Neuropsychiatric aspects of patients with hypothalamic hamartomas

M.J.B.M. Veendrick-Meekes a, W.M.A. Verhoeven b,c,*, M.G. van Erp a, W. van Blarikom a, S. Tuinier b

a Epilepsy Centre Kempenhaeghe, Heeze, The Netherlands
b Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands
c Erasmus University Medical Centre, Department of Psychiatry, Rotterdam, The Netherlands

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Abstract

Hypothalamic hamartomas (HH) are developmental malformations that are associated with gelastic seizures, other types of seizures, cognitive decline, and symptoms related to hypothalamic dysfunction. Although aggressive behavior is frequently described, data on the neuropsychiatric profile are limited. In this article, five patients with HH are described who displayed a wide variety of psychiatric symptoms that, dependent on the time frame, met the criteria for several categorical diagnoses. Major neuropsychiatric symptoms comprised aggression that is only partial context dependent, compulsive behavior, psychotic symptoms not responding to treatment, and organic mood instability. HH should therefore be considered a neuropsychiatric syndrome with a highly variable expression that can be best captured by a thorough description of behaviors, symptoms, sequelae of epilepsy, and hypothalamic dysfunction.

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1. Introduction

Hypothalamic hamartomas (HH) are rare developmental malformations that contain atypical proportions of neuronal tissue elements. Their prevalence is estimated to be 1 in 50,000 to 1 in 100,000. They may cause an epilepsy syndrome with gelastic seizures, followed by multiple types of seizures and precocious puberty. The mechanisms involved in the intrinsic epileptogenesis of the hamartomas have not yet been elucidated [1]. The characteristic epileptic syndrome associated with HH was first described by Berkovic et al. [2] and consists of laughing (gelastic) seizures that are usually followed by other types of seizures, cognitive deterioration, and behavioral abnormalities. Magnetic resonance imaging (MRI) studies have revealed that HHs always involve the mammillary region of the hypothalamus, that in most cases an intrahypothalamic extension is present, and that the site of the HH is associated with central precocious puberty [3,4]. The clinical spectrum of HH-associated epilepsy varies between sporadic and easily controllable partial seizures, seizures partially responsive to antiepileptic drugs, and a syndrome with a catastrophic course for which surgical intervention is primarily indicated [5–8]. In patients with adult onset, gelastic seizures are less prominent and the epilepsy is generally milder [9].

With respect to behavioral abnormalities, it is well known that HH syndrome is associated with varying degrees of aggression, rage, and hyperactivity [10,11]. Although the prevalence of psychiatric disorders, especially psychoses, major affective disorder, and anxiety disorders is relatively high in patients with epilepsy [12], there is a paucity of neuropsychiatric descriptions of patients with HHs [11,13].

In this article, the neuropsychiatric profiles of five adults with treatment-refractory epilepsy and HH admitted to the Epilepsy Centre Kempenhaeghe, The Netherlands, are described together with the treatment regimens.
2. Case reports

The main characteristics of the patients are summarized in Table 1. Psychiatric symptoms from recent history were derived from the elements of the Comprehensive Psycho-pathological Rating Scale [14] and are listed in Table 2.

2.1. Patient 1

Patient 1 was born after a normal pregnancy and followed a normal developmental pattern until, at the age of 9 months, he developed an encephalitis postvaccination with epileptic seizures. In retrospect, it appears that he had already had gelastic seizures at the age of 3 months. Subsequently he displayed oppositional behavior and, later, disruptive behavior. Because of severe epileptic seizures, he was admitted at 6 years of age to a specialized hospital and treated with several combinations of antiepileptic drugs (exact information no longer available). At age 42, he was readmitted to the specialized hospital because of deterioration of behavior with frequent temper tantrums, outbursts of rage, unpredictable verbal and physical aggression, as well as obsessive and perseverative behavior. At that time, he was treated for his epilepsy with carbamazepine and primidone. He was diagnosed with per-vasive developmental disorder not otherwise specified. Subsequently, he manifested such psychotic symptoms as paranoid ideation, bizarre thoughts and fantasies, auditory hallucinations, and thoughts of reference. Administration of antipsychotic drugs (zuclopenthixol and, subsequently, olanzapine) was not successful. Despite polypharmacy with antiepileptic drugs (most recently oxcarbazepine and primi-done), seizure frequency varied between 0 and 5 per month. Treatment with risperidone up to 8 mg daily did not result in symptomatic improvement. He was diagnosed with interictal psychosis. The patient died suddenly.

2.2. Patient 2

Patient 2 had his first seizures, including gelastic seizures, at the age of 4, and thereafter, he developed precoxious puberty. Already during his childhood, he exhibited hyperactive behavior that was later accompanied by dysphoric mood, mood swings, episodic aggression, and compulsive behavior. Treatment with various combinations of antiepileptic drugs (most recently valproic acid and lamotrigine) failed to reduce seizure frequency below 30 per month. Provisional diagnoses of pervasive developmental disorder not otherwise specified and obsessive-compulsive disorder were made.

2.3. Patient 3

Patient 3 developed normally until the age of 1 year, when she had her first gelastic seizures. Because of behavioral problems, including aggression, that were no longer manageable and persistent seizures of various types, she was referred to a specialized hospital at the age of 6. During young adulthood she developed psychotic symptoms with prominent hallucinatory behavior, thought disturbances, paranoid ideation, and bizarre neologisms. At age 32, she underwent stereotactic radioneurosurgery. Thereafter, she was free of seizures under treatment with lamotrigine and oxcarbazepine. She still had aggressive outbursts, and her psychotic state further deteriorated. Treatment with risperidone (4 mg daily) did not ameliorate psychotic symptomatology. Dependent on the actual symptomatology, psychiatric diagnoses varied among schizophrenia, paranoid type, interictal psychosis, psychosis as a result of forced normalization, and pervasive developmental disorder not otherwise specified.

2.4. Patient 4

Patient 4 had her first epileptic seizures within the week after birth. From early infancy on, she manifested temper tantrums, aggressive outbursts, and oppositional behavior. She was diagnosed with precocious puberty and obesity at age 5. In subsequent years, she developed prominent behavioral problems with verbal and physical aggression, as well as an affective instability. Symptomatic treatment with antipsychotic drugs was not effective. Later,
symptoms of a recurrent major depressive disorder became more evident, in that the clinical picture was dominated by crying, inactivity, self-injurious behavior, anxiety, mood instability, and dysphoria. Maintenance treatment with citalopram 40 mg daily resulted in a marked improvement of behavior and remission of depressive symptoms. Her most recent antiepileptic drugs were carbamazepine, phenytoin, and chlorazepate.

2.5. Patient 5

Patient 5 developed seizures shortly after birth and exhibited a clear developmental delay. Apart from obesity and treatment-refractory epilepsy, his history did not include behavioral abnormalities or psychiatric symptoms. His antiepileptic medications were carbamazepine, levetiracetam, and phenytoin. At age 50, his behavior changed as evidenced by mild depressive symptoms such as loss of energy, poor concentration, and lowered mood. A provisional diagnosis of dysthymic disorder was established for which no specific treatment was given.

3. Discussion

In this article, five patients are described who all developed gelastic seizures early in life and, thereafter, intractable epilepsy. In all but one patient (No. 2), HH was diagnosed at an advanced age. One patient (No. 3) underwent stereotactic radiosurgery. All patients manifested cognitive deficits as a result of a progressive decline in intellectual capacities. This observation is in line with other reports [15,16].

With respect to the hypothalamic neuroendocrine dysfunction that is reported in HH [3,17], all patients were obese, two had central precocious puberty, one had hypothyroidism, and two (Patients 2 and 4) were compulsive overeaters. These endocrine abnormalities are possibly the result of ectopic secreting cells functioning independently outside the normal neurophysiological regulation [17]. Four of five patients exhibited some kind of abnormal aggression that was only partially context dependent and was mostly unplanned in front of other people. In addition, the patients had these aggressive outbursts without social control and irrespective of self-harm or damage to their own property. This pattern of aggressive behavior was elegantly described by Weissenberger et al. [11]. In the patients described here, aggressive behavior consisted of unpredictable verbal and physical aggression toward objects and persons. They were jittery, dysphoric, and irritable at the time of the outbursts.

As to the pathophysiology of this type of aggression, it should be stressed that it is well known that the hypothalamus of mammals contains specific areas where defensive or offensive aggression can be provoked by electrical stimulation [18]. In HH, stimulation of the hypothalamus originates from its intrinsic epileptogenesis. The nature of the hypothalamic stimulated aggression in animal experiments closely resembles some of the aggressive behavior of patients with HH, in that attacks lose their normal relationship with other behaviors and occur unpredictably and out of context, but are not without environmental triggers [19,20].

As can be inferred from Table 2 and the case reports, the patients had a plethora of psychiatric symptoms, and their histories revealed additional symptoms that were partially epilepsy related. The literature on psychiatric comorbidity in HH reflects such an array of symptoms that virtually all DSM categories are involved, for example, pervasive developmental, attention deficit, obsessive–compulsive, eating, oppositional defiant, major depressive, dysthymic, and anxiety disorders and phobias [1,11,13,21–23]. This diagnostic foginess demonstrates the inadequacy of categorical classification to capture the characteristics of the syndrome, which can be better described at a purely symptomatic level [24]. Interestingly, no cases with psychosis have been reported so far, which is surprising as there is a strong association between epilepsy and psychotic disorders [25,26]. This may be caused by the low prevalence of HH while the primary focus of the publications is the intractable epilepsy. It should be noted that transient mood swings are typical of patients with either intellectual disabilities or other organic brain disorders [27].

The neuropsychiatric diagnostic process in patients with epilepsy, particularly in those with intellectual disabilities and additional hypothalamic dysfunction, is extremely complicated as the symptomatic profile depends on several
factors such as the epilepsy itself, the potential psychiatric adverse effects of antiepileptic drugs, the presence of cognitive deficits, and the disordered hypothalamus. A major example of a hypothalamic disorder is Prader–Willi syndrome, which presents with, among other symptoms, mood instability and an atypical bipolar affective disorder.[28]

No treatment algorithms have so far been proposed for either the epilepsy or behavioral and psychiatric sequelae in HH. It is noteworthy that psychotic symptoms in these patients do not respond to adequate treatment with antipsychotic drugs. From the neuropsychiatric vantage point, HH should be considered a syndrome with highly variable symptomatic expression depending on the size and site of the hamartoma, the epilepsy and its treatment, the dependence on environmental contingencies, and, at the same time, the inconsistent modulating influence of the environment. Because the DSM system categorizes sets of symptoms and behaviors without an etiology, it is unable to grasp the complex syndrome in HH. The attribution of DSM vignettes can therefore best be replaced by a thorough description of behavior and symptoms.

References