Clinical Trials and Case Studies

Endoscopic Disconnection of Hypothalamic Hamartomas: safety and feasibility of robot-assisted , thulium laser –based procedures

Amedeo Calisto and 5 others

Journal of Neurosurgery & Pediatrics **14**:563 (2014)

SUMMARY: The authors of this trial were clinicians based in Paris and Italy. The aim was to assess the safety when using a thulium laser to disconnect hamartomas from the hypothalamus. They compared their approach to disconnection using monopolar coagulation (a type of electrocautery). In both cases they used a minimally invasive approach (endoscopy) to gain access to the HH. The 20 patients enrolled in the study were all resistant to conventional antiepileptic medications.

The rationale behind using the Thulium laser is that is offers more gentle cutting of the HH and as well as less destruction of adjacent normal tissue compared with monopolar coagulation. The cutting action of the laser only penetrates one half of one millimeter from its tip.

All twenty patients displayed significant improvement at one year follow up. A slightly higher improvement rate was seen in the laser group which also had fewer postoperative complications.

Although the number of patients treated was small, the use of the thulium laser for HH disconnection seems to offer some advantages over conventional monopolar coagulation.

Acute Intralesional Recording in Hypothalamic Hamartoma: description of 4 cases

Nicola Specchio and 12 others

Acta Neurologica Belgica October 10, ahead of print (2014)

SUMMARY: This paper originated as a collaborative effort involving several Italian neurological centers. Recordings of electrical activity within HH lesions were carried out in four individuals and compared with scalp EEG recordings made at the same time. The recordings were made during the course of other HH procedures.

Epileptic activity could be recorded in each of the four HHs thereby confirming previous findings by others. Activity generally was on the same side as the site of attachment to the hypothalamus. Activity recorded in the HH frequently did not match scalp EEG recordings likely because not all periods of HH epileptic activity spread to the cerebral cortex.

Although there was no direct one to one match between HH activity and scalp EEG activity, recordings from HHs may be useful for evaluating HH disconnection procedures.

Memory Outcome One Year after Stereotactic Interstitial Radiosurgery in Patients with Epilepsy Due to Hypothalamic Hamartomas

Kathrin Wagner and 4 others

Epilepsy & Behavior **37**: 204 (2014)

SUMMARY: This study was carried out at the University Hospital Freiburg in Germany. No mention is made regarding when this study was carried out. Thirty-seven patients were treated for HH by having radioactive Iodine (^{125}I) implanted into their tumors (stereotactic interstitial radiosurgery). The reasoning behind this approach is to shrink the size of the tumor (and thereby reduce seizures) along with minimizing side effects (especially memory issues) that can occur when a HH is removed. Of those patients, 26 were able to be assessed for memory functions. Typically the patients were tested before surgery and thereafter over the next 3-36 months (average of 14 months). The ability to recall facts and knowledge (declarative memory) deteriorated in 20-50% of patients. By comparison, when functions related to attention were tested, over 80% of patients were unchanged or slightly improved. With regard to seizure frequency, 14/26 patients did not show significant improvement. It is important to note that stereotactic interstitial radiosurgery is a comparatively uncommon approach to HH treatment.

Classification of Hypothalamic Hamartoma and Prognostic Factors for Surgical Outcome

C.D. Li and 5 others

Acta Neurologica Scandanavia **130**: 18 (2014)

SUMMARY: This study included 214 patients with HH who received treatment in Bejing, China between 1994 and 2008. Most patients became symptomatic during their childhood years. Almost half of the patients (44%) presented with precocious puberty while 37% had gelastic seizures. Ninety-three patients had their hamartomas surgically removed and had a minimum two year follow-up. The HHs were classified into 4 groups according to their location, whether they had a wide or narrow attachment to the hypothalamus and if they protruded into the third ventricle. Larger HHs were associated with a greater likelihood of gelastic seizures but not precocious puberty. Gelastic seizures were most often seen when the HH had a broad area of attachment to the hypothalamus and/or protruded into the third ventricle. HHs attached by a narrow stalk or entirely located in the third ventricle had the best outcomes after surgery with respect to freedom from seizures.

The authors have introduced a new way of classifying HHs adding to several other preexisting classifications. In their opinion the classification agrees well with surgical outcomes. However these cases were done before the advent of laser ablative surgery or HH disconnection. It is not clear if this classification system would be equally useful using these newer surgical approaches.

Cognitive Functioning Before and After Resection for Hypothalamic Hamartoma and Epilepsy

J.V. Wethe and 5 others

Neurology **81**: 1044 (2013)

SUMMARY: This study examined 32 children at the Barrow Neurological Institute in Phoenix who underwent neuropsychological testing following either transcallosal or endoscopic surgery to remove HHs. Overall, surgery resulted in some improvement in the children's ability to process information however there was no significant improvement in memory testing. The factors that had the greatest impact on neuropsychological testing included the duration of epilepsy, the age of the child at the time of surgery and the level of cognition (mental abilities and processes related to knowledge) at the time of surgery. Children with the greatest cognitive deficits and those with shorter durations of epilepsy appeared to show the best gains in intellectual functioning. No patients deteriorated in overall cognitive functioning following surgery.

What Happens to Cognitive Function Following Surgery for Hypothalamic Hamartoma ?

A.Simon Harvey & Jeffrey V. Rosenfeld

Neurology **81**: 1028 (2013)

SUMMARY: Harvey & Rosenfeld have written a brief editorial regarding the previous paper by Wethe. The reiterate much of what is stated in the above summary. One concern they have is that by looking at the patient group as a whole might mask changes in patient subgroups. In addition the small number and variability of the patient population, incomplete follow-up and limitations inherent to certain of the neuropsychological tests can be problematic for drawing conclusions.

Pychiatric Features in Gelastic Epilepsy and Hypothalamic Hamartoma: long-term psychodiagnostic observations

Luca Errichiello and 3 others

Neurologic Science **35**: 469 (2014)

SUMMARY: The authors present a single case report of a 24 year old man with a 21 year history of gelastic seizures due to a 10 mm HH. His seizures were controlled by medication and as such surgery was not required. As a result of various psychiatric findings (delusions, thought disorders, social withdrawal) he was diagnosed as a paranoid schizophrenic. Although the patient's psychiatric issues might be unrelated to his HH, other reports in the medical literature suggest the opposite. The significance of this case is that the psychiatric symptoms occurred even though his epilepsy was controlled by medication.

Hypothalamic Hamartoma: Optimal Approach to Clinical Diagnosis and Treatment

Angus A. Wilfong & Daniel J. Curry

Epilepsia **54** (Suppl. 9): 109 (2014)

SUMMARY: The Baylor College of Medicine in Houston, Texas has been in the forefront of laser ablation surgery for the treatment of HH. The surgeons use a diffuse laser to destroy HH tissue while being guided by MRI scans. The 14 patients who underwent this surgery ranged in age from 2 months to 20 years of age. The patients were resistant to conventional antiepileptic drugs and were have anywhere from 3-48 seizures per day. The majority of patients required only a 1-2 day hospital stay. The majority of patients became seizure free after a minimum of six months follow-up. Surgical complications in this patient group were minimal.

Hypothalamic Hamartoma: Is the Epileptogenic Zone Always Hypothalamic ? Arguments for Independent (third stage) Secondary Epileptogenesis

Julia Scholly and others

Epilepsia **54** (Suppl. 9): 123 (2014)

SUMMARY: The author present two cases ask whether the HH is solely responsible for all seizure types associated with HH of if a second epileptic site has developed elsewhere in the brain as a result of HH activity. Basically, they suggest that a HH can act as a driving force for the development of a second epileptic zone that is anatomically distant from the HH. Both cases involved patients who were adults and had developed seizures during childhood. The seizures had both gelastic components as well as components associated with temporal lobe epilepsy. Although both patients show some improvement after HH surgery, seizure control only occurred following a second surgery to remove a temporal lobe. The authors refer to this phenomenon as “hypothalamic plus” epilepsy in counterpoint to typical HH in which seizures disappear after HH surgery. Hypothalamic plus epilepsy seems to be more common in older individuals suggesting that secondary epileptic sites take time to develop.

Surgical Treatment of Hypothalamic Hamartoma Causing Central Precocious Puberty: long-term follow-up

Chun-de Li and others

Journal of Neurosurgery: Pediatrics **12**: 151 (2013)

SUMMARY: Three cases of children with precocious puberty caused by a HH are described. In contrast to most other reports, these children had long-term follow-up of 9 to 11 years. Precocious puberty refers to the premature development of secondary sexual characteristics normally only seen in adolescence. All three children had their HH removed surgically with subsequent resolution of their precocious puberty and a return to a normal developmental pattern. Long-term follow-up showed that they subsequently entered puberty at an appropriate age and had no learning difficulties. Surgery in these cases is a viable option either when the precocious puberty does not respond to drug treatment or if compliance with long term drug therapy is not feasible.

Lennox-Gastaut Syndrome Symptomatic to Hypothalamic Hamartoma: Evolution and Long-term Outcome Following Surgery

Sandipan Pati and others

Pediatric Neurology **49**: 25 (2013)

SUMMARY: Lennox-Gastaut syndrome (LGS) is a severe type of childhood epilepsy characterized by multiple seizure types along with behavioral, personality and learning disabilities. Up to 75% of patients with LGS appear to have an identifiable cause one of which is HH. In this study from the Barrow Neurological Institute investigators looked back and to evaluate the impact of HH surgery on children with LGS. Of the 21 cases studied, 24% were seizure free when tested 6 months to 4 years after surgery. A further 42% had a greater that 90% decrease in seizure frequency. Overall patients with LGS who also had HH have better outcomes after surgery than those patients in which LGS has a different or unknown cause. However HH patients have better outcomes than those with HH and LGS and this may be related to having seizures over a longer period of time prior to surgery.

Diagnosis and Management of Epilepsy Associated with Hypothalamic Hamartoma: An Evidence-Based Systematic Review

Sandipan Pati and others

Journal of Child Neurology **28(7)**: 909 (2013)

SUMMARY: Clinical studies of HH up to July 2012 were reviewed with the aim of trying to establish a consensus and recommendations regarding the diagnosis, clinical characteristics and management of HH. Ultimately 30 studies were evaluated each of which had at least 10 patients in their study. Unfortunately the fact that the study ended with papers in 2012 makes it somewhat outdated especially considering the advent of laser ablation therapy. Most of their conclusions are in line with what is already known about HH. Their survey supports the fact that surgery generally reduces seizures and that pedunculated HHs (i.e. on a stalk) are usually associated more with precocious puberty than gelastic seizures. There is relatively little evidence that gene abnormalities are associated with HH. The majority of patients had cognitive and/or behavioral problems. There is insufficient evidence to indicate that video EEG monitoring affects the outcome in patients who have undergone surgery for HH.

Hypothalamic Hamartoma.

Part 1. Clinical, Neuroimaging, and Neurophysiological Characteristics

Part 2. Surgical Considerations and Outcome

Sandeep Mittal and others

Neurosurgery Focus **34**: E6 and E7 (2013)

SUMMARY: These papers present a comprehensive review of the basic, clinical and surgical literature pertaining to HH. No new data is presented. They would be most useful to persons with scientific and/or medical training.

Giant Hypothalamic Hamartoma: case report and literature review

Cresio Alves and others

Childs Nervous System **29**: 513 (2013)

SUMMARY: Giant HH refers to a group of rare hamartomas that are greater than 30-40 mm in size. This individual had a 50 x 50 x 40 mm HH that was associated with precocious puberty and gelastic seizures. His precocious puberty resolved with medication however antiepileptic drugs were ineffective in treating his gelastic seizures. There was no mention of a surgical option possibly because in previous cases there have been postoperative complications.

Combined Open Microsurgical and Endoscopic Resection of Hypothalamic Hamartomas

Jonathan Roth and others

Journal of Neurosurgery: Pediatrics **11**: 491 (2013)

Editorial: Hypothalamic Hamartomas

Harold L. Rekate

Journal of Neurosurgery: Pediatrics **11**: 489 (2013)

SUMMARY: Dr. Roth and colleagues present a modified approach to the surgical removal of HH in situations when access is especially difficult due to small ventricles (chambers in the brain that carry cerebrospinal fluid). HHs are typically located in and around the 3rd ventricle. To reduce the risk of tissue damage when approaching the HH while not damaging, they suggest using a conventional approach to access the ventricles and then switching to an endoscopic approach to actually remove the HH. As Harold Rekate points out in his editorial, this will likely increase the availability for HH treatment by overcoming the difficulties presented by patients with small ventricles.

The Benign Spectrum oh Hypothalamic Hamartomas: Infrequent Epilepsy and Normal Cognition in Patients Presenting with Central Precocious Puberty

Priscilla Cukier & others

Seizure **22**: 28 (2013)

SUMMARY: This group looked at 15 patients who had been diagnosed with precocious puberty. Two thirds of the patients did not have seizures and were otherwise normal. Several of the remaining patients who did have seizures demonstrated a lower IQ and cognitive impairment. Patients presenting with both precocious puberty and seizures invariably had flat HHs (sessile tumors) which is consistent with the existing HH literature. Their case study also shows that patients with seizures are more likely to have some cognitive and/or behavioral issues.

Ictal Tachycardia in Patients with Hypothalamic Hamartoma

Victoria San Antonio-Arce & Andreas Schulze-Bonhage

Journal of Neurology, Neurosurgery & Psychiatry - online (17 Dec. 2014)

SUMMARY: Ictal tachycardia refers to an increase in heart rate (tachycardia) during a seizure (Ictal). It is a very common phenomenon in epilepsy. In this retrospective study the authors looked at 251 seizures in 31 patients. Tachycardia was seen in half of all seizures and in the vast majority (84%) of patients. Two thirds of patients had a 50% increase in heart rate. Tachycardia occurred in all seizure types but especially in more complex type seizures and seizures that lasted longer. Ictal tachycardia in HH patients was unrelated to any specific clinical features. The authors suggest that the features of ictal tachycardia is most likely related to tumor location.

Original Research

Firing Behavior and Network Activity of Single Neurons in Human Epileptic Hypothalamic Hamartoma

Peter Steinmetz and 4 others

Frontiers in Neurology **4**: Article 210 (2013)

SUMMARY: This study originates from the Barrow Neurological Institute. The authors were able to record the activity of single nerve cells in HH just prior to its surgical removal. They found that neurons were spontaneously active confirming several other studies. By looking at the activity characteristics of these nerve cells, they were able to determine that there were at least two different types of nerve cell. The nerve cells often acted in harmony (synchronous activity) suggesting that they were part of a nerve network among which may help to explain the epileptic nature of HH.

Hyperactivation of BDNF-TrkB Signaling Cascades in Human Hypothalamic Hamartoma (HH): A Potential Mechanism Contributing to Epileptogenesis

Suzan Semaan and 8 others

CNS Neuroscience & Therapeutics 14 Oct, 2013 – ahead of print

SUMMARY: Cell activity is heavily controlled by cascades of chemical interactions which serve to activate, deactivate or otherwise regulate certain processes. Thus chemical A might activate chemical B which in turn decreases the activity of chemical C. If chemical C plays a vital role in controlling the firing activity of a nerve cell, then that nerve cell will start to fire more slowly or not at all. The study above indicates that certain chemical cascades are hyperactive and these might be part of the reason that HH tissue is epileptogenic.