Aggression and Psychiatric Comorbidity in Children With Hypothalamic Hamartomas and Their Unaffected Siblings

ANNE AUSTIN WEISSENBERGER 1 B.A.
MARY LYNN DELL 2 M.D.,Th.M.
KORE LIOW 3 M.D.
WILLIAM THEODORE 4 M.D.
CAROL M. FRATTALI 5 Ph.D.
DAPHNE HERNANDEZ 6 B.A., M.A.
ALAN J. ZAMETKIN 7 M.D.

1 Ms. Weissenberger is a doctoral candidate at Catholic University, Washington, DC
2 Dr. Dell is a child and adolescent psychiatrist at the NIMH, Bethesda, MD
3 Dr. Liow is a Clinical Assistant Professor in the Department of Medicine, Kansas University School of Medicine, Wichita
4 Dr. Theodore is Chief of the Clinical Epilepsy Section of the National Institute of Neurological Disorders and Stroke
5 Dr. Frattali is a research coordinator for the Speech-Language Pathology Section at the W.G. Magnuson Clinical Center, NIH
6 Ms. Hernandez is a graduate student in applied developmental psychology
7 Dr. Zametkin is a child and adolescent psychiatrist at the NIMH.

Accepted January 23, 2001.

Reprint requests to Dr. Zametkin, National Institute of Mental Health, Bldg. 10, Room 3N 238, MSC 1276, Bethesda, MD 20814-1276.

0890-8567/01/4006-0696©2001 by the American Academy of Child and Adolescent Psychiatry.

ABSTRACT

Objective: To assess aggression and psychiatric comorbidity in a sample of children with hypothalamic hamartomas and gelastic seizures and to assess psychiatric diagnoses in siblings of study subjects.

Method: Children with a clinical history of gelastic seizures and hypothalamic hamartomas (n = 12; age range 3-14 years) had diagnoses confirmed by video-EEG and head magnetic resonance imaging. Structured interviews were administered, including the Diagnostic Interview for Children and Adolescents-Revised Parent Form (DICA-R-P), the Test of Broad Cognitive Abilities, and the Vitiello Aggression Scale. Parents were interviewed with the DICA-R-P about each subject and a sibling closest in age without seizures and hypothalamic hamartomas. Patients were seen from 1998 to 2000.

Results: Children with gelastic seizures and hypothalamic hamartomas displayed a statistically significant increase in comorbid psychiatric conditions, including oppositional defiant disorder (83.3%) and attention-deficit/hyperactivity disorder (75%). They also exhibited high rates of conduct disorder (33.3%), speech retardation/learning impairment (33.3%), and anxiety and mood disorders (16.7%). Significant rates of aggression were noted, with 58% of the seizure patients meeting criteria for the affective subtype of aggression and 30.5% having the predatory aggression subtype. Affective aggression was significantly more common (p < .05). Unaffected siblings demonstrated low rates of psychiatric pathology on semistructured parental interview and no aggression as measured by the Vitiello Aggression Scale.

Conclusions: Children with hypothalamic hamartomas and gelastic seizures had high rates of psychiatric comorbidity and aggression. Parents reported that healthy siblings had very low rates of psychiatric pathology and aggression.

**Key Words:**

hypothalamic hamartomas
seizures
aggression
sibling pathology.

Gelastic seizures are recurrent episodes of inappropriate smiling, giggling, or laughter, accompanied by electroencephalographic changes, and are unrelated to external social or interpersonal stimulation (Go, 1999). Gelastic seizures were first described by Trousseau in 1873 (Trousseau, 1873); Daly and Mulder coined the term gelastic epilepsy in 1957, incorporating gelos, the Greek term for mirth (Daly and Mulder, 1957; Munari et al., 1995). Traditionally, gelastic seizures were thought to originate in the temporal lobes (Arroyo et al., 1993), but are rarely the primary manifestation of a temporal lobe seizure. Gelastic episodes may occur singly or as one of several seizure types (Striano et al., 1999). Numerous structural abnormalities have been reported, including mammillary body and pituitary lesions, encephalitis, meningitis, pineal gland pathology, lipid storage disorders, third ventricle papillomas, and anomalies of neuronal migration (Arroyo et al., 1993; Berkovic et al., 1988; Cascino et al., 1993; Iannetti et al., 1992, 1997). Due to multiple structural and functional anomalies that underlie ictal laughter, the neurocircuity of gelastic seizures is likely to be quite complex and involve the temporal lobes, hippocampus, hypothalamic hamartomas, thalamus, primary sensory and motor areas, midbrain tegmentum, periaqueductal gray matter, and the bulbo pontine nuclei (Arroyo et al., 1993).

Berkovic and colleagues (1988) first described the syndrome of gelastic seizures, hypothalamic hamartomas, mental decline, and precocious puberty. A hamartoma is a discrete lesion that often resembles a neoplasm, but arises from errant organ development and contains atypical proportions of tissue elements. Hypothalamic hamartoma is a rare condition, and its prevalence is estimated to be 1 in 50,000 to 100,000. Only a percentage of patients with hypothalamic hamartomas have gelastic seizures. Some also have precocious puberty with or without the seizures. The hypothalamus is a relatively common site for hamartoma development. Abnormalities are usually evident during the first year of life, often beginning with the unprovoked laughing characteristic of the gelastic spells. A complex seizure picture develops in later childhood, including atonic, tonic-clonic, grand mal, absence, temporal lobe, and/or jacksonian episodes (Tasch et al., 1998). Electroencephalographic findings may include focal temporal epileptiform discharges, activity consistent with tonic-clonic seizures, or diffuse spike-and-wave complexes (Sturm et al., 2000). Specific ictal phenomena that have been reported include facial flushing, epigastric sensations, pupillary dilation, orogestual automatisms, motor activity, incontinence, and deja vu (Cerullo et al., 1998). Seizures are more frequent when hypothalamic hamartomas are sessile and not pedunculated in gross anatomical form (Unger et al., 2000). Arita et al. reported on a series of 11 individuals with hypothalamic hamartomas, classified into two categories according to magnetic resonance imaging (MRI) findings. Seven patients had hamartomas attached to the floor of the third ventricle or attached to the third ventricular floor by a peduncle. One of these seven patients was asymptomatic; the hamartoma was an incidental finding on an MRI ordered for a prior workup for dizziness. The remaining six patients in this subgroup manifested precocious puberty. None of the seven had seizures or mental retardation. The remaining 4 of the 11-patient sample had hamartomas that directly involved or were encased by the hypothalamus, or the tumor encroached on the wall of the third ventricle. One of the patients had precocious puberty, and two had mental retardation and behavioral problems. All four patients had intractable seizures, with one of these individuals undergoing stereotactically targeted irradiation of the hamartoma for better seizure control (Arita et al., 1999). As Berkovic et al. noted in 1988, gelastic seizures associated with hypothalamic hamartomas are extremely difficult to treat or manage with anticonvulsant medications (Arita et al., 1998; Berkovic et al., 1988; Parrent, 1999).

Precocious puberty is present in many, but not all, patients with gelastic seizures and hypothalamic hamartomas (Arita et al., 1999; Starceski et al., 1990; Tasch et al., 1998; Unger et al., 2000; Valdueza et al., 1994). The exact mechanism whereby pubertal maturation is prematurely initiated and maintained is unclear. However, in one case series, six of seven patients with hamartomas attached to the floor of the third ventricle directly or by a peduncle (the parahypothalamic form) had precocious puberty. In contrast, only one of four patients with intrahypothalamic hamartomas fully surrounded by hypothalamic tissue or causing distortion of the third ventricle had precocious puberty (Arita et al., 1999). Typically, if precocious puberty is the only significant clinical manifestation of the hypothalamic hamartoma and there is no seizure disorder, medical treatment seeks to suppress pubertal development. An example of this treatment strategy is the administration of a gonadotropin-releasing hormone analog (Starceski et al., 1990).

The findings of "mental decline" and aggression associated with hypothalamic hamartomas have been less thoroughly studied and described than have the accompanying seizures and precocious puberty. In a case report of two children with hypothalamic hamartomas, intractable gelastic and generalized seizures, and precocious puberty, abnormal behavior was noted but not fully described (Unger et al., 2000). In a case series of six patients with hypothalamic hamartomas diagnosed by MRI findings, four individuals were noted to have behavioral abnormalities, but again these were not discussed in detail (Valdueza et al., 1994).

In the case series of seven patients with parahypothalamic and four patients with intrahypothalamic hamartomas, only two of the four intrahypothalamic-type patients were reported to have severe mental retardation and behavioral disorders, including aggressive behavior (Arita...
In this report we present a case series of 12 children with hypothalamic hamartomas, gelastic and other forms of seizures, and aggressive behavior. The aims of the study were to describe and quantify aggression and identify comorbid psychiatric conditions in these patients, using the patients' siblings nearest in age as a comparison group.

METHOD

Patient Sample and Comparison Sample

The study was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke. The patient sample included 12 children between the ages of 3 and 14 years. Parents gave informed consent for all children participating. Children 7 years of age and older were asked for, and provided, assent to participate in the study. Subjects were recruited from around the United States, mainly from the Hypothalamic Hamartoma With Uncontrolled Gelastic Seizures (HHUGS) worldwide support group. The subjects were representative of the group of patients seen at tertiary-level epilepsy centers. All 12 study subjects demonstrated evidence of hypothalamic hamartomas on head MRIs, as well as unequivocal clinical histories of seizures of any type associated with laughing or giggling at the onset of the seizures. Seizure frequency varied from one per week to more typical reports of 2 to 10 seizures per day, even while treated with standard anticonvulsant therapy. The comparison group consisted of 12 siblings, who were chosen to be closest in age to the patient with seizures, to optimize comparison with the patient group. There were no psychiatric or medical exclusion criteria for the sibling group, and there was one sibling per seizure subject. These siblings did not have any known seizure disorders, CNS disease, or chronic or acute medical illness. The comparison group was studied via parent report, not by personal examination or interview by the authors. Blind interviewing was impossible because of extremely high levels of symptomatology in seizure patients.

Procedures

The 12 study subjects were admitted to the pediatric neurology inpatient service at the National Institutes of Health Clinical Center for 5 days of assessment and treatment review. Head MRIs confirmed the presence of hypothalamic hamartomas in all participating children. Gelastic seizures were confirmed in all children by at least 3 days of video-EEG monitoring. EEG findings consisted of ictal and/or interictal epileptiform spike discharges primarily in the frontotemporal areas. In addition to extensive medical histories, complete physical examinations were performed. Routine laboratory studies were obtained, including anticonvulsant levels. Anticonvulsant medication doses were adjusted during the hospitalization for optimal seizure control.

Parents were interviewed by a trained graduate student about each subject and nearest-age sibling with the Diagnostic Interview for Children and Adolescents-Revised Parent Form (DICA-R-P) (Reich et al., 1991). In addition, parents were interviewed about the study subjects and siblings using the Vitiello Aggression Scale (Vitiello et al., 1990). The Vitiello Aggression Scale differentiates affective and predatory aggression. Scale items consistent with affective aggression include unprofitable damaging of own property, exposing self to harm when aggressive, aggression without a purpose, unplanned aggression, and being completely out of control when aggressive. Items consistent with predatory aggression include hiding aggressive acts, ability to control own behavior when aggressive, planning aggressive acts, stealing, and protecting one's own body when aggressive.

Only five of eight children old enough to complete the Woodcock-Johnson Psycho-Educational Battery-Revised: Tests of Cognitive Ability were able to do so (Woodcock and Johnson, 1990). Parents were also interviewed at length about family medical and psychiatric histories.

Statistical Methods

Chi-square analysis was performed to determine statistically significant differences in rate of diagnosis between seizure patients and controls. To compare whether aggression was more predatory versus affective in nature, two-tailed $t$ tests were performed on data generated by 12 items (4 predatory and 8 affective) on the Vitiello Aggression Scale.

RESULTS

Parents of 10 (83.3%) of the 12 patients with hypothalamic hamartomas reported significant problems of aggression, rage, temper outbursts and tantrums, violence, and other manifestations of emotional lability. Of the two children reported not to be aggressive, only one child had no behavioral abnormalities. A 4-year-old was described as nonaggressive, but demonstrated speech, learning, and communication deficits. Eight patients (66.7%) were receiving anticonvulsant and psychotropic medications for treatment of seizures and psychiatric symptoms. Two (16.7%)
The patients with hypothalamic hamartomas and seizures met diagnostic criteria for disruptive behavior disorders, including oppositional defiant disorder (83.3%) and conduct disorder (33.3%) (Table 1). Attention-deficit/hyperactivity disorder (ADHD) was present in 75% of the patient group. Differences for ADHD and oppositional defiant disorder proved to be significant at the .05 level by chi² analysis. Anxiety and mood disorders were also prevalent (8.3%-25%), including phobias, posttraumatic stress disorder, obsessive-compulsive disorder, avoidant disorder, major depression, and dysthymia. Speech and learning problems were identified in one third of the patients. One third had a diagnosis of precocious puberty, and one child had dysmorphic facial anomalies. Only three of the unaffected siblings met DSM-IV criteria for a psychiatric disorder, including two siblings with generalized anxiety disorder (16.7%) and two siblings with ADHD (16.7%). Of significance is that none of the siblings met criteria for diagnoses in which anger, aggression, or rage are central components, such as oppositional defiant disorder or conduct disorder.

TABLE 1 -- Psychiatric, Medical, and Neurological Findings in Subjects and Controls

<table>
<thead>
<tr>
<th></th>
<th>Gelastic (n = 12)</th>
<th>Controls (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at onset of seizures</td>
<td>6 wk</td>
<td>NA</td>
</tr>
<tr>
<td>Mean age at evaluation</td>
<td>7.7 yr</td>
<td>7 yr</td>
</tr>
<tr>
<td>Male</td>
<td>41.6</td>
<td>75</td>
</tr>
<tr>
<td>Female</td>
<td>58.3</td>
<td>25</td>
</tr>
<tr>
<td>ADHD</td>
<td>75 b</td>
<td>16.7</td>
</tr>
<tr>
<td>ODD</td>
<td>83.3 b</td>
<td>0</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>33.3 c</td>
<td>0</td>
</tr>
<tr>
<td>PTSD</td>
<td>16.7</td>
<td>0</td>
</tr>
<tr>
<td>Phobia</td>
<td>16.7</td>
<td>0</td>
</tr>
<tr>
<td>OCD</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>16.7</td>
<td>0</td>
</tr>
<tr>
<td>Dysthymic</td>
<td>16.7</td>
<td>0</td>
</tr>
<tr>
<td>Avoidant</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Early onset of puberty</td>
<td>33.3</td>
<td>0</td>
</tr>
<tr>
<td>Speech retardation/learning</td>
<td>33.3</td>
<td>0</td>
</tr>
<tr>
<td>impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial anomalies</td>
<td>8.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Except for mean age at onset of seizures and mean age at evaluation, all values are given as percentages. ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder; NA = not applicable.

**a** Diagnostic Interview for Children and Adolescents-Revised Parent Form (Reich et al., 1991).

**b** Significant at $p < .05$ by two-sided chi² and two-tailed Student t test.

**c** Trend ($p = .039$ t test).
Five (45.5%) of the children presented with one of the four predatory aggression characteristics (i.e., can control own behavior when aggressive, very careful to protect self when aggressive, tries to get something from being aggressive, and fights with weaker children), two (18.2%) presented with half of the characteristics, one (9%) presented with all four of the predatory characteristics, and three (27.2%) presented without any of the characteristics. Gelastic seizure patients were significantly more likely to present with affective aggression (\( t_{10} = 2.576, p = .028 \)).

Only 5 (41.7%) of the 12 patients were able to complete the Woodcock-Johnson Tests of Cognitive Ability (Woodcock and Johnson, 1990). Their standard scores in Broad Cognitive Ability ranged from 59 to 98, with a mean standard score of 79.4 (SD 15.34), which is below the norm for chronological age. Of the seven children who could not be tested formally, five (41.7%) were 5 years of age or younger and unable to cooperate fully in the formal testing process. Two (16.7%) children had high frequencies of seizures and behavioral disturbances which rendered them unable to participate in formal testing. In general, the longer or more severe the seizures were, the more cognitive damage the patient had. The severity and duration of the seizure did not bear any direct correlation with aggression or behavior of the patient. Subjects with higher aggression scores were more likely to receive a disruptive disorder diagnosis. Of the 12 children studied, 6 had total involvement of hypothalamus, 4 midline, 1 right, and 1 left. There did not appear to be any correlation between anatomic position and behavior.

DISCUSSION

The findings of this study of 12 patients with hypothalamic hamartomas and gelastic seizures are as follows: (1) compared with sibling controls, these children demonstrate significantly more expressions of aggression and rage; (2) these expressions of aggression and rage are more affective than predatory in nature; (3) by parent report, these patients demonstrate behaviors that meet DSM-IV criteria for oppositional defiant disorder, ADHD, conduct disorder, and mood and anxiety disorders more than their sibling controls; (4) by parent report, one third of this patient group had significant speech and learning problems. These findings support previous case reports of behavioral problems, particularly aggression and rage, in children and adolescents with hypothalamic hamartomas and gelastic and other forms of seizures (Arita et al., 1999; Berkovic et al., 1988; Ungé et al., 2000; Valdueza et al., 1994).

With one of the largest cohorts reported in the literature, this study expands current knowledge of this syndrome. It does this by describing further and subtyping the aggression and diagnosing comorbid psychiatric disorders by use of a semistructured parent interview. As discussed below, the Vitiello Aggression Scale (Vitiello et al., 1990) is based on evidence in animal neuroanatomic and neurochemical literature that aggression can be broadly conceptualized as two types, predatory and affective. Affective aggression is reactive, involving significant autonomic activation, poor behavioral modulation, posturing, and vocalization, and it is fear-induced and unplanned. It may include attacks on one's own or a different species unrelated to basic drives such as eating. Predatory aggression is goal-oriented, appears planned, and involves much less autonomic arousal than does affective aggression; the individual maintains control of his/her motor function. Responses of the hypothalamic hamartoma and gelastic seizure patients support a high percentage of affective aggression, indicating that a majority of aggressive episodes are impulsive or arise quite suddenly and tend not to be premeditated or motivated by ill will toward victims of the aggression.

This study supports a relationship between hypothalamic hamartomas and aggression, although the relationship between seizures and aggression remains unclear and controversial (Herzberg and Fenwick, 1988; Piacente, 1986). Considerable medical evidence exists that seizures associated with aggression are uncommon and are brief events that consist of simple, nondirected, relatively purposeless, stereotyped, combative behavior aggravated by attempts at restraint. Consecutive series of goal-directed aggressive behaviors do not comprise ictal aggression, and only in extremely rare cases do they comprise postictal aggression (Delgado-Escueta et al., 1981; Engel and Rocha, 1992; Gerard et al., 1998; Mendez et al., 1993). Consistent with these facts are the observations of parents of our study sample who report random combative behaviors during actual seizures, as well as interictal aggression that may not only be random, but can also be fearful, impulsive, and highly affectively charged.

The role of the hypothalamus in aggression and rage has been thoroughly studied in cats and rodents, providing elegant animal models for hypothalamic dysfunction in humans. The two primary forms of aggressive behavior in the cat are defensive rage behavior and predatory, or "quiet biting," attack behavior. Defensive rage behavior is composed of sympathetic signs and behaviors such as salivation, pupillary dilation, piloerection, ear retraction, and paw strike. These behaviors are seen when the cat feels threatened by an outside stimulus, such as another hostile cat. The predatory attack behavior is composed of stalking another animal, usually a mouse or another cat, followed by aggressive biting of the back of the neck. Two pathways are involved in the regulation of aggression in the cat. The first includes the medial hypothalamus and its glutamate projections to the midbrain periaqueductal gray for defensive rage behavior. This pathway is extremely excitatory because of excitatory amino acids that act on N-methyl-D-aspartate receptors in the periaqueductal gray. This circuit is augmented by a substance P pathway from the medial amygdala to the medial hypothalamus that helps to suppress signals for predatory attack behavior coming from the lateral hypothalamus. The second pathway involves the lateral hypothalamus and its descending projections for the expression of predatory attack behavior, which, as just noted, can be suppressed by substance P input from the medial amygdala and medial hypothalamus (Cheu and Siegel, 1998; Siegel and Schubert, 1995; Yao et al., 1999). The reciprocal inhibitory pathways between the medial and lateral hypothalamus may have implications for other physiological processes, including feeding and satiety (Cheu and Siegel, 1998), two functions often disturbed in humans with intractable seizure disorders and/or mental retardation. Engel and Rocha (1992) raised the possibility that the human correlates of feline defensive rage might be depression, irritability, and insecurity. Certainly, depressive symptoms and irritability are prominent in this group of children with hypothalamic hamartomas and gelastic seizures. Continued research in animal models of rage and aggression might yield insights into the psychiatric morbidity of humans with comparable neural circuitry abnormalities, whether structural or functional.

Children in our study group were receiving a total of 13 different medications affecting not only the neurotransmitter balance in the CNS, but aggression and psychiatric manifestations as well. A burgeoning literature addresses the role of neurotransmitters in the etiology, perpetuation, and suppression of aggression in animals and humans. Acetylcholine, dopamine, gamma-aminobutyric acid, glutamate, norepinephrine, and serotonin are hypothesized to play key parts in the neurobiology of aggression (Fava, 1997). Anticonvulsants, demonstrated to have treatment efficacy for some types of mood disorders and aggression, ironically have been documented to cause or exacerbate psychiatric symptoms and behavioral problems, particularly depression, irritability, hyperactivity, defiance, and aggression (Brent et al., 1987; Lee et al., 1996; Matles, 1990; Tallian et al., 1996; Voorhies, 1988; Wolf et al., 1996). In addition, anticonvulsant medications, especially when prescribed in combination, interfere with cognitive functioning, including attention, concentration, mental processing, memory, and motor and mental speeds (Reynolds, 1985). These confounding factors are most difficult to analyze in our study patients. All had intractable seizure disorders, and 8 of 12 children were taking anticonvulsant medications, including 3 children taking 2 medications and 3 children who took 3 or more medications in an effort to control their seizures. Anticonvulsant medications are changed with great frequency and serum drug levels are often erratic, even

with optimal adherence to treatment, because of drug-drug interactions and pharmacokinetic considerations inherent to medicating children. Several of the children were prescribed medications that are known to disinhibit or foster irritability and aggression in children without seizure disorders or structural brain abnormalities, greatly confusing the iatrogenic contribution to symptomatology in this patient population.

The role of the hypothalamus in endocrine and hormonal systems is vast and intricate, and hormonal influences on the expression of aggression in children with hamartomas and seizures cannot be ascertained at this time. In animal models, affective aggression is androgen-dependent, but predatory aggression seems largely unaffected by alteration of testosterone levels (Piacente, 1986). Generally, associations between aggression and sex steroids in humans are equivocal. In our patient cohort, particularly those children with precocious puberty, the most significant factor influencing aggression may not be the absolute hormone levels, but the rapid rate of increase of steroid concentrations in a brief interval of time. Further studies in this area may offer clues about therapies that may blunt the cumulative degree of aggression in patients with hypothalamic hamartomas and precocious puberty.

**Limitations**

The major limitation of this study is the relatively small sample size of an uncommon syndrome that restricts the extent to which these findings can be generalized to other patient populations. Semistructured interviews and standardized cognitive and psychological testing in this patient population are extremely difficult and may not have yielded results as accurate and reproducible as in children with lesser impairments. The data are not as complete as was planned because of the inability of some patients to complete the psychological and achievement testing. Given the extreme behavioral presentations and obvious cognitive and social dysfunctions in the patient group and the more developmentally appropriate presentations of the control group, raters could not be blinded. No naturalistic observations of patients and the control group were done to obtain objective, quantitative, and qualitative reports about aggression in either group. This study relied solely on parental reporting of aggression in both groups, raising the possibility of a "contrast effect" in which the differences between the affected siblings and the healthy control siblings are unknowingly or unintentionally exaggerated by the reporting parents. The confounding effects of multiple medications in the patient group are discussed above, and no patients were withdrawn from medications and observed for aggression and psychiatric symptoms in a drug-free state.

All 12 study patients had both hypothalamic hamartomas and gelastic seizures. These conditions are not always comorbid, limiting the degree to which these findings can be generalized to patients with gelastic seizures but no hypothalamic hamartoma, patients with hypothalamic hamartomas and nongelastic seizure forms, or patients with hypothalamic hamartomas and no seizures. The sibling control group was not directly interviewed by the research team. With the exception of parental report of sibling symptoms obtained via the DICA-R-P, more complete information about the physiological arousal, cognitive testing, presence or absence of structural abnormalities of the brain, seizure thresholds and EEGs, and pubertal status was not obtained. Comparison populations should be expanded in future studies to include children with hypothalamic lesions or dysfunctions other than hamartomas, children with other types of seizure disorders, and children with brain lesions outside the hypothalamus that lead to or are associated with rage, aggression, or other psychiatric manifestations. Comprehensive phenomenological studies of first- and second-degree relatives in this and related patient populations would also be invaluable to clinicians working with these patients and their families.

Finally, the implications of the term predatory aggression must be acknowledged. The Vitiello Aggression Scale has retained the words affective and predatory, which were first used by basic science and animal researchers as they strove to describe and categorize aggressive behaviors in the laboratory as a prelude to elucidating the involved neurocircuitry. Although the basic descriptions of the behaviors manifested in the two types of aggression may have clinical relevance for humans with neuropsychiatric disorders, the term predatory implies deliberate intent or motivation to be aggressive and injurious that seems ill-suited to widespread use in young children, especially those with demonstrable CNS pathology, developmental delay, and/or neuropsychiatric illness. It is hoped that with further study and experience in this area, better terms will be agreed upon that still capture the essence of this phenomenon.

**Clinical Implications**

Child and adolescent psychiatrists are frequently asked to evaluate youths whose presentations include varying degrees of aggression and rage. Distinguishing between elements of affective and predatory aggression may be helpful in describing the problem behaviors more comprehensively and accurately.

When presented with a report of inappropriate, seemingly involuntary smiling or laughter, child and adolescent psychiatrists should be reminded of the possibility of gelastic epilepsy, inquire about other forms of seizures often comorbid with gelastic episodes, and ensure that the patient receives complete neurological assessment and appropriate treatment. Physicians should be alert to the possibility of specific anatomical lesions of the brain that often accompany complex seizure forms such as gelastic epilepsy. Finally, clinicians assessing and working with precocious puberty patients should consider the possibilities of comorbid seizure disorders and aggression and should work with other physicians, clinicians, and parents to ensure thorough evaluations and treatment, if indicated.

**REFERENCES**

http://www.mdconsult.com/das/article/body/234398551-3/jorg=journal&source=MI&sp=11913391&sid=...
1. Arita K, Ikawa F, Kurisu K et al. (1999), The relationship between magnetic resonance imaging findings and clinical manifestations of hypothalamic hamartomas. J Neurosurg 91:212-220


http://www.mdconsult.com/das/article/body/234398551-3/jorg=journal&source=MI&sp=11913391&sid=...


31. Striano S, Meo R, Bilo L et al. (1999), Gelastic epilepsy: symptomatic and cryptogenic cases. Epilepsia 40:294-302


42. Yao R, Rameshwar P, Donnelly RJ, Siegel A (1999), Neurokinin-1 expression and co-localization with glutamate and GABA in the hypothalamus of the cat. Mol Brain Res 71:149-158

*This paper was edited with the help of Marisa Alter, B.S., Tamar Yemini, B.A., and Lisa Korenman, B.S.

Copyright © 2011 Elsevier Inc. All rights reserved. - www.mdconsult.com

Bookmark URL: /das/journal/view/0/N/11913391?ja=234988&PAGE=1.html&issn=0890-8567&source=MI