Cognitive and Behavioral Dysfunction in Children With Hypothalamic Hamartoma and Epilepsy

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Hypothalamic hamartoma (HH) syndrome comprises the clinical triad of epilepsy, developmental retardation, and central precocious puberty. A predominant opinion has been that the acquired cognitive and behavioral disorders observed in children with this syndrome are a direct effect of their seizure activity. A review of the recent literature suggests that this opinion needs to be revised because it is only partially supported by the data. The size of the HH and its anatomic attachment/location, in addition to the seizure history, appear to contribute to the cognitive and behavioral disturbances in children with HH. Small sample sizes and the inability to use standard neuropsychological testing scales in more severely affected HH patients complicate the study of causality. The present literature, however, suggests that multiple factors contribute to the cognitive and behavioral problems of these children.

The size of the hypothalamus is less than 1% of the total volume of the brain, but it is a highly complex structure that has extensive interconnections with both cortical and limbic neuronal networks. Saper suggests that “the functional organization of the hypothalamus can be best appreciated in terms of its role as an integrative structure.” It influences several integrative functions such as sleeping, dreaming, eating, drinking, temperature control, reproduction, and sexual behavior. It also appears to play an important role in the modulation of aggressive behaviors as they relate to a variety of functions necessary for survival. Kupfermann further notes that the hypothalamus may be important for evoking drive states (and associated activating systems) involved in the process of reinforcement. Thus, disturbances of the hypothalamus (in the absence of abnormalities elsewhere in the brain) theoretically could lead to a series of cognitive and behavioral disorders because they may possibly influence the learning process.

The term hamartoma refers to a nonneoplastic developmental lesion that represents an “error” or “mistake” of nature. Hypothalamic hamartomas (HHs) are “nonneoplastic malformations resembling gray matter composed of hyperplastic neural tissue of varying size.” They are intrinsically epileptogenic for gelastic seizures, which appear to contribute to the development of secondary epilepsy. The seizures associated with HH are typically refractory to medical treatment. This article summarizes the recent literature on the cognitive and behavioral disorders reported in children who have HH and attempts to relate these disorders to potential etiological factors.

The HH Syndrome and Neuroanatomic Considerations

Although reports describing cognitive and behavioral disturbances of patients with HH have existed in the literature for many years, Berkovic and colleagues were the first to fully delineate the HH syndrome. Clinical features associated with HH typically consist of the clinical triad of epilepsy, developmental retardation, and central precocious puberty (CPP). Berkovic and coworkers described in detail 4 patients who were first evaluated from ages 3.5 to 19 years and who were followed for several years thereafter. They drew attention to the dynamic nature of the syndrome, reporting that with the passage of time each patient showed cognitive and behavioral disturbances that appeared progressive in nature. Despite
intelligence quotient (IQ) scores (some were in the average to low average range), each patient had difficulty in school. They suggested that with the first decade of life, these patients showed clear cognitive deterioration paralleled by a progression of their epileptic condition, evolving from purely gelastic seizures to mixed seizure types, including ultimately secondary generalized epilepsy. They noted that the progression of the epileptic condition occurred in these patients between ages 4 and 10 years. Furthermore, CPP was unequivocally present in 1 of the 4 patients, and signs of early pubertal change were seen in the other patients. The potential role of CPP in contributing to the cognitive and behavioral disorders was not discussed. Cognitive problems were thought to be primarily a result of the patient’s worsening epileptic condition.

The behavioral problems of these 4 patients were of an equally serious nature as their cognitive impairments and seizure disorder. Uncontrollable violent rage (ie, rage reaction) was described as occurring without provocation. Patients were not only physically violent but verbally abusive. One patient was described as speaking in a very loud voice, coupled with intermittent laughter. This patient often engaged in verbal onslasts of socially inappropriate comments. The clinical impression one gets in reading this article is that these patients lacked all of the social graces and were showing extremely primitive behaviors often associated with lack of frontal lobe development.

Berkovic and coworkers also presented neuroimaging findings on these patients and noted that in 3 of the 4 patients there was distortion and displacement of the inferior part of the third ventricle. In 1 patient (patient 4), who was described as having extremely poor verbal and nonverbal memory, it was noted that the HH was attached in the region of the right mamillary body.

These observations of Berkovic and coworkers influenced how researchers approached the cognitive and behavioral problems associated with HH. The progressive nature of the epilepsy appeared to play a major role in the development of cognitive and behavioral deterioration seen in these patients. A later literature review emphasized that when surgical interventions resulted in a cessation of seizures, the cognitive and behavioral problems were at best improved and at worst showed no further signs of deterioration.

Valdueza and coworkers reported on 6 patients with HH whose diagnosis was based on the magnetic resonance imaging (MRI). Four patients had epilepsy including gelastic seizures. Behavioral abnormalities were also observed in 4 patients and CPP and visual impairment in 2 patients. These authors suggested that if the HH was attached to the tubular cinereum, and there was no displacement of the hypothalamus; it was likely that the patient would show only CPP or be asymptomatic. This was described as a “pedunculated” HH. If the HH had a broad-based attachment, it was described as “sessile” in type. This type of HH often displaced structures of the hypothalamus and the wall of the third ventricle. Progressive seizures and cognitive and behavioral abnormalities were considered to be likely in this condition. Figures 1 and 2 from Nguyen and coworkers provide a graphic representation of the 2 types of HH that have been noted repeatedly in the literature.

Arita and coworkers presented MRI findings on 11 patients and divided the patients into 2 categories. Seven patients were described as “parahypothalamic” (ie, the HH was attached to the floor of the third ventricle or suspended from the inferior hypothalamus by a peduncle). Four patients were described as having “intrahypothalamic” lesions in which the HH involved or enveloped the hypothalamus and distorted the third ventricle. They note that 6 patients with the parahypothalamic type of HH exhibited CPP or were asymptomatic. These patients were described as having no seizures or any mental retardation. However, all 4 patients with the intrahypothalamic type had seizures, 1 had CPP, and 2 were described as mentally retarded with behavioral disorders including aggression.

More recently, Freeman and coworkers reported on the MRI findings of 72 patients with HH who also had refractory
epilepsy. They note that the intrahypothalamic lesion type was common (in 97% of the patients). Moreover, they noted that in these cases the HH “tended to displace the postcommissural fornix and the hypothalamic gray matter anterolaterally, such that the HHs nestled between the fornix, the mamillary body, and the mammillothalamic tract.” They conclude that the intimate relationship between these 3 structures and the HH may play an important role in the development of epilepsy and the associated cognitive and behavioral problems seen in this subgroup of HH patients.

The literature on the cognitive and behavioral disturbances seen in HH children repeatedly suggest that the location (and size) of the HH, as well as the seizure history, are important in understanding the neuropsychological and neuropsychiatric disturbances that they show.

**What Factors Are Responsible for Cognitive Dysfunction Observed in Children With HH?**

The landmark study of Berkovic and coworkers noted that during the first decade of life the HH syndrome is characterized by cognitive deterioration. They also noted that during this time the clinical and electrophysiological features of secondary generalized epilepsy occurred. The logical conclusion is that the worsening of the seizure disorder, which is poorly controlled in most of these children, is responsible for the cognitive and perhaps some of the behavioral disorders that they show. This view was reinforced by Deonna and Ziegler who after reviewing the literature and providing a detailed longitudinal case study of a child concluded “the acquired cognitive and behavioral symptoms seen in the majority of cases of this special epileptic syndrome result from a direct effect of the seizures.” They are explicit about their interpretation of previous studies that lead them to this conclusion. They offer the following considerations: (1) children diagnosed with HH and refractory epilepsy usually have no history of retarded or abnormal development before seizures begin, (2) most children subsequently seem to stagnate and deteriorate with major behavioral problems both in association with and coincident with the worsening of seizures, (3) HH in themselves do not apparently interfere with development and behavior because children with HH and CPP, but without epilepsy, do not present cognitive and behavioral problems, and (4) in patients with HH and epilepsy who were intensively studied with structural and functional imaging data, with some exceptions, do not indicate dysplastic or brain malformations outside the hypothalamus, which could be responsible for the neurobehavioral symptoms. In light of these compelling arguments, what does the more recent literature say?

Unfortunately, the studies that are available often include small sample sizes and missing data because some of the HH children are not testable or easily engaged in neuropsychological assessments. Nevertheless, important observations have been made. Frattali and coworkers studied the cognitive deficits of children with gelastic seizures and HH. They report in 8 children, ranging in age at time of seizure onset from 4 years 11 months to 13 years 8 months, that cognitive deficits range from mild to severe. Measures of seizure severity and seizure frequency correlated significantly with a broad measure of cognitive impairment. Age at seizure onset and HH volume did not correlate with the degree of cognitive impairment observed. The possible role of CPP contributing to the cognitive impairments was not considered. They noted in this group that long-term retrieval and processing speed difficulties were pronounced, but some children showed cognitive impairments in other domains, including language function. They acknowledged that antiepileptic drugs given to these HH children could also contribute to their cognitive impairments, but they present no data on this possibility.

Nguyen and coworkers reviewed their clinical findings on 7 patients aged 8 to 38 years. Patients varied as to the age of

![Figure 2](A) Sagittal and (B) coronal representations of a sessile hypothalamic hamartoma. (Reprinted with permission.)
seizure onset. IQ scores were available for 4 patients (case 1, Verbal IQ [VIQ] = 89, Performance IQ [PIQ] = 98, Full Scale IQ [FSIQ] = 92; case 3, VIQ = 89, PIQ = 98, FSIQ = 92; case 5, VIQ = 114, PIQ = 89, FSIQ = 102; and case 7, VIQ = 106, PIQ = 90, FSIQ = 98).

Although patients varied in terms of level of cognitive functioning, it was noteworthy that all were described as having difficulties coping with the demands of day-to-day life. One case was especially informative (case 7). Imaging revealed a large HH with cystic components, with attachment to and abnormal MRI signal changes involving the left hypothalamus. This patient developed CPP at age 9 months, with no seizure activity reported. The child, however, was considered to be developing slowly in the areas of speech and motor development. At age 5 years 7 months, she obtained a VIQ of 106 with a PIQ of 90 and an FSIQ of 98. At age 13 years, she had a measured VIQ of 83 with a PIQ of 82 and an FSIQ of 81. Seizures occurred at age 13 and were certainly paralleled by a decline in IQ scores. Note, however, that there were signs of subtle brain abnormalities that occurred before the onset of seizures in a child who had very early onset of CPP.

Striano and coworkers reported on 6 patients, 5 of whom had seizure onset between 6 months and 7 years of age. All 6 had sessile HH (ie, broad-based attachments, which tended to be intrahypothalamic) between 0.8 and 1.7 cm in diameter. They report the following: “Severe cognitive impairment developed in the patient with secondary generalized epilepsy, and a mild cognitive defect in two others.” They suggest that patients with HH below 1 cm in volume did not show neuropsychological or behavioral disturbances. They noted, however, that 5 of the 6 patients were on antiepileptic drugs, which did not reduce seizures, except in 1 patient. None of their patients had CPP.

Quiske and coworkers recently reported on 13 juvenile and adult patients, all who had intrahypothalamic lesions. According to the Valdueza and coworkers classification system, they had type 2b HHs (ie, they were medium to large in size, had a sessile attachment, and the origin of the HH was the tuber cinereum and the mammillary bodies). In this older group of patients (mean age, 27.7 years; standard deviation, 10.9 years; no age ranges were presented), the volume of the HH had the strongest correlation with neuropsychological impairments. Age at onset and duration of epilepsy did not correlate with any cognitive measure. There was, however, a relationship between the monthly frequency of partial seizures and a measure of cognitive flexibility. The authors acknowledge, however, that their patients had a relatively late onset of epilepsy (ie, 4.5 years; standard deviation, 3.9), and this may in part account for their findings.

Prigatano and coworkers studied 58 patients with HH and refractory epilepsy. Although some patients were “not testable,” these investigators attempted to evaluate how age of seizure onset, age at time of testing, lifetime duration of seizures, size of the HH, anatomic features of the HH, and the presence or absence of CPP correlated with the cognitive status of these HH patients. Ages ranged from 5 to 55 years, with 55.2% (32 of 58) of the subjects being between ages 5 and 14 years, and 19% (11 of 58) of the patients were between ages 15 and 18 years. Three subtests of the Wechsler Intelligence Scale were administered: vocabulary, block design, and digit symbol-coding subtests. A sum of these 3 subtest scores was also calculated for each patient.

Correlation analyses failed to reveal any significant correlation between duration of epilepsy (measured in months) and cognitive test performance. The volume of the HH (measured in cm$^3$) revealed a negative correlation relationship to cognitive performance, although with modest statistical significance as follows: size of HH versus vocabulary ($r = -0.241$ ($P = .102$, $n = 47$), block design $r = -0.288$ ($P = .049$, $n = 47$), digit symbol-coding $r = -0.275$ ($P = .064$, $n = 47$), and sum of the 3 Wechsler subscales $r = -0.281$ ($P = .065$, $n = 44$). In contrast, and somewhat unexpectedly, the absence of CPP revealed a positive correlation with cognitive performance: absence of CPP versus vocabulary $r = 0.384$ ($P = .008$, $n = 46$), block design $r = 0.325$ ($P = .027$, $n = 46$), digit symbol-coding $r = 0.394$ ($P = .007$, $n = 45$), and sum of the 3 Wechsler scales $r = 0.415$ ($P = .006$, $n = 43$). It should be noted, however, that the absence of CPP was negatively correlated with the size of HH ($r = -0.389$, $P = .003$, $n = 57$).

Moreover, the relationship between the absence of CPP and volume of HH was studied just in those patients whose seizure onset was within the first month of life. Data were available on 25 patients. The correlation was $-0.449$ ($P = .024$). Eighteen of these 25 patients also had completed the 3 subtests of the Wechsler Scale of Intelligence. For this subgroup of patients, the size of the HH and the sum of the 3 Wechsler scaled scores had a highly significant negative correlation at $-0.644$ ($P = .004$, $n = 18$). In this subgroup, the relationship between the absence of CPP to the sum of the 3 Wechsler scaled scores was $-0.737$ ($P = .127$, $n = 18$). The data suggest that larger HHs and the presence of early seizure onset together may be important predictors of cognitive status, at least as measured by these 3 estimates of intellectual ability.

Prigatano and coworkers also noted the continuum of neuropsychological test findings observed in their patients. Three major types of neuropsychological status were identified. Neuropsychology type 1 was described as having essentially normal intelligence as estimated by their vocabulary and block design subtest scores. A portion of these subjects, however, showed below average processing speed scores as reflected by their digit symbol-coding subtest scores. Type 2 patients were individuals who showed “unevenness” in their vocabulary and block design subtest scores. In this group of patients, 1 of these 2 subtest scores was at least 1 standard deviation below average, whereas the other was within the average range. A third type of patient was also identified. Type 3a patients were those individuals who had clear mental retardation but could be tested with IQ measures. Type 3b patients were those who had mental retardation who could not be tested because of severely restricted cognitive abilities or who were behaviorally uncooperative.

In their analyses of variables that correlated with these basic neuropsychological subtypes, Prigatano and coworkers noted that the presence of CPP was associated with higher incidence of mental retardation ($\chi^2 = 12.16$, $P = .02$).
In keeping with the earlier literature, patients who were described as mentally retarded (types 3a and 3b) also had a higher incidence of larger intrahypothalamic hamartomas ($\chi^2 = 16.75, P = .05$). Although these typologies may reflect different points on the continuum of cognitive function of HH patients with intractable epilepsy, it is also possible that type 2 patients may, in fact, represent that subgroup of HH patients who are showing a decline in neurocognitive status with time. It should be noted, however, that type 2 patients did not differ from the other patients regarding the lifetime duration of their epilepsy or the age of onset at which their seizures began.

In addition to the cognitive deficits, which are indeed quite variable in HH patients with refractory epilepsy, a wide range of behavioral and/or psychiatric disturbances have been noted in these children.

### What Factors Are Responsible for the Behavioral and Psychiatric Disturbances in HH Children?

Weissenberger and coworkers$^{14}$ specifically addressed the question of behavioral and psychiatric disturbance in 12 children with HH, gelastic seizures, and other mixed seizure types. Their patients ranged in age from 3 to 14 years at time of examination. They note that 83.3% of these children had significant difficulties controlling angry outbursts, aggressive tendencies, and many could be described as having an oppositional-defiant disorder. Seventy-five percent (75%) met criteria for attention deficit hyperactivity disorder. Thirty-three percent (33.3%) met criteria for a conduct disorder. Early onset of puberty was noted in 33.3% of these cases, but this variable was not specifically related to their behavioral and psychiatric findings. They do note that in their sample of children, 33.3% had speech retardation and learning difficulties. Perhaps an important and often overlooked issue in research in this area, they note that only 5 of the 12 children (41.7%) were able to complete the Woodcock-Johnson Tests of Cognitive Abilities (ie, there are many children who show significant cognitive and behavioral problems for whom traditional psychometric data cannot be obtained and these children are often excluded from important analyses). They concluded, however, that severity of the seizure disorder did not have an obvious correlation with the behavioral disturbance.$^{14}$

Savard and coworkers$^{15}$ provided an insightful longitudinal psychiatric history of 1 patient with HH and refractory epilepsy. They note that their patient did not exhibit the typical sham rage reactions seen with hypothalamic lesions in animals. Rather, they note that many factors seem to contribute to the aggressive behavior that their HH patient showed. They noted the patient showed signs of anxiety and had limited cognitive capacity. The patient’s aggressive and angry outbursts at times had a manipulative quality and served as a retaliatory function when upset with some frustration. These findings emphasized that multiple factors may contribute to the psychiatric and aggressive behaviors seen in HH patients.

Prigatano et al$^{16}$ have recently summarized the various psychiatric and associated behavioral diagnoses that have been applied to HH patients with refractory epilepsy who were referred for possible neurosurgical intervention. The list is impressive for its variety of diagnostic terms. Although terms such as oppositional-defiant disorder and attention deficit disorder are common, many other diagnostic terms are applied to this patient group. They included autism spectrum disorder, Asperger’s disorder, mood disorder (especially major depression), borderline personality characteristics, paranoid disorder, and obsessive-compulsive disorder. It is equally common to see diagnostic terms, which reflect various forms and levels of severity of developmental disability. It is interesting to note that there are some children whose parents did not first identify cognitive and behavioral disorders, but rather they described the child as somehow “being different” from their other children. In those instances, parents described these children as having problems with feeding and failure to show normal emotional responsiveness to a parent during infancy. This may be an early manifestation of these children who are later described as having an autistic spectrum disorder.

### A Case of a 7-Year-Old HH Child With “Behavioral Problems”

A recent case highlights some of the factors that need to be considered when evaluating the behavioral difficulties of children who have HH. A 7-year 11-month-old boy with a history of HH was seen for a neuropsychological evaluation. The child was carried to term but delivered via an emergency cesarean section for failure to progress. At birth, he weighed 9 pounds 12 ounces and was without postnatal complications. The mother notes that her son was slow to speak. Records indicate that he began talking at 2 years of age but only began to put sentences together by 4 years of age.

When the child entered kindergarten at age 5, the teachers noted significant difficulties in learning. This prompted a medical evaluation, which included MRI of the brain. MRI showed a nonenhancing hypothalamic mass, isointense on both T1- and T2-weighted sequences, 8 mm in maximal diameter, and most consistent with a hypothalamic hamartoma. The HH was attached to the inferior aspect of the hypothalamus on the left, immediately anterior to the mamillary bodies. There has been no change on serial MRI studies, and the remainder of the brain appeared normal.

Although no seizure activity has been reported, the electroencephalogram at age 6 years 3 months showed a mild degree of right temporal slowing and frequent right frontal spike and slow wave discharges (F4 and T8 electrode positions). The patient was not diagnosed as having epilepsy, and only after his present evaluation was a trial of antiepilepsy drugs attempted. The patient does not have a history of precocious puberty.

The child received special education services during his
first and second year of school. He was noted to have considerable difficulties learning to read and, at his present age of 7 years 11 months, still could not read words, even though he can identify letters of the alphabet. He was described by his attending neurologist as having “borderline developmental delay, particularly involving speech and language.” Moreover, his neurologist considered him to have “minor or at most moderate behavioral problems without evidence of seizure activity.”

The patient’s mother describes her son as having an extremely low tolerance for frustration and is easily angered. She notes that if something does not work out according to his desires, he can show severe angry outbursts, including striking out and hitting those in the home environment. She notes that these outbursts occur only at home and are directed toward family members (herself and his grandparents). She reports that during these times, it is difficult to reason with him, but occasionally he will calm down as she speaks with him. She notes, however, that in most instances he is not comforted by her efforts. Somewhat surprisingly, she reports that at school no such behavioral difficulties emerge. She indicates that teachers describe him as cooperative and not a behavioral problem. They report that he does not yell or hit anyone in school. The mother was perplexed as to why these behaviors do not occur at school but do occur at home.

This child was extremely difficult to engage in the neuropsychological examination. He passively engaged in some of the tasks, and with effort and prompting on the part of the examiner, he put forth acceptable levels of effort. Various reinforcers had to be used to keep him focused on the task at hand. FSIQ estimates could not be obtained, but he obtained a Verbal Comprehension Index score of 61 (0.5 percentile ranking), a Perceptual Reasoning Index score of 71 (percentile ranking of 3), and a Working Memory Index of 74 (percentile ranking of 4). All scores are severely below normal limits. He also performed on a comparable level when completing the coding subtest (scaled score = 5, average value is 10 with a standard deviation of 3). He could not read the words “yes” or “no” and, therefore, could not complete the symbol search subtest. Estimates of cognitive functioning would be in the borderline range of intelligence to mild mental retardation.

Although this child would occasionally smile and showed no aggressiveness during the neuropsychological examination, it was clear that it was difficult to motivate him. The patient’s mother notes that her son has the type of personality that “he will do what he wants to do and won’t do what he doesn’t want to do.” She notes, however, that male figures often can get the child to be more engaged in tasks.

When asked about whether or not her child ever expresses any sadness over not learning at a level comparable to other children, she reports none. She states that he will ask why other children can read and he cannot but does not appear to show any emotional distress over his failure to read. The patient’s mother also notes that when her son hits someone else, he never spontaneously apologizes for his actions. He does not seem to experience remorse for his misbehavior.

This case shows that children who have HH and are not diagnosed as having epilepsy (although they may show abnormalities on EEG) may show significant neurodevelopmental problems that impact cognitive, behavioral, and affective development. It is not difficult to see how these disturbances could lead to a wide variety of psychiatric diagnoses. The significance of the abnormalities on the interictal EEG, in the absence of clinical seizures, also deserves further consideration. The findings suggest that multiple factors, including environmental influences, can alter the expression of angry outbursts in some HH children.

Revisiting Deonna and Ziegler’s Conclusions

In light of more recent evidence, the conclusions of Deonna and Ziegler requires modification. Recent studies on cognitive dysfunction in HH children with refractory epilepsy suggest that different variables correlate with different cognitive measures in this patient population. Frattali and coworkers findings support Deonna and Ziegler’s premise that seizure frequency and seizure severity are associated with cognitive impairment. Quiske and coworkers did not find lifetime seizure duration to be significant but did relate cognitive function to HH lesion size. The findings reported by Prigatano and coworkers suggest that both size of HH and early seizure onset may interact to influence the cognitive status of the HH patients who have refractory epilepsy. The concept that seizure activity in and of itself leads directly to cognitive impairment (“epileptic encephalopathy”) in HH patients remains unproven. The same conclusion could be made regarding the behavioral problems of these children and perhaps with more certainty. In 1 group study, seizure history of the patient did not relate to their aggressive behaviors.

Case 7 reported by Nguyen and coworkers, as well as the case described earlier, argues 2 points. First, selected developmental delays (such as language impairments) can be observed in HH children before the onset of epilepsy. Second, some children show global cognitive impairments (eg, mental retardation) before their seizure activity emerges. These observations raise an interesting question. Could it be that HHs in and of themselves interfere with important integrative functions necessary for learning? Are basic drive states not experienced in a normal fashion, and therefore the need to speak and to remember information is compromised? Careful history taking of families regarding the development of an HH patient during infancy suggests that there may be subtle changes in normal affective and cognitive development that occur before the onset of seizure activity and certainly months, if not years, before worsening of seizure types to severe secondary generalized epilepsy. In light of these observations, the following propositions are offered.

1. Children with HH and no gelastic seizures (or other seizure types) and with or without PP may show unequivocal developmental abnormalities suggestive of an underlying brain disorder before epilepsy starts (eg, case 7 of Nguyen and coworkers).
2. Intrahypothalamic hamartomas in and of themselves may interfere with normal brain development producing cognitive, affective, and behavioral disorders that exist before the onset of epilepsy. Refractory epilepsy, however, may produce further cognitive decline.

3. Children with HH can have behavioral problems before the onset of refractory epilepsy. These behavioral disturbances seem to be caused by several factors, including limited cognitive (coping) skills and reduced tolerance for frustration (perhaps a mark of failure to develop normal brain function).

4. Some of these children may be viewed as autistic or showing oppositional-defiant disorders precisely because they do not experience a sense of guilt over their misbehavior or subjectively report sadness with failures that they experience in school. “Emotionally” they appear different in addition to whatever cognitive and behavioral problems are observed by parents and teachers. Disturbances of frontal-limbic neurocircuits may be responsible for these behavioral abnormalities.

Other Questions to Consider

Is CPP in HH patients a benign sign with respect to cognitive and neurobehavioral function? In some cases, it may be, and, in others, it may not. In the cases of pedunculated HH in which there appears to be no displacement of the hypothalamus, CPP may not be affiliated with any cognitive abnormality, as others have suggested. However, when there is an intrahypothalamic hamartoma that disturbs several integrative brain functions, including sexual development, then CPP may not be a benign sign. Further studies will need to assess whether or not CPP associated with pedunculated HH versus CPP associated with intrahypothalamic hamartomas results in different cognitive outcomes. Interwoven with this question is, of course, the question of how HH volume influences the clinical picture. The larger the HH, there is a higher likelihood that more hypothalamic centers will be disturbed. It may be important whether or not those centers lie posterior versus anterior on the hypothalamic axis. This is also an area that needs to be further investigated.

With these considerations in mind, it is helpful to review the observations and model of Lesser and coworkers for addressing the methodological issues involved in determining whether or not mental impairment and deterioration in seizure patients is a direct effect of epilepsy. Lesser and coworkers reminds us that a brain lesion that can cause seizures can also directly affect how the person functions in the real world (ie, their psychosocial functioning). If they are having learning difficulties in school, this will result in further decline on cognitive measures with the passage of time. Moreover, cerebral lesions that can produce epilepsy can also produce neuropsychological (including cognitive) impairments. The most obvious example is that mesial temporal sclerosis not only can produce seizures but also memory impairment relative to intelligence. Early seizure onset has also been related to worse neuropsychological status.

The model that Lesser and coworkers presented emphasizes the importance of thinking about cognition and epilepsy as a multifactorial process (Fig 3). There is a complex interaction between the actual nature of the underlying brain lesion, the seizures that emanate from it, and the psychosocial reactions that come from both the cognitive impairments and the seizures produced by a brain disorder. To add to the complexity of the problem, epileptic patients also are on anticonvulsant medications. These medications may also contribute to some of the cognitive impairments observed in HH patients. This point has been noted by others, but no study to date has specifically addressed this question.

The study of children with HH provides an unusual opportunity to evaluate how lesions affecting deep brain structures communicate with limbic and cortical networks. The present data on HH children suggest that the HH itself may disturb cognitive and affective development when the lesion is intrahypothalamic and displaces crucial brain structures, such as the mamillary bodies and the columns of the fornices. Collectively, these findings suggest that the hypothalamus may, in its own right, be important in cognitive and personality development.

References


Figure 3 There are a variety of potential cerebral substrates (Y1 . . . Yn) which would relate to intrinsic intelligence and personality as well as to preexisting structural lesions or inherent degree of cortical epileptogenicity. An individual substrate could affect age of seizure onset and tractability of seizures once they begin, as reflected in seizure duration (ie, how many years seizures are present), and could also affect severity, as reflected by the duration of individual seizures as well as by seizure number and type (eg, grand mal, status). The underlying cerebral substrate, and seizure severity and duration, would together result in alterations, or the absence of alterations, of cognitive functioning (Y1’ . . . Yn’). The underlying cerebral substrate (Y1 . . . Yn) also would result in a variety of personality styles (Y1” . . . Yn”), but these would be affected by interpersonal and environmental influences, which in turn would be affected by seizure duration and severity. Increased seizure severity possibly would result in the use of higher doses of anticonvulsants and these, in predisposed individuals, might alter cognitive or emotional functioning. (Reprinted with permission.)