Neuroepidemiologic Trends in 105 US Cases of Pediatric Opsoclonus-Myoclonus Syndrome

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Opsoclonus-myoclonus syndrome (OMS) is a rare, autoimmune neurological disorder that is poorly recognized and undertreated. Neuroblastoma is found in one half of the cases. Because of the high incidence of spontaneous regression of neuroblastoma, it is unknown whether not finding a tumor means there was none. To define demographic trends and the standard of care in the first large series of OMS, 105 children were recruited over a 13-year period in a retrospective questionnaire survey. Children with and without a tumor differed little in viral-like prodrome and neurological symptoms. Earliest neurological symptoms were staggering and falling, leading to a misdiagnosis of acute cerebellitis. Later symptoms included body jerks, drooling, refusal to walk or sit, speech problems, decreased muscle tone, opsoclonus, and inability to sleep. Tumor resection alone did not provide adequate therapy for most. Adrenocorticotropic hormone (ACTH), prednisone, and intravenous immunoglobulin were used with equal frequency, but ACTH was associated with the best early response. More than one half of the children had relapses. Residual behavioral, language, and cognitive problems occurred in the majority. The delay in diagnosis (11 weeks) and initiation of treatment (17 weeks) is unacceptably long.

Key words: *Kinsbourne syndrome, ataxia, neuroblastoma, paraneoplastic syndrome*

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Background and Significance

Opsoclonus-myoclonus syndrome (OMS) has been called by various names, such as Kinsbourne syndrome, myoclonic encephalopathy (Kinsbourne, 1962), dancing eyes (Cushing & Wolbach, 1927), opsoclonus-myoclonus-ataxia (Cooper et al., 2001), and opsomyoclonus (Talon & Stoll, 1985). Because the appearance of the syndrome can herald occult neuroblastoma (Solomon & Chutorian, 1968), most symptomatic children are screened for tumors by various neuroimaging studies, as well as blood and urine tumor markers (Haase, Perez, & Atkinson, 1999; Posada & Tardo, 1998; Shapiro, 1995). Nurse practitioners and other health care members in pediatric oncology are often perplexed when no tumor is found. The high index of suspicion usually results in repeated retesting, fueled by rare reports of finding a tumor years after initial presentation (Pranzatelli, 1992).

In children without a demonstrated tumor, a viral etiology is inferred, often based on a "viral prodrome"

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consisting of upper respiratory or gastrointestinal symptomatology (Boltshauser, Deonna, & Hirt, 1979). Occasionally, the presence of a neurotropic virus, such as coxsackie B, Epstein-Barr, parvovirus B19, enterovirus 71, and St Louis encephalitis, has been reported (Estrin, 1977; Gennery, Cant, & Forsyth, 2001; Kuban, Ephros, Freeman, Laffell, & Bresnan, 1983; McMinn, Stratov, Nagarajan, & Davis, 2001; Sheth, Horwitz, Aronoff, Gingold, & Bodensteiner, 1995; Tabarki, Palmer, Lebon, & Sébire, 1998), but extensive or systematic viral screening in OMS is not routine. However, presence of a viral prodrome or cerebrospinal fluid pleocytosis does not rule out a neuroblastoma (Boltshauser et al., 1979; Mitchell & Snodgrass, 1990). Also, neuroblastoma had a notorious tendency toward involution (Everson & Cole, 1966).

We wished to determine if there were significant differences in the demographics of the 2 etiologic subgroups, as a way of exploring the hypothesis that neuroblastoma may have spontaneously remitted in the cases in which no tumor was found. We also wanted to gain insight into treatment practices and outcomes pertaining to conventional immunotherapy, chemotherapy, and tumor resection. Finally, we sought to determine how timely and accurate diagnosis and initiation of treatment were in the United States. To accomplish these goals, we surveyed parents of the children with OMS who were recruited through our center.

Methods

Subject Population

One hundred five children with OMS were recruited through the National Pediatric Myoclonus Center and its Web site www.omsusa.org from 1990 to 2003. The diagnosis was made by a pediatric neurologist or hematologist/oncologist. The children recruited were representative of the OMS population as a whole (Boltshauser et al., 1979; Pranzatelli, 1992; Talon & Stoll, 1985).

Questionnaire

Parents were asked to answer 62 questions in an OMS Parental Survey. Parents were asked to provide the following demographic information: child's age, gender, race, and education. They also answered questions regarding the history of their child's illness. Parents were asked to rank prodromal symptoms and signs of OMS stated in lay terms. Items included if the child had a tumor or not, what treatment was given both medically and surgically, and what was the outcome. Other questions detailed relapse information and behavioral and cognitive problems. Fifty-two questions were in a "yes/no" format, and 5 others required a Likert-type scale grading system. Thirteen questions, some of which were subsections of other types of questions, required specifying an age or a length of time. One question required ranking by order of symptom appearance. The research assistant made a telephone call to follow up on any unanswered questions.

Statistical Analysis

The prevalence of different categories for each variable was analyzed, and results were given as percentages. The 3 main independent variables we evaluated were OMS etiology (tumor vs no tumor), age of OMS onset (infant, toddler, preschool and older), and treatment (adrenocorticotropic hormone [ACTH] or steroids vs other). Comparisons between study groups for discrete variables were performed with the chi-square (χ^2) or Fisher's exact test. Continuous variables were compared by *t* tests or nonparametric tests where appropriate, and the data are presented as means and standard deviations. A *P* value of $<.05$ was considered statistically significant. The statistical analysis was done using the SAS system (SAS Institute Inc., 2002).

Results

Demographics

The distribution of OMS cases tended to follow US population density (Figure 1). White non-Hispanics accounted for most patients (Table 1). The mean age of onset was not significantly affected by etiology (Figure 2): 1.6 ± 0.7 years in the no-tumor group and 1.8 ± 1.0 years in the tumor group. There were no significant gender differences. There were no familial cases; this included several families with a twin sibling.

Table 1. Clinical Information

Parameter	Number of Patients	%
Gender		
Male	49	47
Female	56	53
Race		
White/non-Hispanic	92	88
White/Hispanic	6	6
African American	4	4
Indian	1	1
Asian/Oceanic	0	0
Native American	1	1
Etiology		
Tumor	44	42
No tumor	61	58
Tumor location		
Thoracic	7	30
Abdominal	11	48
Other	5	22
Tumor type		
Neuroblastoma	38	88
Ganglioneuroblastoma	5	12

Parental Information

At the time of the child's birth, maternal age (n = 70) was 28.6 ± 5.0 years (range, 17-37 years), and paternal age (n = 66) was 31.2 ± 5.2 years (range, 18-43 years). Eighteen percent of mothers who worked had jobs in health care. Sixty-three percent worked during pregnancy, and 34% reported being sick. There were no significant differences in the tumor and no-tumor groups.

Prodrome

Antecedent nonneurological symptoms were irritability, upper respiratory symptoms, ear infections, fever, lethargy, vomiting, and diarrhea (Figure 3). Irritability was the most common prodromal symptom, occurring in 50%. Fever and symptoms of upper respiratory infection occurred in at least 25%, with all other symptoms occurring below that frequency. Rashes were very uncommon.

In a statistical comparison of prodromal symptoms by OMS etiology, there was a significantly higher frequency of upper respiratory symptoms ($P = .0013$, χ^2) and fever ($P = .022$) in the no-tumor group, with nearly significantly higher frequencies of lethargy ($P = .050$) and diarrhea ($P = .087$). The presence of vomiting did not reliably differentiate between the 2 OMS etiologies. No prodromal symptom was found exclusively only in 1 etiologic subgroup of OMS.

Neurological Onset of OMS

The earliest neurological symptoms by rank order were ataxia, falling, myoclonus, tremor, and drooling. Later symptoms included refusal to walk or sit, speech problems, decreased muscle tone, and opsoclonus. Fifty percent of the children were unable to sleep through the night. Behavior problems became more prominent and difficult to control. Seventy percent of parents thought the child's tremulousness was generalized. Fifty-seven percent noted opsoclonus on tracking, 49% at rest. Expressive language was most affected, ranging from mutism to severe dysarthria that was unintelligible to nonfamily members.

Antecedent Immunizations

More than 85% of the children had received immunizations (measles, mumps, rubella; hemophilus influenzae type B; oral polio vaccine, polio, hepatitis B, diphtheria, pertussis, tetanus [DPT]; or diphtheria, tetanus toxoids, and acellular pertussis) prior to onset of neurological problems. However, the interval from the last DPT to diagnosis (n = 70) was 32.5 ± 29.8 weeks (range, 0-182 weeks). Only 2 children received DPT within 1 week of OMS onset.

Diagnosis

Most children with OMS were initially misdiagnosed. There was an average delay to correct diagnosis of almost 3 months, with a maximum delay of 26 months (Table 2). The most common misdiagnosis was acute cerebellitis, but other diagnoses included otitis media, labyrinthitis, and Guillain-Barre syndrome.

Screening for Neuroblastoma

Forty-one percent of the children were positive for a tumor, which was most often neuroblastoma but also ganglioneuroblastoma. Tumor location was usually

Figure 1. Geographic Location of Participating Opsoclonus-Myoclonus Syndrome (OMS) Families
NOTE: Each dot represents the residence of a child with OMS. Using standard regional boundaries, 26 were from the Northeast, 14 from the Southeast, 34 from the Midwest, and 19 from the West. The map was generated using Mapland 2002 for Microsoft Excel.

abdominal or thoracic, sometimes pelvic; the sites did not differ significantly in frequency.

Timeliness of Therapy

For all treatments, there was an average delay in initiating therapy for at least 2 months, and for most, it was several months (Table 2). The delay was shortest for steroids and longest for plasmapheresis. For ACTH, steroids, and intravenous immunoglobulin (IVIG), OMS etiology had no significant effect on elapsed time until treatment.

Effect of Immunotherapy

The most commonly prescribed treatments for OMS included ACTH, steroids, and IVIG. A dramatic initial response to ACTH was reported in 83% of the cases, whereas it occurred in only one half of the cases treated with steroids or IVIG. Less than one third of the responses to azathioprine, cyclophosphamide, or plasmapheresis were deemed dramatic, but the sample size was too small to be reliable.

Thirty percent of children with tumors (n = 44) were treated with chemotherapy, which was significantly lower than those managed without chemotherapy ($P < .0001$). The most common agent was cyclophosphamide (62%). Other agents included carboplatin, doxorubicin, and VP16. Parents who rated chemotherapy effectiveness (n = 8) thought there was improvement or no change.

Effect of Tumor Resection

Only 37% of children with a tumor (n = 41) improved neurologically after tumor resection. Another 32% remained unchanged. The remaining 32% actually worsened.

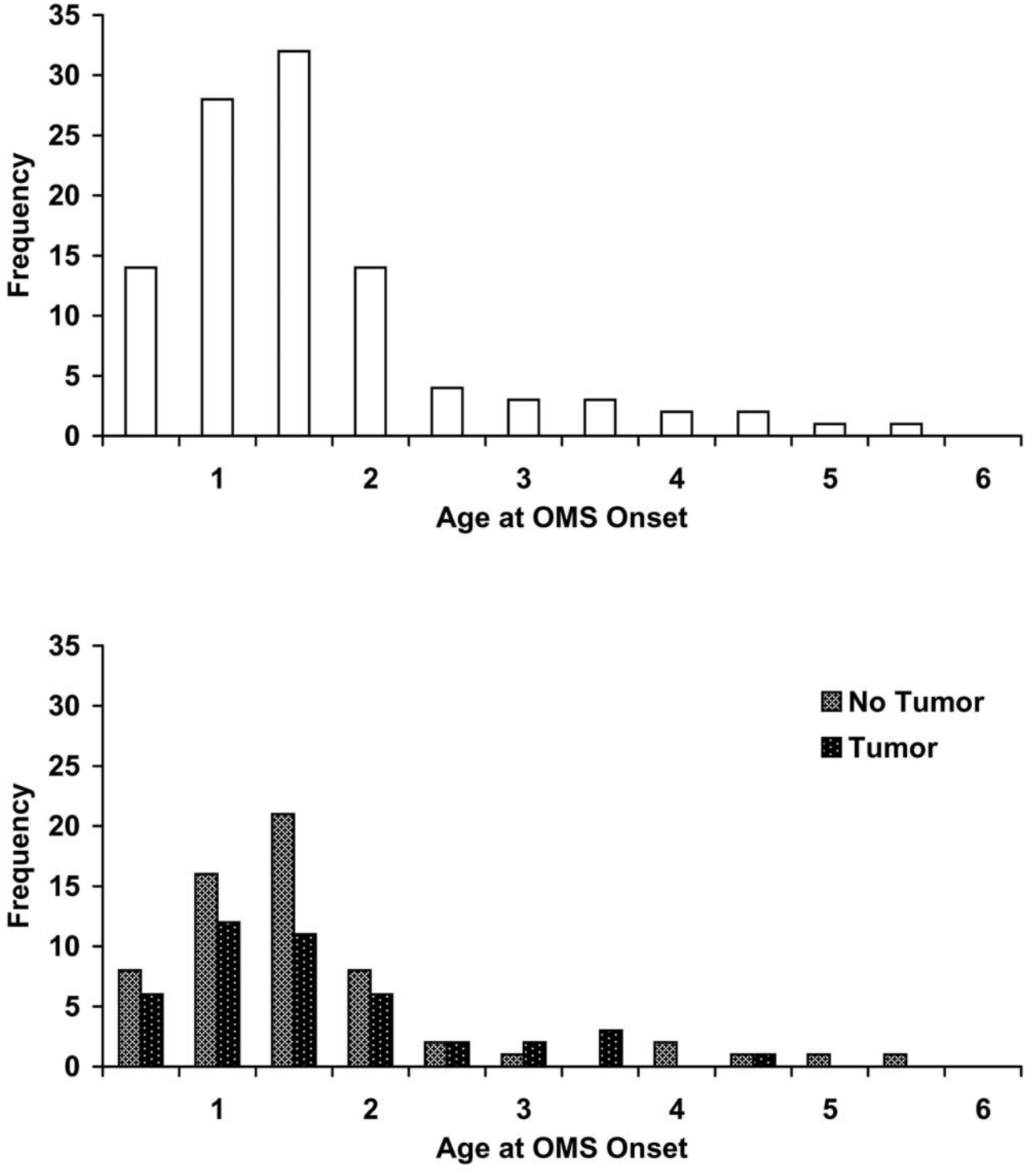

Figure 2. Frequency Plot of Age at Opsoclonus-Myoclonus Syndrome (OMS) Onset in All OMS (upper) and According to Presumed Etiology (lower)
NOTE: The no-tumor and tumor groups were not significantly different.

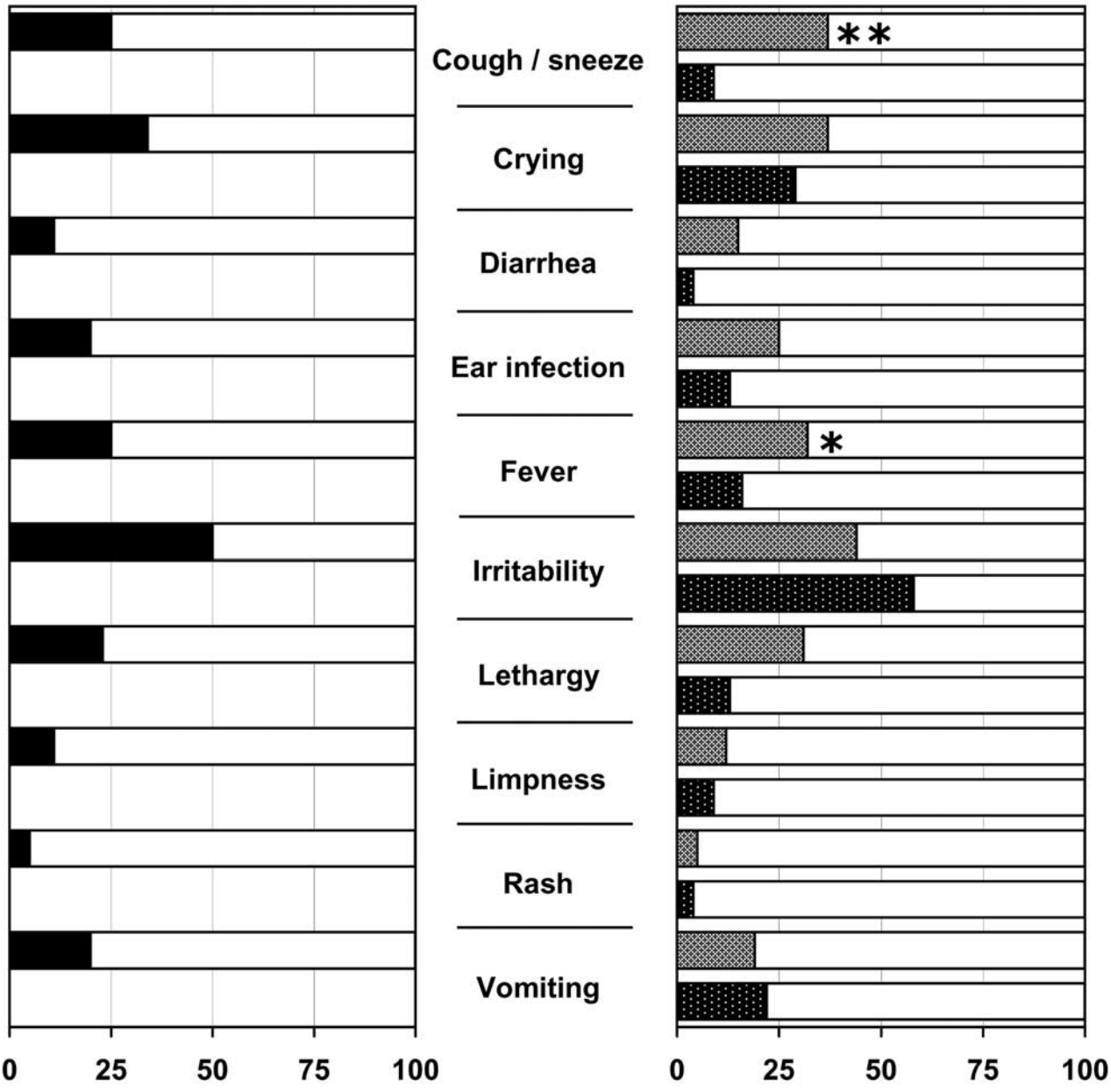

Figure 3. Histogram of Prodrome Symptoms in All Opsoclonus-Myoclonus Syndrome (left) and in Etiologic Subgroups (right)
NOTE: Throughout the right figure, the no-tumor group (upper bar) alternates with the tumor group (lower bar). Asterisks signify statistical significance by χ^2: *.01 ≤ P < .05; **.001 ≤ P < .01.

Relapse

Neurological relapse occurred in 52% of 100 cases. Fifty-eight percent of the respondents answered it was provoked by illness with fever. Another precipitant was drug tapering (52%), specifically ACTH (70%). Illness increased shakiness (myoclonus) in 86% (n = 88), and the severity was moderate or severe in 83% of those. There was no significant effect of OMS etiology.

Relapse frequency information was available for 29 children. On average, 2 to 4 relapses were reported, 1 to 3 of which were mild. Fifty-nine percent of relapsing children had at least 2 relapses.

Table 2. Elapsed Time to Diagnosis and Treatment

Variable	Etiology	Number of Patients	Mean Time (weeks)	Range*	$P^{\dagger}$
Until correct diagnosis					
	All opsoclonus-myoclonus syndrome (OMS)	72	11.3 ± 20.9	0.14-130	
	Tumor	29	8.3 ± 19.2	0.14-104	.33
	No tumor	43	13.3 ± 21.9	0.14-130	
From diagnosis to treatment					
	All OMS	80	6.0 ± 14.3	0.25-104	
	Tumor	38	7.2 ± 17.2	0-104	.48
	No tumor	42	4.9 ± 11.2	0-72	
Until specific treatment					
	Steroids				
	All OMS	55	9.7 ± 12.6	0-52	
	Tumor	21	10.2 ± 14.0	0-52	.83
	No tumor	34	9.4 ± 11.9	0.14-52	
	Adrenocorticotropic hormone				
	All OMS	50	15.8 ± 23.0	0-104	
	Tumor	22	17.9 ± 28.8	1-104	.60
	No tumor	28	14.2 ± 17.6	0.14-86	
	Intravenous immunoglobulin				
	All OMS	44	17.5 ± 22.8	0-88	
	Tumor	22	15.9 ± 22.5	1-86	.65
	No tumor	28	19.1 ± 23.5	0-88	
	Cyclophosphamide	5	13.1 ± 8.8	4-26	
	Azathioprine	7	78.1 ± 47.8	26-156	
	Plasmapheresis	2	84.5	65-104	

*Values are means ± SD.
†Statistical comparisons were made between the tumor and no-tumor groups.

Neurological Sequelae

Neurological sequelae were common in OMS (Figure 4). OMS etiology had no significant effect on the frequency of neuropsychiatric signs. No neurological abnormality was found solely in one OMS etiologic subgroup. Each of the sequelae is detailed in the following sections.

Schooling and Adjunctive Nonpharmacological Therapies

Of school-age children (n = 49), 41% were in special education, 24% in mainstream, and 35% in combined programs. There was no significant difference between the categories. Twenty-nine percent had been held back a year, 4-fold more in the tumor group (P = .012, χ^2). About one half were receiving physical, occupational, and speech therapies, but there were no significant differences in therapy based on OMS etiology.

Sleep Problems

Forty-six percent of 68 children had insomnia, and 77% had nighttime awakening. Nightmares and sleep-talking occurred in about one half. It took an average of 23.0 ± 30.9 minutes to fall back to sleep. Sleep-walking (somnambulism) was reported in less than 10%. Thirty-eight percent snored. There were no significant sleep differences between the tumor and no-tumor groups.

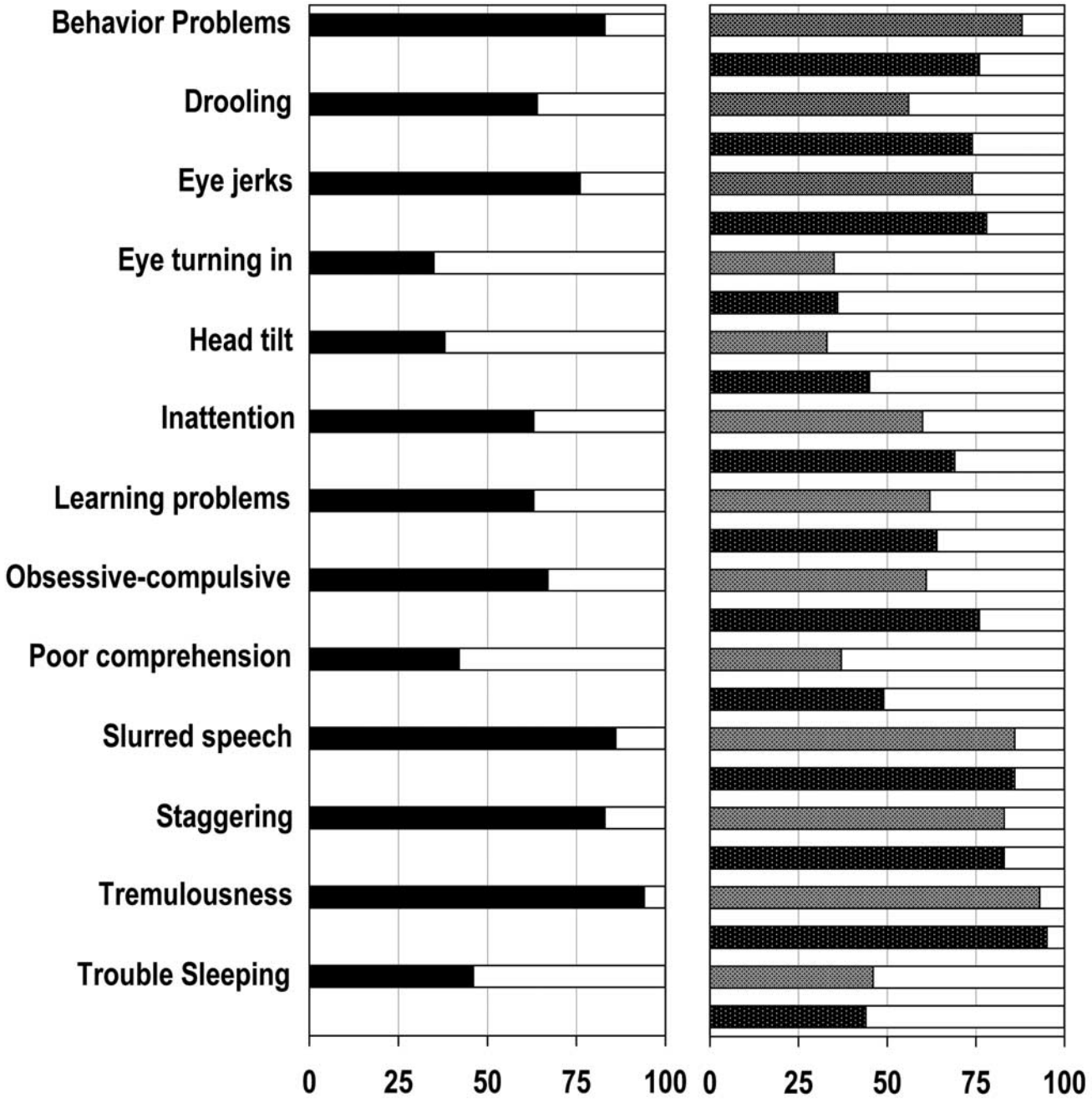

Figure 4. Histogram of Neuropsychiatric Signs in All Opsoclonus-Myoclonus Syndrome (OMS) (left) and in Etiologic Subgroups (right)

NOTE: Throughout the right figure, the no-tumor group (upper bar) alternates with the tumor group (lower bar). OMS etiology had no significant effect.

Mood and Behavioral Problems

Neuropsychiatric symptoms were reported in most children. They included obsessions/compulsions (58%), oppositional-defiant behavior (65%), rage attacks (79%), hyperactivity (47%), depression (29%), and attention deficit (19%).

Child's Biggest Residual Problem

Parents were asked to identify their child's biggest residual problem from a list in a "yes/no" format (n = 89). The "yes" ratings were ataxia (49%), expressive language impairment (40%), behavior problems (25%), receptive language problems (21%), tremulousness (15%), opsoclonus (9%), obsessions/compulsions (9%), drooling (7%), attention deficit (3%), and strabismus (2%). The number of cases of strabismus that responded to immunotherapy and those that required surgery was comparable. Significantly more parents of children with tumors said "yes" to behavior problems ($P = .04$, χ^2) and receptive language problems ($P = .02$, χ^2). Otherwise, OMS etiology had no significant effect.

Pain Response

Forty-nine percent of 99 parents stated that their child had an abnormal response to pain. Thirty-five percent reported that the pain response was decreased, and in 14%, it was increased. Significantly more reported increased pain response in the no-tumor group ($P = .016$, χ^2).

Severity Assessment

Thirty-one percent of 79 parents rated their child as severely affected, another 44% as moderately affected, and the remainder as mild. There was no significant difference in the numbers of children at each level of severity. Forty percent to 60% of parents rated ataxia and expressive speech problems as severe. Twenty percent to 30% rated tremulousness, behavior problems, opsoclonus, and obsessive-compulsive symptoms as severe.

Language Problems

Multiple speech and language problems were reported (n = 49). In one half, only 50% of the speech was deemed understandable. The quantity of speech was reduced in 82%. Sentence formation was impaired in 71%. There were verbal comprehension problems in 85%. The degree of severity of expressive or receptive language deficits did not differ significantly. Other than a higher percentage of sentence difficulties in the no-tumor group ($P = .04$, χ^2), there was no significant effect of OMS etiology.

IQ

Only a fraction of the parents (n = 15) reported on the details of formal IQ testing. Both Wechsler Intelligence Scale for Children–Revised (WISC-R) and Stanford-Binet Scale results had to be combined for statistical analysis. The average IQ was 81 ± 18.

Discussion

How Does Our Study Compare With Other Studies?

This report has several novel aspects. The sample size is about twice that of the largest previous study. It provides detailed information on relapse frequency, and to our knowledge, it draws attention to obsessive-compulsive symptomatology and the specifics of sleep disturbance in OMS for the first time. It concurs with earlier studies showing a nearly equal gender ratio (Boltshauser et al., 1979; Pohl, Pritchard, & Wilson, 1996), predominance of stage I tumors (Koh et al., 1994), prevalence of prodromal symptoms attributed to antecedent illness (Pohl et al., 1996) even in the presence of a tumor (Boltshauser et al., 1979), high relapse frequency (Koh et al., 1994; Pohl et al., 1996; Pranzatelli, Tate, Wheeler, et al., 2002), initial responsiveness to ACTH or steroids (Pohl et al., 1996; Rudnick et al., 2001), and frequent neuropsychiatric morbidity (Hayward et al., 2001; Koh et al., 1994; Papero et al., 1995; Pohl et al., 1996; Rudnick et al., 2001; Russo, Cohn, Petruzzi, & deAlarcon, 1997). It is likely that our center attracts more refractory patients, in which case the incidence of relapse may be somewhat inflated by referral bias.

Is Neuroblastoma Currently Underdiagnosed?

Of concern was the lack of significant difference in age of onset, severity, or relapse between the tumor and no-tumor-found groups. While this could be explained

by a common denominator of brain or immune system vulnerability during a critical period, it is also possible that there is no real epidemiological difference between the 2 populations. This idea is supported by the lack of difference in age of onset of paraneoplastic OMS and neuroblastoma without OMS (Rudnick et al., 2001). Also, cerebrospinal fluid and blood immunophenotyping studies did not find a difference between OMS with and without a tumor found (Pranzatelli et al., 2004). That would mean that neuroblastoma may be greatly underdiagnosed in children with OMS. Mass screening of normal infants has revealed occult neuroblastomas that regress spontaneously (Nishihara et al., 2000). We are evaluating nonradiologic means to test that hypothesis. Outcome studies in pediatric OMS, which could be used to compare the tumor and no-tumor-found groups, have suffered from small sample size.

What Is the US Standard of Care for OMS?

Our study, as a survey of OMS treatment practices in the United States, indicates that ACTH, corticosteroids, and IVIG are routinely used in the therapy of OMS. It should be of help to parents whose insurance carriers refuse to cover the cost of ACTH or IVIG. Although there are no Food and Drug Administration–approved therapies for OMS and many other orphan diseases, it is clear that the standard of care now includes these agents. Their use is also supported by case studies and small clinical series (Edmondson, Nichter, Selman, & DeVivo, 1992; Petruzzi & deAlarcon, 1995; Pranzatelli et al., 1998; Pranzatelli, Tate, Kinsbourne, Caviness, & Mishrah, 2002; Sugie, Sugie, Akimoto, Endo, & Shirai, 1992).

ACTH, the first agent used to treat OMS (Kinsbourne, 1962), was associated with the best initial response, yet most of the children were first tried on oral steroids. The delay in starting ACTH was almost twice as long as for starting steroids. Why? Because of the rarity of the disorder, there have been no controlled studies. Lower cost and the convenience of an oral medication over injections are certainly draws for steroids, and we have frequently encountered the misperception on the part of physicians and parents that steroids have fewer side effects and are less dangerous than ACTH. Our high-dose ACTH protocol yields an excellent response rate even in children who have only partial or no response to steroids (Pranzatelli et al., 1998).

Tumor resection alone did not provide adequate therapy of the paraneoplastic syndrome. This observation, which was also made from one literature review (Boltshauser et al., 1979), is clinically important because immunotherapy is often deferred until the tumor has been removed, delaying the initiation of appropriate treatment. Oncologists are often satisfied once the tumor issue has been handled, and no further therapy is given. We believe that once the autoimmune process has been activated, immunotherapy for OMS is required, regardless if therapy is directed at the tumor.

Does Early Treatment Make a Difference?

While some authors state that delay in early treatment makes no difference in outcome (Koh et al., 1994; Mitchell et al., 2002; Pohl et al., 1996), our study shows that very few children with OMS actually receive early treatment. The idea that autoimmune disorders can be left untreated for days, weeks, and months without serious consequences should be reconsidered. The present study, which essentially looked at conventional therapy, will provide a point of comparison with future outcome data from our therapeutic innovations.

Why Is the Diagnosis of OMS and Initiation of Treatment So Unacceptably Delayed?

Our study suggests the problem is multifactorial. No doubt, the rarity of the disorder has resulted in underrecognition even among child neurologists and pediatric oncologists. The fact that staggering and falling were the earliest signs of OMS, not opsoclonus or myoclonus, undoubtedly contributes to the confusion with acute cerebellar ataxia. Clinicians making the diagnosis of acute cerebellar ataxia or labyrinthitis in a toddler should keep neuroblastoma and OMS in mind (Pranzatelli, 2004). The presence of opsoclonus precludes the diagnosis of acute cerebellar ataxia no matter how ataxic the child appears (Connolly, Dodson, Prensky, & Rust, 1994). Also, postponement of medical treatment pending surgical resection in tumor cases, which according to our study is still a common practice, delays therapy of the autoimmune disorder.

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