Psychiatric aspects of patients with hypothalamic hamartoma and epilepsy

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ABSTRACT – Uncontrolled rage, while long associated with hypothalamic hamartoma, has not been as extensively studied as the epilepsy. Rage can be more detrimental to quality of life than seizures. It is now realized that behavior and aggression improve after a complete resection of the hypothalamic hamartoma correlating with a good seizure control post-surgically.

We report on the longitudinal psychiatric history of a patient with hypothalamic hamartoma and rage whose severe and refractory epilepsy was ultimately treated by thalamic and intrahamartoma chronic stimulation. Our patient did not exhibit sham rage typical of hypothalamic lesions, but rather multifactorial aggressive bouts typical of challenging behaviors seen with mental retardation. The anxious and social features of the aggression suggest that psychiatric interventions, which have been neglected as the emphasis has been on seizure control, are worthwhile in the overall management of this difficult case.

KEY WORDS: aggression, hypothalamus, hamartoma, behavior, psychiatry, epilepsy

Hypothalamic hamartoma (HH) represents a rare migrational disorder of the central nervous system. Clinical manifestations include seizures, precocious puberty, intellectual deterioration and behavioral disruption. A striking seizure type, referred to as gelastic seizure (gelos from Greek, meaning mirth) and characterized by ictal smiling, giggling or laughing [1], typically occurs in the first years of life and can go undetected at first. More malignant seizure types, including drop attacks and complex partial seizures with secondary generalization, can occur in childhood [2]. The epilepsy is often medically refractory and severe, and its association with progressive cognitive deterioration has led to the suggestion that this syndrome be classified among the catastrophic epilepsies of childhood [3]. Modern imaging techniques such as magnetic resonance scanning (MRI) permit prompt diagnosis [2].

In the last decade, the discovery that ictal generators are within the HH, and the delineation of novel surgical approaches to resect or inactivate the HH, represent significant advances [3].

The neuropsychiatric features, especially rage attacks, are disabling, sometimes more so than the epilepsy [3, 4]. These have not been studied as extensively as the epilepsy. While little is reported about their behavioral...
or psychopharmacological treatments, these features are generally expected to improve following complete resection of HH correlating with good seizure control post-surgery [3, 5-7].

We present the longitudinal neuropsychiatric history of a patient with medically refractory seizures and HH who was treated surgically, first by callosotomy, then by thalamic and intrahamartoma chronic stimulation. We review the literature on the behavioral aspects of HH and highlight some limitations encountered in this body of literature, including the lack of standardized pre- and post-operative psychiatric assessments. We suggest that the existing emphasis on aggressive behavior in a cognitively challenged population does not render justice to the patient’s psychiatric complexity and to the multitude of psychosocial and psychiatric interventions indicated [2].

Method

We reviewed retrospectively all charts from the pediatric, psychiatric, and neurological centers where the patient had been seen since birth, until admission for insertion of the deep brain stimulators. We report our psychiatric assessments pre- and post-deep brain stimulation (one year follow-up).

Case

The patient is a 41 year-old, ambidextrous male with mild mental retardation and little schooling due to delinquency and aggressive outbursts necessitating placement in institutions by age 12. The intellectual quotient (IQ) was rated at 60 at age 14, on the Barbeau-Pinard scale [8]. He has never learned to read or write, but always proved adept at traveling alone to familiar places and at taking care of simple activities of daily living. Serial assessments of IQ revealed a slow deterioration: verbal IQ at 73 and non-verbal of 68 at age 17, and verbal IQ at 55 and non-verbal of 37 at age 35. Serial assessments at the ages of 23, 28 and 35 on the Adaptive Behavior Scale, documented that despite the drop in IQ, he maintained his autonomy in activities of daily living and social interactions [9].

The patient was the product of a normal pregnancy and delivery. Developmental milestones were reached slowly. Gelastic seizures consisting of forced laughing lasting 30 s followed by generalized stiffening started by age 2, went unnoticed, and were first mentioned 23 years later in a retrospective medical note. Partial complex seizures followed at age 3, occurring several times a day, and by age 5, could not be localized clinically or electroencephalographically (EEG). Precocious puberty, with a bone age of 11 years, was noted by age 8, at which time pneumoencephalography and arteriography revealed only an enlarged 3rd ventricle. Drop attacks followed by clonic movements of all four limbs developed later, leading to self-injuries including scalp and facial lacerations and jaw fracture. In his mid-twenties, the seizures consisted of sternal pain, dropping, staring and automatisms, confusion and muteness for 3 min, with or without secondary tonic-clonic movements. At 26 years, he was having eight or more seizures a day. Attacks were medically intractable. Neurological examination and routine blood work were normal. EEG abnormalities recorded during video monitoring were not lateralizing. An MRI of the brain revealed an intra-axial space-occupying lesion at the level of the hypothalamus indicative of HH, and cortical atrophy. Blood testosterone levels were normal. He underwent a right frontal craniotomy and an anterior one-third section of the corpus callosum. On post-op day 1, he had 2 generalized seizures and on post-op day 5, he had a transient akinetic and mute state.

At one year follow-up, there was no sustained improvement in seizure control, and physical assaults perpetrated by the patient were increasing while sexual assaults were less frequent. No specific behavior modification treatment was in place. On numerous EEGs, active non-localized epileptiform abnormalities were seen bilaterally, right more than left. Neuro-ophthalmological examination was normal.

After treatment failure with valproate, phenobarbital, gabapentin, lamotrigine, clobazam, zaronit, he was admitted at age 40. Earlier that year, he had had a small subdural hematoma seen on CT scan acquired after one of his habitual drop attacks. Resection of the HH or extension of the callosotomy were consistently refused by the patient and radiosurgery or leukotome lesioning were felt to be associated with too high morbidity. Seizure monitoring with EEG scalp and depth electrodes but without tapering of antiepileptic medications was performed with the stimulators turned off and on. Seizure onset of a gelastic attack was recorded on one occasion from the intra HH electrode. Deep brain stimulation (DBS) with a view to functionally inactivating the epileptic generator (insertion of an intra-HH electrode) and to prevent propagation of seizures (insertion of a left anterior thalamic electrode) was started. Pre- and post-operative dynamic hypothalamic pituitary axis endocrine evaluations were normal.

At one year follow-up post-DBS, the gelastic seizures had stopped, the partial complex seizures with or without secondary generalizations were rare, but drop attacks continued unabated. He had a second small subdural hematoma, post drop attack, confirmed on CT. Resective surgery or further extension of the callosotomy were refused by the patient.

Familial psychiatric antecedents are noteworthy for the father’s alcoholism and the mother’s chronic depression necessitating psychiatric admissions. There are three healthy siblings.
Psychiatrically, the patient’s past diagnoses have varied from “delinquency” and “oppositional, impulsive behavior problems, reactive to a dysfunctional family” at age 14, to sociopathy at age 19, to substance abuse (alcohol) at age 26, without reference to formal diagnostic classifications. The diagnosis of sociopathy followed an interview with a psychologist that revealed lying, stealing, and the regular overestimation by the patient of his abilities. He was described as passive, intolerant to frustration, oppositional, socially isolated, anxious and paranoid. The lack of socially positive models of behavior was emphasized. While his aggressive behavior repeatedly resulted in placement failure, a detailed description of the assaults was not available in charts. Prescriptions for haloperidol 5 mg QD PRN had been available, but information about the pattern of use and benefit was lacking.

When admitted to the MNH for the insertion of deep brain stimulators, we observed the patient’s aggressive outbursts and met with his caregivers who assured us that the outbursts in MNH were typical of those occurring in the foster home. Of note, outbursts never occur in the community or at the workshop. Typical precipitants seemed minor, like a delay in obtaining care for an infiltrated intravenous line or a change in the planned date of discharge. Each time, he made an immediate fuss by pacing with fists clenched, shouting obscenities, and interfering with ward routine by repeatedly asking reassurance about unrelated matters. Not venting his feelings efficiently, the nursing personnel failed to be alarmed. Eventually on the same day, the patient was admonished for disturbing the peace and was told to retire to his room and refrain from contacts with staff or fellow patients. He complied, but his attitude turned vindictive. Hours passed during which he discreetly packed all his things, and then, assaulted a nurse. The delayed aggression seemed unexpected and could have caused serious harm to the victim, but no self-injury. It responded to a show of force and to restraints, and was fully recalled by the patient who never expressed remorse. Such outbursts were not related to seizure occurrence, modifications of antiepileptic drugs, stimulator insertion or the batteries being turned on or off.

In his foster home, he has developed a privileged relationship with a female educator who has known him for 15 years. She is adamant that these outbursts can be reliably aborted by herself and others who, instead of neglecting early the fuss and withdrawing later the privileges, intervene promptly and manage the patient’s anxiety and his mistakenly perceived need for revenge. These outbursts have never been the focus of a behavior modification treatment plan because of the difficulty to time the behavioral reinforcers. Sleep and appetite have always been preserved and there was never evidence of mania, hypomania, major depression, isolated phobia, obsessions and compulsions, generalized anxiety, spontaneous panic attacks or post-traumatic stress disorder as per DSM IV-TR criteria [10]. In psychotherapeutic interviews, he displayed poor communicative skills and his collaboration fluctuated. He resented all testing. There was psychomotor agitation with teary eyes, redness of the face, sweaty palms and motor restlessness. He confided fears: losing money or visiting privileges. He was quick to show aggression when unable to understand the subject at hand. There were paranoid ideas, but no psychosis.

Discussion

The neurobiological basis of mirth and laughter has long been a subject of fascination, and the speculation about which distinct anatomical substrates exist for the feeling of merriment and for the accompanying motor expression of laughter is still ongoing [1, 11, 12]. In our patient, the laughter is at times mechanical and at other times hilarious and contagious. Given his lack of recall of the seizure, it is impossible to ascertain if there is associated merriment or happy mood. Gelastic seizures are the semiologic hallmark of HH, but gelastic seizures can also occur in frontal and in temporal lobe epilepsies [1, 2]. In the presence of HH, ictal generators within the HH have been demonstrated, but aberrant connections between HH neurons and the amygdala through the mammillary bodies, additional midline or hemispheric malformations, mechanical pressure on the 3rd ventricle may also be present [7]. Pedunculated, parahypothalamic forms of HH with no displacement of the hypothalamus may not present with seizures or behavior or cognitive problems, but only with PP [13]. Interestingly, cases with very small HH have been reported to have a “pressure to laugh” rather than actual laughing: these cases did not develop refractory seizures or cognitive deterioration and illustrate a mild end to the clinical spectrum of HH [3, 14]. The deep brain stimulation (DBS) literature in Parkinson’s disease, reports transient, reproducible laughter with merriment in two patients, upon stimulation of the posterior hypothalamus [15]. In our patient, the HH was large (1.5 cm by 1 cm), both para- and intrahypothalamic, invading the posterior hypothalamus.

The role of the hypothalamus in aggression or sham rage, in memory problems and in sociopathy has been another fascinating subject [16]. The case report of a woman with a third ventricle tumor but no epilepsy who reacted with blind rage when approached, had full recall of her rage and genuinely apologized afterwards, is illustrative of a type of aggression seen with destruction of the hypothalamus [17]. Rage upon direct stimulation of the posterior hypothalamus has been reported more recently in a patient undergoing DBS for the treatment of Parkinson’s disease [18]. Aggression can exceptionally be aggravated after callosotomy, but only in patients who had preoperative behavior disturbances [19]. Hypotheses about true precocious puberty also include stimulation of anterior hypothalamus, mechanical interference with the posterior hypothalamus.
In our case, PP was present by the age of 8, but he never showed hyperphagia, and the endocrine profile remained normal when measured as an adult. It was difficult to conclude anything about a putative link between the aggression, testosterone levels and PP in our case. His aggression was not strictly identical to sham rage as it was delayed, could be modified by environmental (restraints) and psychotherapeutic (cognitive restructuration) interventions, and occurred only in one setting. Little is known about the physiopathology of the cognitive deterioration seen in patients with HH. Hypothalamic lesions can be accompanied by memory difficulties [16]. Another hypothesis is that excitotoxic damage to the mammillary bodies and medial thalamus may occur [20]. In this patient, IQ deterioration was progressive in contrast to the stability of his deficient social skills. Lastly, it should be stated that aggression is not the rule in the mentally retarded, and that when present, like any challenging behavior, is usually multifactorial.

Our review of the literature on HH and epilepsy surgery revealed that in the majority of the reports, the emphasis is on the medical and surgical aspects while the psychological and behavioral aspects are poorly characterized [3-7, 21-23]. A summary of behavioral and cognitive data prior to and following surgery is presented in Table 1. Taken together, the reports suggest that the majority of patients with HH had behavioral problems, especially autistic and aggressive behavior. Cognitive difficulties ranged in severity from normal development to severe mental retardation (MR). Formal testing was not performed in the majority of cases, probably because of the lengthy technical nature of cognitive testing, which is not feasible in many of these children [3]. The lack of reliable and reproducible testing resulted in heterogeneity of results, and hampered valid comparison.

Not all patients with HH and gelastic seizures exhibit cognitive and behavioral deterioration as shown by our patient. Similar deterioration appears more obvious in those who develop a form of secondary generalized epilepsy with drop attacks and generalized slow spike and wave discharges. Patients without catastrophic cognitive and behavioral deterioration present minor attacks, both gelastic or partial complex, and their lesions are often smaller and protrude into the lumen of the third ventricle [14, 24]. In such patients, surgical treatment has not been generally undertaken. Surgical treatment is currently considered in patients in the former group [3].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Behavioral and cognitive aspects (N): pre- and post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>13; (2-33)</td>
<td>Irritability and aggression (10); hyperactivity (8); loss of inhibition (5). Moderate to severe cognitive deterioration (13). Both behavior and cognition improved post-operatively.</td>
</tr>
<tr>
<td>5</td>
<td>1; (17)</td>
<td>Sudden, unprovoked bouts of uncontrolled rage with no relationship to seizure occurrence. Progressive intellectual deterioration (not further elaborated). Marked improvement in cognitive function post-operatively.</td>
</tr>
<tr>
<td>22</td>
<td>1; (5)</td>
<td>Autistic behavior. Severe mental retardation. Postoperatively, persistence of mental retardation although autistic behavior improved.</td>
</tr>
<tr>
<td>6</td>
<td>5; (4-13)</td>
<td>Aggression (2); hyperactivity (1); obsessiveness (1); and autistic behavior (1), language (1), memory (2) and intellectual problems (4). Two children with normal behavior. Postoperatively, improvement in language and learning, and behavioral problems.</td>
</tr>
<tr>
<td>23</td>
<td>8; (1-32)</td>
<td>Behavior abnormalities not clearly described, although post-operatively, behavioral improvements noted (2). Cognitive abnormalities not elaborated.</td>
</tr>
<tr>
<td>24</td>
<td>1;</td>
<td>Pervasive developmental and attention deficit disorder. Post-operative data not available.</td>
</tr>
<tr>
<td>7</td>
<td>2; (6-13)</td>
<td>Abnormal behavior. Follow-up 54 months post-surgery, reintegration to public school.</td>
</tr>
<tr>
<td>4</td>
<td>1; (7)</td>
<td>Aggression, irritability, self-injury, compulsive behavior and tics. Cognitive abnormalities present and extremely disabling. Poor cognitive and behavioral outcome.</td>
</tr>
<tr>
<td>13</td>
<td>11; (3 months-76)</td>
<td>Aggression present in two of four intrahypothalamic cases. None in parahypothalamic cases (7). Cognitive abnormalities also noted in three of four intrahypothalamic cases. None in parahypothalamic cases (7). Post-operative behavioral course not available in two surgical cases.</td>
</tr>
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</table>
Two recent prospective studies with a primary objective of examining cognitive and behavioral aspects of gelastic seizures and HH have been reported for the same group [25, 26]. Weissenberger and colleagues evaluated 12 children between 3 and 14 years of age, along with parents and age-matched siblings [25] with the Test of Broad Cognitive Abilities and the Vitiello Aggression Scale. The study revealed that children with HH and gelastic seizures, compared with their siblings as controls, had statistically higher psychiatric morbidity, such as oppositional defiant disorder (83.3% versus 0%), and attention deficit-hyperactivity disorder (75% versus 16.7%). Other disorders disproportionately represented in the HH group included: conduct disorder (33.3%), speech and learning retardation (33.3%); and affective disorders (16.7%). Children with HH fared poorly in the Broad Cognitive Abilities test, ranking below age-matched controls. Greater cognitive impairment correlated with more severe epilepsy. The Vitiello Aggression Scale [27] categorizes the aggression as affective and predatory. Predatory aggression is defined as planned behavior that is executed with low autonomic arousal and good control of voluntary motor activity. In contrast, affective aggression appears reactive, poorly planned or modulated, and accompanied by high autonomic arousal. On this measure, high predatory aggression (18.2%) and affective aggression (72.7%), scores were noted in the HH group. Aggression did not appear to correlate with the severity of epilepsy. There may be clinical relevance in categorizing aggression according to the schema outlined above: Vitiello and colleagues refer to animal studies implicating in predatory aggression, cholinergic-facilitating pathways (at least in rats), and in affective aggression, dopaminergic-facilitating pathways and GABAergic and serotoninergic inhibitory pathways.

Frattali and colleagues evaluated eight children with gelastic seizures and HH (age range: 5 to 13.75 years) for cognitive function [26]. All children demonstrated mild to severe cognitive deficits. Seizure severity and frequency correlated with severity of cognitive deficits. Both studies [25, 26] acknowledged the presence of concomitant antiepileptic medications as potential confounders. One major limitation to the literature on HH and epilepsy is that it is based on small numbers of subjects, which may reflect the infrequent occurrence of HH.

Of significance however, is that in a number of neurosurgical cases, behavior and cognition improve post-HH-resection. The degree of improvement in both seizure control and behavior seems to correlate with the completeness of resection of the HH. Some reports noted improvement in behavior despite unchanged frequency of seizures post-operatively, but in most, behavioral gains depended on seizure control. Clearly, behavioral and cognitive outcomes are important postoperative measures. Further studies are needed to correlate these outcomes with size and topography of the HH, seizure outcome, changes in medication, alterations in IQ and social aptitude.

Our case presented with mixed affective and predatory aggression that occurred interictically, and that was modifiable by environmental and psychotherapeutic interventions. It is not known why the sexual aggression almost abated while the physical and verbal aggressions worsened post-callosotomy. At one year follow-up after DBS, the aggression goes on in the context of continuing drop attacks, recurrent head injury and polypharmacy. Psychiatric prognosis is guarded. Nevertheless, even if it is understood that, as long as the HH is not resected or better inactivated, the seizures, sociopathy and aggression could go on, we recommend that behavior modification be attempted even if challenging, combined with a trial of serotonergic medication, in part because of the presence of affective and anxiety features, and in part because of the patient’s ability to establish privileged relationships, behavioral elements that were overshadowed in the search for seizure control.

In conclusion, review of this case supports our impression that the literature on HH and epilepsy surgery has emphasized rage as the key psychiatric manifestation in HH, while underestimating the complex behavioral aspects of these cases and consequent opportunities for psychiatric intervention.

References


