Cerebellar function or finger-to-nose and heel-to-skin testing may be normal (43,44,75). Some reports of opsoclonus and ataxia make no mention of myoclonus (113). It is unclear if this is a biologic subgroup (119).

Early descriptions of the syndrome of "acute cerebellar ataxia of childhood" probably included some cases of opsoclonus-myoclonus. In a few, myoclonic movements (120,121), "trembling" (122), "jerking movements of the eyes" (122), or "action tremor" (123) were described. Even without those cases, however, there are more similarities than differences between the two syndromes, including a predilection for gait disturbance more than truncal or appendicular ataxia (120,121,123–125), encephalopathy, and behavioral and cognitive neurologic sequelae. There is enough overlap between opsoclonus-myoclonus and acute cerebellar ataxia syndromes so that children with the latter diagnosis should have urine catecholamine determinations made.

Tremor

Although tremor has been described in opsoclonus-myoclonus, the use of various other words or phrases has made it unclear whether true oscillatory tremor exists in this syndrome. "Intention tremor" has been described (6,11,18,43,58, 65,77,83,107), as well as "gross" or "coarse tremors" (27,42,51) and "shaking tremor" (86). Less clearly differentiating from fine myoclonic jerks are the terms "trembling" (11,117), "tremulousness" (43,52,80,97,101,126,127), "shakiness"

or "quivering" (11,29), "shaking tremors" (77), and "shaking spells" (77). Associated intention tremors have also been equated to stimulus-sensitive myoclonus (78).

Encephalopathy

Mental and emotional features have been less well documented, but are suggested by use of such terms as anxiety (2), nervousness (102), lethargy (128), malaise (129), fretfulness (130), or irritability (20). Approximately half of the pediatric cases, regardless of etiology (65), are regarded as encephalopathic, but mental clouding is not usually a feature in children (12,77). Irritability may be dissociated from motor abnormalities which it may outlast (65).

In adults, encephalopathy ranges from irritability or mild emotional lability to coma and death (42,131). Altered mental status (apathy, lethargy, confusion) occurred in 58% of 19 adults with paraneoplastic opsoclonus (62,67,83,91,99,128, 123,133), and encephalopathy progressed to stupor or coma in 26% (91,99,128, 132). There was no apparent correlation of encephalopathy with other neurologic abnormalities, suggesting that it is not an obligate feature of the syndrome.

Other Neurologic Problems

Speech problems such as dysphasia, dysarthria with unintelligible speech, or mutism have been reported (5,11,12,18,29,65,71,110,134). Speech may also be normal (44,62,78).

Deep tendon reflexes are normal (20,43,44,78,100,104), decreased (11,53,86, 93), or increased (6,45,51,85,107). Babinski's sign may be present (58,62) or absent (43,44,107).

Muscle tone and strength are usually normal (45,51,104), but hypotonia (7,11, 12,20,45,53,100,106,135), which may be profound (3) and persistent (100), as well as increased tone (11,85) have been noted. A few patients are flaccid (58). Some patients have no head control (3). Only rarely has weakness been reported (36). Apparently, none of the patients have come to muscle biopsy.

Sensory examination is normal (44,45,53,77,85,86).

Other clinical features occur occasionally. Some older patients describe "dizziness" (44,78,100,110) or "vertigo" (62,128,136). Head nodding (20), urinary retention (53), drooling (11), or dysphagia (11,12,137) may occur. Focal or asymmetric features have been found. These include walking to one side (5), head tilt (12,138) or head deviation to one side (77), hemiparesis or unilaterally altered muscle tone (42,77), and asymmetric cerebellar signs (36). Hearing loss as an initial symptom occurs rarely (55). The diagnosis of posterior fossa neoplasm (12,26,29,124,139) or degenerative disease (12) is sometimes suggested. One patient lacked facial expression and tears (11).

DIFFERENTIAL DIAGNOSIS

Tumors outside the CNS and viral infections are the principal etiologies in children and adults, but other etiologies are not uncommon in adults. As many as

half of the cases may be infectious in etiology (65). In pediatric cases, the mean age at onset is about 18 to 20 months (64,65). The youngest child with opsoclonus-myoclonus was apparently 4 months old (35,63). Only 13% of pediatric cases are older than 2 years (65). The age range of adult cases is broader, beginning usually with the third decade. Women are slightly more often affected than men (1.4:1) regardless of etiology. Non-neurologic prodromes occur in 36% within a month of onset of opsoclonus-myoclonus (64). These include upper respiratory or gastrointestinal symptoms with equal frequency (63,140). A minority of cases received vaccinations within a month of neurologic signs (11,12,137–139). Neurologic symptoms may reach full expression earlier in nontumor-related cases, even within one week (65).

Infectious

Several different types of infections are associated with opsoclonus-myoclonus (Table 2) (2,11,12,42–44,51,80,85,96,101,102,141–156). A viral etiology may be the most common cause. The term "benign brainstem encephalitis" has been used (157,158). Viral prodromes of upper respiratory infections or gastroenteritis are typical, but do not rule out an underlying tumor (63). This is especially interesting in view of a proposed viral etiology of neuroblastoma (159). A small but definite group of viral pathogens has been identified from various body fluids of affected patients. Often, an infectious etiology can only be suspected (135,146,148).

Paraneoplastic Syndrome

Paraneoplastic opsoclonus-myoclonus (62,64,65,102,160) (Table 3) is distinct from other paraneoplastic disorders of the nervous system (161,162), such as cerebellar degeneration (163), myasthenic syndrome (Eaton-Lambert) (164), neuropathy and myopathy (165–167), encephalomyelitis (168), and limbic encephalitis (169). Paraneoplastic movement disorders are uncommon except for opsoclonus-

TABLE 2. *Infectious etiologies of opsoclonus[A] or myoclonus[B]*

Agent	Reference
Coxsackie B_3[A,B]	51, 104
Epstein-Barr[A,B]	80
Hemophilus influenzae meningitis[A(B[a])]	85
Herpes zoster[A,B]	141
Immunization[A,B]	12, 154
Lymphocytic choriomeningitis[A]	12
Mumps[A]	44, 141, 143
Neurosyphilis[A]	2
Polioencephalitis[A]	141, 144, 145, 146, 147, 156
Psittacosis[A(B[a])]	101, 148
Rubella[A]	11
Salmonella typhi[A]	149
St. Louis encephalitis[A,B]	43, 150, 151
Tuberculous meningitis[A]	151, 96
"Viral encephalitis"[A,B]	44, 47, 155, 146

[a] Not all cases of opsoclonus were associated with myoclonus.

TABLE 3. *Opsoclonus-myoclonus as a paraneoplastic syndrome*

Clinical feature	Infants		Adults	
Reference	65	65	62	102
Number of cases	45	44	19	11
Sex ratio (male:female)	0.6	0.7	1.1	0.6
Mean age at onset (yr)	1.6 (0.5–5)		57.4 (29–77)	59.1
Prodrome with vomiting	8 (18%)	10 (10%)	14 (74%)	
Onset of neurologic syndrome				
Within 1–2 wk	15[b] (56%)		12 (63%)	
After 1 wk	12[b] (44%)		6 (32%)	
Ataxia	45 (100%)	44 (100%)	18 (95%)	8 (72%)
Myoclonus	45 (100%)	35 (80%)	12 (63%)	5 (54%)
Opsoclonus	45 (100%)	41 (93%)	19 (100%)	11 (100%)
Dysarthria			4 (21%)	
Encephalopathy	19[a] (42%)		11 (58%)	
Course				
Complete recovery		15/25 (60%)		
Remitting-relapsing	10 (22%)	5/25 (20%)	4 (21%)	
2-year survival	(90%)		1 (<1%)	

[a] Irritability.
[b] Of 27 cases described in sufficient detail.

myoclonus. A syndrome of chorea changing to dystonia has been reported in an adult with small cell undifferentiated (oat cell) carcinoma and multiple medical problems (170).

There are a variety of associated neoplasms (Table 4) (3,4,7,20,26,27,29,36,46,56,58–60,62,67,72,83,88,91,97–100,102,109,120,128,131,133,152,171–174). In children, neural crest-derived tumors predominate, such as neuroblastoma. "Gross nystagmoid movements of the eyeballs" were described in a child with neuroblastoma by Foster-Kennedy (175), but a direct connection between neuroblastoma and opsoclonus (58) and opsoclonus-myoclonus (176) was postulated later. In adults, the associated neoplasms are more heterogeneous. Some are also derived from neural crest cells, such as medullary thyroid carcinoma and oat cell carcinoma. However, many neural crest-derived tumors do not induce opsoclonus-myoclonus (Table 5). One such example is the pheochromocytoma, one of the more common pediatric endocrine neoplasms, which secretes pressor catecholamines and induces many symptoms but not myoclonus.

Neuroblastoma originates from primitive sympathetic neuroblasts in the adrenal gland or sympathetic ganglion that do not differentiate (177). Neural crest-derived tumors may be located throughout the body at any site along the pathway of cell migration (65,178,179). The neural crest-derived tumors are more often thoracic when associated with opsoclonus-myoclonus (49–61% mediastinal) (5, 65,180) then nonthoracic (46,181,182), but may originate at abdominal-retroperitoneal (13%), adrenal (13%), sacrococcygeal (1%) or superior cervical ganglion locations (based on 23 cases). Neuroblastoma is the most common extracranial malignant neoplasm of early life (179). Ganglioneuroblastoma and ganglioneuroma occur one fifth and one tenth as often, respectively (183). In patients less than 14 years of age are found about 80% of neuroblastomas and 50% of ganglioneuromas (183). The ganglioneuroblastoma, with its different histologic

TABLE 4. *Tumors associated with opsoclonus[A] or myoclonus[B]*

Primary tumor	Reference
Bladder	
Anaplastic Ca[A,B]	132
Brain	
Glioblastoma[A]	17, 171
Pineal[A]	
Breast	
Infiltrating duct Ca[A,B]	62, 182
Adeno Ca[A]	131
Chondrosarcoma[A]	133
Fallopian tube	133
Adeno Ca[A]	
Lung	
Adeno Ca[A,B]	72
Small cell[A,B]	62, 128
Undifferentiated Ca[A,B]	56, 99
Large cell[A,B]	67
Epidermoid[A]	62
Squamous cell[A]	172
Lymphoreticular	
Lymphoma[A]	88
Adrenal/sympathetic	20, 59
Neuroblastoma[A,B]	3, 4, 26, 29, 58, 98
Ganglioneuroblastoma[A,B]	7, 27, 29, 46, 58, 100, 173
Ganglioneuroma[A,B]	109
Sympathiconeuroblastoma[A]	36, 60
Sympathicoblastoma[A]	120
Pancreas	
Adeno Ca[A]	
Pharynx	
Squamous cell Ca[A]	56
Thyroid	
Medullary Ca[A]	84
Uterus	
Ca[A,B]	91, 174

Ca = carcinoma.

subtypes (184) and sites of occurrence which affect prognosis (185), does occur in adults but apparently is not associated with opsoclonus-myoclonus.

Only 2–3% of neuroblastoma cases present as the paraneoplastic opsoclonus-myoclonus syndrome (28,177,182,186). A 0.5% incidence of occult neuroblastoma

TABLE 5. *Relation of neural crest-derived tumors to opsoclonus-myoclonus*

Induces syndrome	Does not induce syndrome
Neuroblastoma	Pheochromocytoma
Ganglioneuroblastoma	Islet cell tumor
Ganglioneuroma	Carcinoid
Medullary thyroid carcinoma	Paraganglioma
Oat cell carcinoma	Schwannoma
	Neurofibroma
	Merckel cell tumor
	Melanoma

has been reported in one autopsy series of infants less than 3 months of age (187). Spontaneous regression, which occurs by maturation into a ganglioneuroma or by cytolysis (177), is highest for neuroblastoma (188,189). Magnetic resonance imaging (190) and computed tomography (100,109,191–194) with or without ultrasound are more sensitive in detecting neuroblastoma than intravenous pyelogram (sensitivity 50%), plain radiography of chest or abdomen (40%), radionuclide bone scans (^{99m}Tc or ^{67}Ga) (50%), or physical examination (36%) (109,195–197). A 24-hour urine screen for catecholamines is routine. All of these measures may not detect the tumor. Bone marrow aspiration and skeletal surveys are not useful (65).

Failure to find a neuroblastoma does not preclude it as a cause of opsoclonus-myoclonus because it may be difficult to find (38,198) due to the possibility of spontaneous regression of the tumor (26,29,45,189). In 60% of cases, the tumor is found within 3 months (65). A delay in being able to diagnose neuroblastoma for up to four years after opsoclonus-myoclonus first appears may occur (7). The index of suspicion is so high that some patients without neuroblastoma have been followed for tumor for 12 years (35).

Rarely, opsoclonus-myoclonus may follow rather than precede removal of a neuroblastoma (6,199). Delayed onset of 15 months has been reported (199).

In adults, the instigating tumors are often local (56,62,67,72,102,128,173), but may be widely metastatic (62,133,200).

Reports of paraneoplastic opsoclonus without mention of myoclonus (56,58,62,87,91,96,102,133,149,171,172,201) are too frequent to dismiss. However, the absence of myoclonus or other dyskinesias that might actually have been myoclonus is seldom documented (100).

Unlike adults, children with tumor-associated opsoclonus-myoclonus have an excellent prognosis regarding survival: 90% two-year survival rate compared to 30–34% in other patients with neuroblastoma (46,65,182,202–205). Earlier diagnosis and lower tumor stages (206,207) at the time of diagnosis only partially account for improved prognosis. However, some of the tumors are metastatic (7,29,36) and deaths have been reported (7,29,36,120,208). Some of these deaths apparently have been postsurgical complications (7) or, rarely, due to inoperability (120).

Opsoclonus-myoclonus also is frequently associated with pervasive and permanent neurologic and cognitive deficits even after the tumor is removed surgically (16). Psychomotor retardation may persist even when opsoclonus-myoclonus abates (26,29,31,58).

Relapses of opsoclonus-myoclonus are associated with intercurrent illnesses, tumor therapies, changes in medications, and other factors (65). The clinical course may chronically fluctuate (12,18,24,65,116,209) or spontaneously remit (65,96,130,155).

Neuroblastoma may be associated with other neurologic syndromes besides opsoclonus-myoclonus involving the peripheral (Horner's syndrome and palsies of peroneal, phrenic, recurrent laryngeal, or facial nerves or Erb's palsy) or central nervous system (intracerebral, intraspinal) (172,182,210). Occasionally, paraneoplastic opsoclonus-myoclonus may occur with other central involvement such as intradural extension of an abdominal retroperitoneal neuroblastoma (199).

Toxic-Metabolic

Many drugs induce myoclonus at toxic or pharmacologic doses, fewer drugs evoke opsoclonus, and the co-occurrence of drug-induced opsoclonus and myoclonus is uncommon (87,105,153,210,211–260) (Table 6). Some cases are reversible, such as the stimulus-sensitive action or intention myoclonus induced by tricyclic antidepressants (261), whereas others are not. Ketamine hydrochloride reversibly exacerbated opsoclonus and myoclonus in an infant with neuroblastoma-associated opsoclonus-myoclonus (40).

While myoclonus is a feature of several different inborn errors of metabolism, few are associated with opsoclonus. The syndrome of opsoclonus-myoclonus has been observed in an adult with hyperosmolar nonketotic coma (52,95) and a child with multiple carboxylase deficiency (262).

Other Conditions

Opsoclonus occurs in apparently normal newborns (76,263) and rarely (with or without myoclonus) in association with congenital malformations, vascular genetic, metabolic, degenerative, and other acquired disorders (2,52,71,81, 95,262,264–281) (Table 7). Unusual associations of opsoclonus-like movements have also been described (66,91,282).

LABORATORY TESTS

Electroencephalography

Electroencephalography is commonly performed in cases of opsoclonus-myoclonus. Most encephalograms (EEGs) have been normal (3,5,11,12,18,20, 27,29,35,40,43,45,51,89,100,103,190). No epileptiform activity has been reported except in meningitis (85). Slowing, almost always diffuse, usually mild but occasionally severe is sometimes seen in both infants (45,58) and adults (19,62,67,68,78,86,91,95,99,102,218). The EEG may normalize during steroid treatment, but no causal relation has been established.

Clinical seizure activity is extremely rare. In the few reported cases, only a few seizures occurred (45,283,284).

Evoked Potentials

Normal (45,285) as well as abnormal (286) brainstem auditory, visual-evoked and somatosensory responses have been reported. Three children with opsoclonus-myoclonus had mildly abnormal brainstem auditory evoked potentials which were interpreted as indicating tegmental pontine lesions affecting the lateral lemniscus and brachium conjunctivum (106). Delayed wave *V* and prolonged interpeak latencies were found.

Electromyography

Electromyography (EMG) may be used to confirm the myoclonic nature of the dyskinesias (15). EMG bursts are typically brief (20–60 msec) (35). EMG has

shown independent, asynchronous myoclonic jerks at rest, aggravated by voluntary movements (89), with a silent period (19). No correlation has been found between electroencephalography and EMG activity on routine testing (27).

Neuroimaging

Two adults with opsoclonus-myoclonus following an upper respiratory illness were found to have pontine tegmental lesions on magnetic resonance imaging (MRI) (53). One of the cases had visual hallucinations, a lesion at the junction of the pontine basis and tegmentum, and an old lacunar infarction in the right putamen (also shown on cranial computed tomography, CT). However, normal head MRI studies have also been reported in adults (62,102,285). A questionable T_2 hyperintensity in the central and left posterior midbrain was reported in an adult with opsoclonus (287).

Cranial CT scans in most cases of opsoclonus-myoclonus have been normal in children. A low-density cerebellar lesion posterior to the fourth ventricle has been reported (97). One child with opsoclonus-myoclonus had a lesion in the cerebellar vermis (288).

Early studies reported normal skull series (42,43,77,100,101,174), brain scans (100,101,172), and cerebral angiography (56,91,275). Cerebellar atrophy has been noted infrequently on pneumography (27,29,116), but most pneumoencephalograms have been normal (19,71,172).

Cerebrospinal Fluid Studies

Lumbar punctures are usually performed in the acute phase of the illness. Cerebrospinal fluid (CSF) may be normal (11,12,18,27,29,40,45,56,77,78,89, 103,107,113), show isolated pleocytosis (3,18,19,26,42,44,45,51,90,120,149), or pleocytosis with increased protein in intracranial tumor (171) or encephalitis (43). CSF glucose is typically normal. In adults with a paraneoplastic etiology, CSF shows lymphocytic pleocytosis often with slight protein elevation (53%) (62).

CSF immunoglobulins may be normal (18,27), but increased IgG and IgM have been found in a few cases of opsoclonus in CSF (20,80,85,106,172) and serum (172).

CSF oligoclonal bands have been reported (62,80,102,104,106,107).

In cases of extracranial neuroblastoma without opsoclonus-myoclonus, increased lumbar CSF homovanillic acid (HVA) compared to other extracranial tumor controls has been reported (289). HVA, hydroxymethoxyphenyl ethylene glycol (HMPG) and vanillylmandelic acid (VMA) were elevated in six patients with intracranial or cranial neuroblastoma (mean age 5 years) compared to 16 patients (mean age 2 years) with extracranial neuroblastoma. However, controls were not age-matched (mean age 17–33 years), and it is well known that lumbar CSF catecholamine levels are higher in infants than children, which are, in turn, higher than adults.

There has only been one report of CSF neurotransmitter metabolites in opsoclonus-myoclonus (290). In a study of 10 patients, CSF 5-hydroxyindoleacetic acid (5-HIAA) and HVA were decreased in patients with opsoclonus-myoclonus

TABLE 6. *Drugs or toxins associated with opsoclonus[A] or myoclonus[B]*

Substance	Reference
Amitriptyline[A,B]	212, 213, 214
Chlordecone[A,B]	215
Cocaine (intranasal)[A,B]	216
DDT[A,B]	217
Diazepam[A]	87
Lithium-haldol[A]/Lithium[B]	218, 219, 220
Organophosphates[A,B]	105, 221
Phenytoin[A,B]	87
Thallium[A]	201
Toluene[A]	222
Alcohols[B]	229
Amphetamine[B]	229
Apresoline[B]	229
Bemegride[B]	105
Benzamides[B]	252
Biguanides[B]	229
Bismuth salts[B(A?)]	223, 224, 225
Borates[B]	229
Buflomedil[B]	226
Carbamazepine[B]	227, 228, 251
Camphor[B]	105
Cefmetazole[B]	257
Chloralose[B]	235
Chlorambucil[B]	230
Clomipramine[B]	253
Codeine[B]	229
Cycloserine[B]	105
Dextropropoxyphene[B]	229
Dibenzoxazepines[B]	258
Enflurane anesthesia[B]	231
Ethylene glycol[B]	229
Etomidate anesthesia[B]	232, 249, 250
Fentanyl[B]	245
Fluoracetate[B]	105
Hydrazides[B]	232
Imipramine[B]	234
Insulin[B]	229
Isoniazid[B]	153, 229
L-dopa (parkinson patients)[B]	235, 236
Lead[B]	237
Menthol[B]	229
Mercury and its salts[B]	237
Metaldehyde[B]	229
Methaqualone[B]	238
Methyl bromide[B]	239
Metoclopramide[B]	240, 259
Morphine[B]	241
Naloxone[B]	256
Nicotine[B]	229
Nikethamide[B]	229
Norpethidine[B]	242
Paradichlorobenzene[B]	229
Penicillin[B]	242
Pentetrazole[B]	244
Phencyclidine[B]	246

(continued)

TABLE 6. *Continued*

Substance	Reference
Phenelzine[B]	252
Phenol[B]	105
Picrotoxin[B]	229
Piperazine[B]	247
Propfenone[B]	260
Sodium santonin[B]	237
Strychnine[B]	281
Sufentanil[B]	255
Sulfamides[B]	229
Theophylline[B]	229
Tris(hydroxymethyl)aminomethane[B]	229

[a] Described as atypical opsoclonus.

who were 4 years old or younger but not in older children compared to 21 age- and sex-matched controls. None of the patients exhibited increased CSF 5-HIAA. No clinical differences were seen in the subgroup with low CSF 5-HIAA.

The presence of interferon was reported in the CSF of a child with opsoclonus-myoclonus of presumed viral etiology (291).

Tumor Markers and Growth Factors

Both cellular and circulating markers for neuroblastoma have been described (292). Cellular markers include antigens detected by monoclonal antibodies, oncogenes, and radiolabelled MIBG ([^{131}I]meta-iodobenzyl guanidine), a guanethidine analog. The [^{131}I]MIBG scan has replaced the radionuclide scan as a clinical tool to detect neural crest-derived tumors in opsoclonus-myclonus because it is much more sensitive (293). Circulating markers found in blood or urine include

TABLE 7. *Other disorders associated with opsoclonus[A] or myoclonus[B]*

Disorder	Reference
Amaurosis congenita of Leber[A]	264
Congenital/neonatal[A]	76, 263, 264
Vertebrobasilar disorders[A,B]	265, 266
Tectocerebellar dysraphia with occipital encephalocele[A]	267
Multiple sclerosis[A]	71, 268
Friedreich's ataxia[A]	71
Craniofacial dysmorphism[A]	269
Smith-Lemli-Opitz syndrome[A]	270
Familial cerebellar vermis atrophy[A]	271
Thalamic hemorrhage[A]	272
Pontine hemorrhage	102
Hyperosmolar nonketotic coma[A,B]	52, 95, 273
Demyelinating disease[A]	2
Multiple carboxylase deficiency[A,B]	262
Hydrocephalus[A]	81
Lafora disease[A,B]	272
Head trauma[A,B]	275, 276
Palatal myoclonus[A,B]	275, 277, 278, 279, 280

neuron-specific enolase, ferritin, and gangliosides (294). Elevated plasma and tumor concentrations of the disialoganglioside G_{D2} is detected in children with undifferentiated neuroblastoma but not with ganglioneuroblastoma or ganglioneuroma. Tumors lacking G_{T1b} may signify a poor prognosis. Mediastinal neuroblastomas contain more complex b-series gangliosides (G_{D1b} and G_{T1b}) than monosialogangliosides, indicating a more differentiated cellular or membrane composition.

Endogenous and exogenous factors determine the diferentiation and proliferation of neuroblastomas. Endogenous factors include patient age, biological tumor maturation, tumor site innervation, proto-oncogenes, cellular receptors, and peptide growth factors (295). Nerve growth factor (NGF) exerts both differentiating and mitogenic effects on neural structures. Little use of these various tumor markers has been made in opsoclonus-myoclonus.

Clinical and Molecular Genetics

Neuroblastomas have occurred in siblings (296,297), and familial cases often involve multiple primary tumors and are diagnosed at younger ages than sporadic cases. Benign and malignant tumors of neural crest origin occur with increased frequency in neurofibromatosis, an autosomal-dominant disorder. Host or genetic factors are also supported by the hereditary association of essential myoclonus (not opsoclonus) and malignant melanoma (298). A small group of neuroblastomas are associated with deletion of chromosome 13, and may be accompanied by congenital malformations. These observations led to the "two-hit hypothesis" of neuroblastoma, i.e., at least two gene abnormalities are requisite for tumorigenesis, allowing for an inherited factor and some other factor (299). The hypotheses of pathogenesis in paraneoplastic opsoclonus-myoclonus (20,27,29,159,299) are as follows:

Primary carcinogens, simultaneous but independent brain damage and tumor induction. Extrinsic carcinogen may be chemical or virus
Brain damage from metabolite (catecholamine?) liberated by tumor
Immune-complex disease
Hereditary factors in genesis of tumor and neural damage with extrinsic carcinogen

Chromosomal deletions and DNA amplifications have been found in human neuroblastoma. The deleted genes (short arm of chromosome 1) may be tumor-suppressor genes, whereas the amplified genes (multiple gene copies) are cellular oncogenes (300). DMs (double minutes) and HSRs (homogeneously staining chromosome regions) are the sites of amplification of N-myc (chromosome 2p). Amplified L-myc (chromosome 1p) genes are found in human small cell lung cancer cells. N-myc is highly expressed in undifferentiated neuroblasts but not in differentiated ganglion cells. The clinical correlate of N-myc expression appears to be advanced tumor stage (Evans III–IV) (206) and worsened prognosis. N-myc is also amplified in normal fetal brain. Significant aneuploidy (near triploid) in the absence of chromosome 1p deletions and N-myc amplification carries a good prognosis in contrast to near diploidy (301).

Opsoclonus-myoclonus has been reported in second cousins (24). Opsoclonus-myoclonus with neuroblastoma has been reported in Turner syndrome and hemoglobin SC disease (302,303). In four neuroblastomas from children with opsoclonus-myoclonus, single copies of the N-myc oncogene have been found (304).

Monoamines

Catecholamines are often secreted by neuroblastomas and are detected in the urine as the metabolites VMA and HVA in 47–95% of the cases (305–308). The methionine metabolite, cystathionine, is present in urine in 50% of children with neuroblastoma but not in normal children (309).

Could excessive tumor-secreted catecholamines or metabolites induce opsoclonus-myoclonus? It seems unlikely. Most opsoclonus-myoclonus cases with neural crest tumors are not associated with increased urinary catecholamines (4,310, 311), and when they are, tumor removal returns circulating catecholamine levels to normal, but opsoclonus-myoclonus may persist or return (5). Catecholamine neurotransmitters are not lipid-soluble and do not cross the blood-brain barrier. Most hormone-secreting neural crest tumors are not associated with opsoclonus-myoclonus (27). Pheochromocytomas secrete the same catecholamines (other chemicals also), but are not associated with opsoclonus-myoclonus or other dyskinesias.

Tumor catecholamines have been measured as well (312). They do not correlate well with urinary catecholamine excretion patterns or with the degree of histologic differentiation, as seen by light microscopy. A more favorable clinical stage (I, II, IV-S), age more than 1 year at diagnosis, and survival are associated with tumors exhibiting more differentiated patterns of catecholamine metabolism (206). In these tumors, norepinephrine is increased relative to dopamine and dopa (as urine normetanephrine and VMA are increased relative to dopamine and HVA). Serotonin uptake also has been reported in cultured neuroblastoma cells (313).

Immunologic Tests

Several lines of evidence support an immune mechanism of paraneoplastic and parainfectious opsoclonus-myoclonus (20,29,49,314–319) as follows:

- Natural history of spontaneous regression of neuroblastoma
- Lymphocytic infiltrates in tumors from patients with good prognosis
- Lymphocytes cytotoxic to neuroblastoma from affected patients
- Anti-neurofilament antibodies
- Neurologic improvement in some patients after tumor resection or chemotherapy
- Response to ACTH or steroids—immunosuppressive?
- Quantitative serum IgG abnormalities with CSF plasmacytosis
- Better prognosis for survival of patients with paraneoplastic syndrome (implies enhanced autoimmunity which controls tumor growth and spread)

The immune-mediated disorder, myasthenia gravis has been a presentation of neuroblastoma (320). The author is aware of a child with both paraneoplastic opsoclonus-myoclonus and myasthenia gravis.

Circulating anti-neurofilament protein antibodies (MW 210K) were found in sera from two children with opsoclonus-myoclonus (no tumor disclosed) using the immunoblot technique (49). The antibodies, which were not found in CSF, disappeared during treatment with adrenocorticotropic hormone (ACTH) or steroids, when clinical symptoms were alleviated. One of the cases also studied by immunofluorescence exhibited antibodies (IgG) which weakly stained neurofibrillary and membrane components of guinea pig Purkinje cells and rat peripheral nerve axons (321). His immunofluorescence titers fell 5 weeks after beginning ACTH therapy. Sera from 21 children with other neurologic disorders did not stain any proteins in the brain homogenate. Neurofilaments are crucial to the developing nervous system; however, neurofilament protein antibodies have been found in sera from several degenerative neurologic disorders as well as normals (322), and may therefore lack specificity.

In six children with opsoclonus-myoclonus, circulating cerebellar-specific immunoreactivity (MW 27K, 35K, and 62K) was found (323).

No anti-CNS antibodies were found in an adult patient with opsoclonus with ataxia and oat cell carcinoma of the lung (129). Serum antibodies to human Purkinje cells were present in a woman with Stage I intraductal breast cancer, and tumor RNA contained the message coding for paraneoplastic cerebellar degeneration (PCD)-related protein (200,324). In several cases of PCD, circulating antibodies to Purkinje cells have been found (325–329). A few of the patients improved after tumor resection or treatment, which correlated with a fall in antibody titer in one case (330).

In adults, certain autoantibodies suggest a paraneoplastic syndrome due to a specific tumor. Anti-Yo is associated with cerebellar degeneration and gynecological cancers (325), Anti-Hu with small cell lung cancer (331–333), and Anti-RI with opsoclonus and breast cancer (334).

The absence of an autoantibody does not rule out a paraneoplastic syndrome, since many patients do not harbor measurable autoantibodies. This appears to be particularly true for children with opsoclonus-myoclonus who do not exhibit any of the antibodies found in the adult paraneoplastic syndromes (334). It should be noted that the cerebellum is the brain region used to test for autoantibodies. Whereas the rationale for this is strong in adult paraneoplastic cases where cerebellar pathology has been found, it is weak in its application to pediatric cases. There have been no studies using brainstem, which may be more appropriate.

More than 50 monoclonal antibodies have been reported to bind to neuroblastoma cells, but no truly neuroblastoma-specific monoclonal antibody has been found (335). A panel of highly specific monoclonal antibodies is required to diagnose neuroblastoma. Neuroectodermally derived cells possess common antigenic determinants or molecules on the cell surface membrane. Autoantibodies to neuroblastoma cell surface antigens have been reported in neuropsychiatric lupus (336). Neuroblastoma cells contain immunoreactive neurofilament proteins (337). Cross-antigenic reactions between T-cell subsets and Purkinje cells have been reported (338).

Leukocytes from children with opsoclonus showed an abnormal reactivity to neuroblastoma extract (32). Suppressor T-lymphocyte function was depressed in

an adult patient with opsoclonus and breast carcinoma, and the abnormality was reversed with prednisone in parallel with improvement of opsoclonus (339).

Circulating autoantibodies to ACTH were found in one of six children with opsoclonus-myoclonus studied, who had been treated with ACTH for several years with loss of efficacy (340). Lymphocytic infiltrate was noted in the tumors of several patients with opsoclonus-myoclonus (134,302).

TREATMENT

ACTH and Steroids

Symptomatic initial responsiveness to ACTH in children (40 IU per day) may occur in 80–90% of cases (Table 8) (12,20,27,29,65,103). ACTH trials have not been reported in adults. Initial response to ACTH in a few days and complete resolution of opsoclonus and myoclonus in 2 weeks has been reported (12,117) (tumor had been resected). Response to ACTH rather than steroids has been described; however, there have been no controlled comparative studies of ACTH versus steroids (12,20,45,46,103,113). One patient completely responded to a single injection of ACTH (20 units) (12). Apparent ACTH dependence may occur with return of symptoms when the dose of ACTH is lowered. The threshold dose is not absolute (25 IU QOD). Some patients with opsoclonus-myoclonus have remained on ACTH or steroids for years (11,340). Side effects from ACTH include cushingoid appearance, cardiovascular abnormalities, hyperpigmentation, and slowed growth (310). ACTH therapy may result in a false-positive gallium scan (107). Not all patients respond to either ACTH or steroids (5,45) and one case apparently worsened (5).

$ACTH_{1-24}$ (208,276,341) and $ACTH_{1-39}$ (Acthar) (3,12,120) have been used successfully, but no trials of ACTH fragments have been reported in opsoclonus-myoclonus. Dexamethasone (11,45,86,112), prednisone (100,102,107,112,117, 287), prednisolone (7,19), triamcinolone (11), β-methasone (18), hydrocortisone (20), and unspecified steroids have been used successfully. Rapid response to steroids (within 3 days) (45) and steroid dependence (11,45) have been reported.

Response to ACTH or steroids does not differentiate patients with and without tumors (65), and therefore should not preclude need for extensive diagnostic evaluation. There are no data regarding whether early treatment with ACTH or steroids masks or lessens the chances of being able to diagnose an underlying neoplasm. In one infant, ACTH treatment failed and subsequently tumor was found (3). ACTH and steroids may be only symptomatic therapies since long-term outcome does not correlate with drug response (65,137,139). One author reserved prednisone for paraneoplastic cases resistant to cyclophosphamide (342).

It may be noteworthy that an adult patient with metastatic medullary carcinomina of the thyroid (and multiple endocrine neoplasia type I) developed opsoclonus-myoclonus after adrenalectomy for ectopic production of ACTH causing Cushing's syndrome (83).

Drug Therapy

Several other drugs have been used in opsoclonus-myoclonus syndromes (19,23,45,46,62,65,84,88,91,103,104,111,128,131,133,134,137,142,261,282,287,315,

TABLE 8. *Attempted pharmacologic therapies*

Drug	Reference
Acetylcholine	
Trihexiphenidyl	46, 19
ACTH	
$ACTH_{1-39}$	3, 12, 120
$ACTH_{1-24}$	209, 276, 341
Adrenergics	
Propranolol	23, 45, 65
Anticonvulsants	
Carbamazepine	19, 128
Diphenylhydantoin	3
Phenobarbital	3, 102
Primidone	128
Diazepam	3, 19, 60, 91, 103
Clonazepam	45, 62, 84, 114, 134, 141, 282, 343, 384
Nitrazepam	26, 345
Paraldehyde	3
Sodium valproate	128
Chlorazepate	142
Antihistaminics	
Diphenhydramine	3
Meclizine	3
Calcium channel blockers	
Cinnarizine	128
Depleters	
Reserpine	111
Dopamine	
L-dopa	91
Bromocriptine	91
Lisuride	62
Prochlorperazine	128, 287
Promethazine	46
Haloperidol	19, 91
GABA	
Baclofen	62, 133, 287
Other	
Thiamine	62, 83
Piracetam	62
Azathioprine	134
Biotin	262
Nialamide	45
Serotonin	
L-5-HTP	89, 104
Periactin	46
Methysergide	46, 62
Steroids	
Dexamethasone	11, 45, 85
Prednisone	100, 101, 107, 117, 112
Prednisolone	7
Triamcinolone	11
β-Methasone	18
Hydrocortisone	20

343–345) (Table 8), but there have been no large or controlled studies. Anticonvulsants, including diphenylhydantoin (3,11), phenobarbital and diazepam (3,12), and paraldehyde are not effective, but thiopental abolished opsoclonus and myoclonus intraoperatively (40). Often, the anticonvulsant was not specified or drugs

were used in rapid succession without washout. Patients infrequently respond to clonazepam (84); but response to clonazepam was reported in two patients who failed to respond to corticosteroids and propranolol (282,343). The results of propranolol have been mixed: No response (45,65,282) versus improvement (23) (the two responders had not improved with steroids). Other drugs used unsuccessfully in a few cases include haloperidol, L-dopa, bromocriptine, baclofen, meclizine, promethazine, prochlorperazine, trihexyphenidyl, and cyproheptadine. Improvement of myoclonus was reported following intravenous 5-hydroxy-L-tryptophan (L-5-HTP) in one steroid-dependent child (88) and in two adults (104). However, opsoclonus responded in the adults but not the children. Myoclonus responded to thyrotropin-releasing hormone (TRH) or a TRH analog in the same two adult patients (104). Thiamine-responsive opsoclonus was reported in a case of bronchogenic carcinoma (56) but other patients with paraneoplastic opsoclonus have not responded to thiamine (287). Biotin-responsive opsoclonus-myoclonus was reported in a case of multiple carboxylase deficiency (262). The novel antimyoclonic drug piracetam, which is effective in half the cases of cortical myoclonus of other etiologies but in no cases of subcortical myoclonus (346), was not effective in one adult with paraneoplastic opsoclonus-myoclonus (62). The pharmacologic treatment of myoclonus has been reviewed elsewhere (347).

Plasmaphoresis

Plasmaphoresis has been used unsuccessfully in a few cases of paraneoplastic opsoclonus-myoclonus in adults (62,136).

Tumor Therapy

Tumor removal may permanently decrease opsoclonus and myoclonus (3,59, 67,73,103,175), have a partial effect (102), no effect (172), or cause exacerbation. Slow spontaneous resolution of neurologic symptoms may take months or years (5,29). In one case, institution of radiation therapy appeared to be associated with exacerbation (103). As many of half of the cases were found to show neurologic improvement within one month following surgical excision of neuroblastoma (65).

Chemotherapy, which is also immunotherapy, without surgical resection or radiation, although effective tumor therapy, has induced neurologic remission in a few (46,62). Chemotherapy has included cyclophosphamide (45,58), vincristine (302), both (7), plus other drugs (29). More often, chemotherapy, surgical, and radiation therapies are combined (58). The tumor usually does not recur (4,26,27, 31,58,59,114,302), neurologic remission sometimes occurs (7) but is not the rule (29,38,45,46,302). In cases with previously elevated urinary VMA levels, treatment of the tumor may normalize the levels within days (103). In one case, persistently elevated levels of VMA in the urine despite surgery, radiation, and chemotherapy prompted a second laparotomy, with the finding of tumor recurrence (7).

γ-Globulin

Recently, several patients have been given γ-globulin injections empirically. Word-of-mouth reviews are mixed. There are no published data.

NEUROLOGIC OUTCOME

Neurologic outcome does not appear to depend on etiology, age of onset, early treatment, or relapses after infection. Comments on tumors and treatments have already been made.

There is a paucity of data on the clinical features of the chronic syndrome. Myoclonus, opsoclonus, ataxia, and cognitive problems may each respond differently to therapy (11), and cognitive problems may persist in the apparent absence of motor problems (26,29,31,58). The most common chronic motor abnormality is ataxia (16,134).

The nature of cognitive abnormalities is less clear. Several authors use the term mental or psychomotor retardation which occurs in 61 to 82% of the cases regardless of etiology (5,16). Exact results of neuropsychiatric testing are seldom given. IQs of 58–66 have been documented in a few cases (63): Subscores were not provided, but trouble with language was noted. An IQ of 105 was reported in another child with complete recovery (35). One four-year-old child scored only 50 on the Stanford-Binet test.

In one study, 7 of 10 patients had deficits in cognition or intellect, hyperactivity, impulsivity, or emotional lability (284). Hyperactivity, poor speech, and short attention span were found in a few children with severe intellectual impairment (11,29,302). In another report, in 6 of 26 cases not found to be mentally retarded, significant educational handicaps were found (16).

Fatalities are uncommon, but have been reported even for opsoclonus-myoclonus without tumor (16). There are no other reports of a shortened life expectancy. Long-term outcome studies in opsoclonus-myoclonus are needed.

PHARMACOLOGIC HYPOTHESES OF PATHOGENESIS

While altered neurotransmission is the basis of myoclonus (347), there is little direct information linking opsoclonus-myoclonus to a specific neurotransmitter or abnormality. Several lines of evidence, however, suggest a pharmacologic model, although the data are still insufficient to construct one (348).

Molecular Action of ACTH

ACTH may exert its antimyoclonic action by its effects on the brain, functioning as a neurotransmitter or modulating the activity of neurotransmitters. Focus on the brain is appealing because it would explain how ACTH could be effective treatment despite diverse etiologies of opsoclonus-myoclonus.

ACTH may alter neurotransmission in several ways. The redundancy of behavioral information in ACTH peptides is consistent with a multiplicity of binding sites (of high affinity and low capacity) in brain (349). Micromolar activity of $ACTH_{1-39}$ or $ACTH_{1-24}$ has been reported in vitro at serotonin (5-HT) (350), *N*-methyl-D-aspartate (NMDA) (351), opiate and dopamine (352–355), but not benzodiazepine receptors (356). It is interesting that, at all neurotransmitter receptors for which $ACTH_{1-39}$ and $ACTH_{1-24}$ have shown activity in vitro, the

nonsteroidal fragments $ACTH_{4-9}$ or $ACTH_{4-10}$ have been less active or inactive (357).

Only the long ACTH fragments potently increase cyclic-AMP, stimulate phosphoinositide hydrolysis and inhibit protein kinase phosphorylation, enhance lipid fluidity of synaptic plasma membranes, and stimulate protein synthesis (358–359). Besides weak effects at classic neurotransmitter receptor sites, ACTH also increases dendritic arborization in developing brain (360) and exercises other neuromodulatory effects on neurotransmission (349,361,362). The significance of micromolar receptor effects of ACTH is uncertain in view of all the different effects of ACTH which may contribute to its clinical properties. Peptides, because of their tertiary conformation, may interact nonspecifically with a variety of receptors. Although trophic effects on receptor density with chronic ACTH administration have been reported (363–366), the rapid effect of ACTH clinically may require action as a neurotransmitter rather than a neuromodulator. ACTH is found in brainstem in theoretical proximity to "myoclonic centers" (367–368) and its secretion is under monoaminergic regulation in man (369).

Glucocorticoids, which are a consequence of ACTH treatment, stimulate adrenergic differentiation of neural crest tumor cells in culture (370). Although ACTH may modify paraneoplastic opsoclonus-myoclonus through an effect directed at tumor, not brain, this mechanism would not explain its efficacy in opsoclonus-myoclonus due to other etiologies.

Tumor Receptors

If one accepts the assumption that the underlying mechanism of opsoclonus-myoclonus is immunologic (29), then it is necessary to identify the antigenic stimulus shared by tumor and brain. There are many possible candidate substances, but a lipoprotein surface-membrane antigen, one which is involved in neurotransmission and the pharmacology of myoclonus, would appear logical. There is evidence that both host and tumor factors participate in the pathogenesis of this paraneoplastic syndrome. The neurobiological problem is that the mechanism by which only the minority of peripherally located neural crest tumors induce brain dysfunction has remained both intriguing and elusive. Neural crest tumors which induce opsoclonus-myoclonus may be biologically different, since patient survival is greater, the tumor is histologically more differentiated, levels of circulating catecholamines are lower, and the tumor is more often a ganglioneuroblastoma and of thoracic location (46,97,109,312). It is possible that excessive monoamines could be immunogenic, since autoantibody formation associated with methyldopa therapy has been reported (371).

The hypothesis that brain neurotransmitter receptors are the target of autoantibodies to neural tumor receptors or receptor-active tumor products is novel (348). This hypothesis is supported by the identification of neurotransmitter receptors relevant to opsoclonus and myoclonus, such as serotonin, adrenergic, opiate, and cholinergic receptors, in rodent neuroblastoma hybrid cell lines (372–382), research development of monoclonal antibodies to neurotransmitter receptors (383–385), the finding of antibodies in opsoclonus-myoclonus (49), and evidence that

antibodies to neurotransmitter receptors cause neurologic disease (386–388) by autoantibody destruction of neurotransmitter receptors or intrinsic biological activity at those receptors (389). In the central nervous system, autoantibodies directed against GABAergic neurons have been found in stiff-man syndrome (390). Cross-antigenic reactions have also been found between natural killer cells and nervous tissue and between subgroups of T cells and Purkinje cells (338,391).

Human neural crest-derived tumors contain different populations of neurotransmitter receptors. The serotonin 5-HT_{1A}-like receptor recognition site may be a new biologic marker differentiating human ganglioneuroblastomas from neural crest-derived tumors (392–393). The finding that 5-HT_{1A}-like sites are expressed by ganglioneuroblastoma, the tumor most often associated with pediatric opsoclonus-myoclonus, but not by neuroblastoma or ganglioneuroma (394), is highly relevant to animal studies linking myoclonus to 5-HT_{1A} receptors (395). 5-HT_3 and 5-HT_{1E} binding sites have been found in human neuroblastomas (396). Tumor serotonin receptors may be relevant because L-5-HTP is useful in some forms of myoclonus, particularly posthypoxic action myoclonus (397,398). Its therapeutic action is dependent on decarboxylation to 5-HT in the CNS. 5-HT has equal affinity for the various 5-HT_1 receptors. Chronic treatment with L-5-HTP in the rat alters cortical 5-HT_2 receptors (399). Delineation of the role of each of these subtypes in human myoclonus and in the action of L-5-HTP is incomplete. In rodents, involvement of the 5-HT_{1A} and the functionally linked 5-HT_2 receptor has been identified (395). However, the other newer sites have not been studied. Antibodies to 5-HT_{1A} receptors have been reported in CSF of some patients with autism (400). However, other neural crest tumors beside ganglioneuroblastoma evoke opsoclonus-myoclonus.

Receptors must be measured in tumors which evoke the paraneoplastic syndrome to test this hypothesis. Further, without a complete survey of neurotransmitter receptors on human neural crest-derived tumors, it would be premature to focus on any one receptor. Some human neural crest tumors also contain peripheral benzodiazepine receptors (401). Nerve growth factor receptors are found both in neuroblastoma and cerebellar Purkinje cells. Receptors for NGF are located on the cell-surface membrane, neuronal synaptic terminals, and the nucleus. A "slow" NGF receptor on the plasma membrane is the probable NGF binding site for biological responses such as neurite outgrowth.

Cell surface receptors on neural crest-derived tumors have implications both for oncogenesis and chemotherapy. 5-HT receptors and perhaps other tumor receptors, which mediate the effect of 5-HT as a growth and differentiating factor in developing brain, may trigger malignant transformation; the 5-HT receptor functions as a protooncogene (402). In contrast, tumor receptors may also be a target for chemotherapy. The neurotoxic analogue of dopamine, 6-hydroxydopamine, enters neuroblastoma cells via surface catecholamine receptors, and reduces tumor growth (403).

The *p,p'*-DDT Myoclonic Model

Since the insecticide DDT induces opsoclonus in humans and myoclonus in both humans and animals (404,405), it may be useful to review the involvement of

neurotransmitters in its action. The cerebellum may be the principal site of action of DDT (405). In the *p,p'*-DDT mouse model, L-5-HTP is antimyoclonic (406). Microinjection of *p,p'*-DDT into the inferior olive, cerebellar dentate nucleus, or the red nucleus (280,407) (Guillain-Mollaret triangle) induces myoclonus in the rat.

A related insecticide, chlordecone, increases 5-HT turnover, reduces the density of 5-HT_1 but not 5-HT_2 receptors in striatum and hippocampus, and induces tremors blocked by 5-HT antagonists (408).

A new, potential antimyoclonic therapy is the glycine prodrug milacemide (2-*n*-pentylaminoacetamide). Milacemide, an effective anticonvulsant, readily penetrates to the brain and is metabolized primarily to glycine and glycinamide (409). γ-Aminobutyric acid (GABA) levels are also increased in the basal ganglia. The therapeutic index of milacemide is high (410). In the *p,p'*-DDT model, milacemide is antimyoclonic (411). Monoamine oxidases participate in the deamination of milacemide to glycinamide.

REM Sleep Myoclonus and Atonia

Sporadic myoclonus occurs physiologically, although paradoxically, during the rapid eye movement (REM) periods of active sleep (412) when the body is otherwise functionally paralyzed and flaccid (atonia) (413). Sleep also regulates eye movements (414,415). This is a dynamic process which is actively regulated, but may fail. Atonia may be pathologically absent during REM sleep (416). Because pathologic myoclonus and opsoclonus may persist during sleep, the neural mechanisms of REM motor control also may be dysfunctional in the opsoclonus-myoclonus syndrome. The anatomic and pharmacologic basis of those mechanisms may shed light on the pathophysiology of the opsoclonus-myoclonus syndrome. The classic view is that myoclonus is evoked by sensory influxes at the medullary level when forebrain inhibition is lost (417).

Myoclonus due to lesions of the lower brainstem or spinal cord increases during light non-REM (NREM) sleep, but attenuates during REM (418). Activation of myoclonus under these circumstances may be due to dissociation of spinal α- and γ-motoneuronal activity. In NREM, α-motoneuron activity is depressed but γ-activity is unchanged, whereas in REM, the activity of both motoneurons is depressed (419). In contrast, opsoclonus-myoclonus is diminished in light NREM (Stage 2) and reappears in REM (86). This same pattern applies to the ocular oscillations and myoclonus of palato-ocular myoclonus which results from various intrinsic brainstem lesions (66).

REM periods are characterized by increased motoneuron inhibition which results in atonia, and bursts of overpowering excitation, which result in myoclonus. The inhibition [large amplitude inhibitory postsynaptic potentials (IPSPs)] is apparently mediated by glycine. The excitations [excitatory postsynaptic potentials (EPSPs)], which are mediated by a non-NMDA neurotransmitter (420), begin as hyperpolarization but are followed rapidly by a depolarizing shift and an action potential (420).

Myoclonus may reflect the high activity of the nervous system during REM

sleep, when cortical and subcortical neurons discharge at uncharacteristically rapid rates and activity along motor pathways is enhanced (421).

Both tonic and phasic aspects of REM sleep result from brainstem activity (422). Deinhibitory drive originates in the pons with a cholinoceptive trigger zone in the dorsolateral pontine tegmentum, which may be the nucleus pontis oralis (420,423) or the peri-locus ceruleus alpha (424). The excitatory drive emanates from the medulla in the nucleus gigantocellularis reticularis (420,423) or the adjacent nucleus reticularis magnocellularis (424). The nucleus gigantocellularis reticularis is known from previous studies to be a myoclonus generator (417). Microinjection of NMDA agonists into the nucleus magnocellularis of the decerebrate cat induces myoclonus (and increased muscle tone) and NMDA antagonists block the myoclonus (but not the muscle tone) (425). Of possible relevance to opsoclonus-myoclonus is the observation that corticotropin-releasing factor (CRF), which releases ACTH in brain, also inhibits NMDA agonist-induced myoclonus.

The Saccadic System

The saccadic system depends on the interaction of "burst" cells and "omnipause" cells both of which reside in the brainstem (426). Burst neurons, located in the paramedian pontine reticular formation, are silent until just before or during a saccade, when they drive ocular motor neurons to create saccades (427). In contrast, omnipause neurons cease firing when burst cells fire and inhibit burst cells during fixation (426).

The mechanism of opsoclonus or ocular flutter have been attributed to a disorder of burst cells (428) or in pause cell control of burst neurons (427). Increased saccadic velocities with normal amplitude (428) would favor excessive burst cell discharge, but have not been uniformly recorded (429). The presence of this "brainstem generator" for saccades suggests a brainstem origin for opsoclonus and a cerebellar locus for ocular flutter and dysmetria (2,272). There is no consensus, however. The mesencephalic tegmentum (171) has been implicated in opsoclonus. The continuum of opsoclonus, ocular flutter, and ocular dysmetria has also been related to cerebellar disease (429). The influence of the cerebellum on eye movements (430,431) has led some to argue that opsoclonus is purely cerebellar (432). Similarly, myoclonus has been attributed to the cerebellum (433,434), but such cases are more likely due to a brainstem mechanism for myoclonus possibly with cerebellar inputs which the cerebellar lesion has disrupted. Supratentorial mechanisms also influence saccades (435,436).

Putative omnipause neurons in two patients with opsoclonus associated with oat cell lung carcinoma were normal by light microscopy (437). However, the location of the respective neurons in humans has not been established. In an idiopathic case of opsoclonus-myoclonus, no abnormalities were seen in the paramedian pontine reticular formation of the caudal pons (438).

The neurotransmitters for burst cells and omnipause cells are not known. Methyltyrosine (439) and L-tryptophan (440) produce square-wave jerks in normals implicating monoamines in pause cell control (439). Saccades can be modified experimentally by GABA-ergic drugs (441).

Neuropathologic Clues

In one autopsied case, brain changes were restricted to the cerebellum and included peridentatal demyelination, gliosis, and loss of Purkinje cells (110).

In adult paraneoplastic syndromes, variable histologic abnormalities have been described including mild Purkinje cell loss, lymphocyte infiltration, cerebellar gliosis, edema, and demyelination around the cerebellar dentate nucleus (99,174, 442).

Pathologic changes in patients with clinical brainstem involvement have been found most often in the medulla or pons, especially in the inferior olivary nuclei (168,443–445). A so-called idiopathic case had both cerebellar and inferior olivary lesions (438). Findings suggestive of midbrain encephalitis have been described as a remote effect of malignant neoplasm (446).

A child with opsoclonus-myoclonus was biopsied because neuroradiological studies indicated a lesion in the cerebellar vermis: Purkinje and granular cell loss with gliosis were found (288). Pathologic changes of encephalomyelitis restricted to lower medulla and upper cervical spinal cord were found in an adult with opsoclonus-associated oat cell lung carcinoma (287). Loss of internuncial spinal neurons was found in a case of opsoclonus with myoclonus but the brainstem was not studied (447). A frontal cortical biopsy in another child revealed no significant histological abnormalities (12).

It has been suggested on the basis of stroke anatomy in the vertebrobasilar circulation in four patients that opsoclonus with palatal myoclonus indicates lesions of the upper cerebellar crus (path of the dentato-olivary fibers and fibers connecting the cerebellar flocculus with oculomotor nuclei) (279). Palatal myoclonus alone suggests lesions instead of the cerebellar dentate nucleus and central tegmental tract of the brainstem. There was a delay of 1.5 to 4 months before opsoclonus and/or myoclonus appeared. Opsoclonus (with myoclonus) may occur with ocular bobbing, which is usually pontine (448).

Cognitive Functions of Cerebellum and Motor Nuclei

It has been suggested that the occurrence of mental retardation in opsoclonus-myoclonus indicates a more widespread effect on the CNS than on the cerebellum alone (7). However, in animals, there is evidence that the cerebellum and inferior olives influence learning (449). It has been proposed that the cerebellum is the seat of motor learning through the mechanism of climbing fiber synapses on Purkinje cells (450). However, lesions of the inferior olives, from which climbing fibers emanate, prevent motor learning, suggesting that the inferior olives are principally involved (451). The cerebellum contributes to oculomotor plasticity. There is some evidence that the cerebellum also has a role in cognitive behaviors besides motor learning, for which the repository site of learning may be the cerebellar target areas rather than the cerebellum itself (449,452). These behaviors include spatial learning (connections between cerebellum and frontoparietal association cortex, limbic system, and superior colliculus), discrimination learning (projections to cerebellum via pontine nuclei), and emotions such as fear (reticular activating system, limbic system, and hypothalamus) (449). In adults with psychi-

atric disorders and cerebellar lesions, cerebellar dysfunction may contribute to a syndrome of reduced memory, concentration, abstraction, labile affect, and impaired social skills and environmental adaptation (453). In children, cerebellar pathology has been described in autism (454).

CONCLUSIONS

Myoclonus in opsoclonus-myoclonus is predominantly evoked by action and sensory stimuli and often results in major functional impairment of gait and sitting. The tremulous appearance of these patients is more likely due to the characteristically small amplitude and rapid myoclonic jerks than to the presence of tremor. The relative contribution of cerebellar dysfunction in opsoclonus-myoclonus is unclear because myoclonus-induced motor incoordination may be difficult to differentiate from primary cerebellar ataxia. Both may contribute to the dysarthria of some patients. While the syndrome may resolve, permanent neuropsychiatric sequelae are common in children, and myoclonus has less of a place in the chronic phase than ataxia and learning and behavioral problems. The occurrence of anxiety is so common in the acute phase that hypothesizing an associated anxiety disorder may contribute to understanding the pathophysiology.

Opsoclonus-myoclonus is one of the few recognized paraneoplastic dyskinesias; it is a remote effect of certain tumors. As a putative autoimmune-mediated dyskinesia, it is part of a group that includes Sydenham's chorea, and chorea of CNS-lupus. It also overlaps with the syndrome of acute cerebellar ataxia of childhood. Opsoclonus-myoclonus is a syndrome, not a single disease, which also may be induced by drugs and toxins, metabolic disorders, congenital and degenerative disorders, and infections. An immunologic theory of opsoclonus-myoclonus may explain its association with a viral syndrome or with peripheral tumors. The tumors in children tend to be histologically and biochemically more differentiated, more often thoracic, and associated with a greater survival rate than those without a paraneoplastic syndrome. Molecular genetic studies of cellular oncogenes have not identified a difference between tumors with and without a paraneoplastic syndrome, despite the chromosomal and DNA abnormalities found in human neuroblastoma. Various circulating anti-CNS antibodies have been found in paraneoplastic syndromes in adults, but only an anti-neurofilament protein antibody has been detected in pediatric opsoclonus-myoclonus. The absence in children with opsoclonus-myoclonus of the autoantibodies typically found in adults may be due to using the wrong brain region against which to test for antibodies: cerebellum rather than brainstem.

Understanding the locus of opsoclonus-myoclonus may rely more on theoretical clues than from neuropathologic or neuroradiologic studies, which are unrevealing in the majority of cases. The proximal and distal generalized distribution of myoclonus, absence of enlarged somatosensory evoked potentials, and rarity of associated seizures favors a subcortical origin of myoclonus. Opsoclonus has only slightly greater localizing value than myoclonus, but a primary brainstem mechanism for each is likely with regulatory inputs from cerebellum and cerebrum. The mechanism for opsoclonus and myoclonus are independent but neighboring since

either disorder may occur separately but their co-occurrence is not random. If the occurrence of opsoclonus-myoclonus were indicative of a diffuse injury, convulsions, other dyskinesias besides myoclonus, paresis, and coma should be more prevalent; but in children with opsoclonus-myoclonus, they are rare. Therefore, the injury of subcortical structures with dual motor and cognitive functions, such as the inferior olive and cerebellum, is plausible (this may be analogous to the occurrence of obsessive-compulsive disorders in Sydenham's chorea). A brainstem origin is supported by the location of burst and omnipause cells of the primate saccadic system and the role of the brainstem in both the tonic and phasic aspects of REM sleep, during which myoclonic jerks may appear. Failure of glycine-mediated inhibition or excessive activity of a non-NMDA excitatory neurotransmitter in the medullary reticulum has been proposed.

Little is known about the pharmacology of opsoclonus-myoclonus because neurochemical data are lacking and there have been inadequate clinical drug trials. ACTH is the most often used and effective drug in childhood-onset opsoclonus-myoclonus but is also problematic. The main issue which must be clarified is whether ACTH exerts its antimyoclonic action by suppressing ongoing antibody-mediated injury to the CNS or by modifying neurotransmission, as a neurotransmitter or neuromodulator. If ACTH is providing only symptomatic therapy, then it may be supplanted by other more selective and less toxic drugs. Clonazepam, propranolol, or L-5-HTP sometimes may be useful. Biotin- and thiamine-responsive etiologies, though rare, should be ruled out. The induction of opsoclonus-myoclonus by a variety of drugs and chemicals supports a neurotransmitter disturbance as the basis of opsoclonus-myoclonus, but no single neurotransmitter seems to mediate the effects of all the diverse drugs and chemicals which can induce opsoclonus or myoclonus. Neurotransmitter receptors on human tumors may provide the link between pharmacologic and immunologic models of opsoclonus-myoclonus. However, since there is no animal model of paraneoplastic opsoclonus-myoclonus, this remains speculative. The capacity of the insecticide *p,p'*-DDT to induce myoclonus in human and animals may be important because the glycine prodrug, milacemide, is antimyoclonic in the *p,p'*-DDT animal model. More basic research in opsoclonus-myoclonus is needed before treatment can be improved for these unfortunate patients.

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