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Surgical and postpartum hereditary brachial plexus attacks and prophylactic immunotherapy

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Abstract

Introduction—Surgery and childbirth can trigger attacks of hereditary brachial plexus neuropathy (HBPN), and inflammation was suggested as a component of the pathogenesis.

Methods—HBPN patients who underwent surgery or parturition from Jan.1,1996 to Dec.31,2009 were studied.

Results—Twenty-five HBPN patients underwent 48 surgeries or parturitions. Seventeen patients (68%) had attacks, including 13 periprocedural and 7 postpartum by varied anesthesia types. Three patients who had 8 earlier combined attacks (after thyroidectomy, laminectomy, and Caesarean section) were given prophylactic immunosuppressive therapy (corticosteroids ± immunoglobulin). None suffered postoperative attacks, which is uncharacteristic of their prior experience. Five had perioperative attacks as their first HBPN manifestation. Median follow-up was 11(3-48) months. Attacks occurred in the operated limb (n=6) or distant (n=7) to surgical sites. All attacks interfered with daily living, with frequent incomplete recovery. Five patients had a *SEPT9* mutation.

Conclusions—Corticosteroid may prevent parturition and surgical HBPN attacks in some patients. Diverse surgeries, anesthesia and childbirth frequently trigger HBPN attacks.

Introduction

Surgical procedure-related nerve injuries are frequently attributed to compressive mechanisms.[1] However, there is growing recognition that some perioperative nerve injuries arise from an inflammatory process.[2] Hereditary brachial plexus neuropathy (HBPN), also known as hereditary neuralgic amyotrophy (HNA), is an autosomal dominant disorder characterized by episodic attacks of debilitating pain, weakness, and atrophy affecting patchy multifocal locations of the brachial plexus and its nerves.[3,4] Surgery and childbirth are known triggers for these attacks.[5-10] Among some families, mutations of the *SEPT9*

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gene, either by missense[11, 12] or duplication abnormality[12] have been identified. However, for many families the genetic cause remains unknown.[13] Nerve biopsies of upper extremity nerves at times of attacks provide evidence for an inflammatory component to these attacks.[6] Because HBPN is uncommon, comprehensive focused reviews of postsurgical or postpartum attacks are lacking. Corticosteroids have long been observed to attenuate pain associated with attacks, but it is not known if prophylactic corticosteroids could help to prevent recurrent surgical and postpartum attacks. [6,14]

In this report we focus on the occurrence of postsurgical and postpartum HBPN attacks among HBPN patients who were evaluated by neurologists and anesthesiologists at our institution. We also described the clinical features and outcomes of 3 cases that were followed longitudinally through multiple attacks. They were studied prospectively after receiving prophylactic preoperative or prepartum corticosteroids.

Methods

Evaluation of HBPN patients

Institutional review board approval and patient consent were obtained. An established research database of HBPN patients and an institution-wide electronic record retrieval was utilized to identify all patients with HBPN or HNA (hereditary neuralgic amyotrophy) master sheet diagnosis who had undergone a surgical procedure at Mayo Clinic and those who experienced periprocedural (either surgery or childbirth) attacks that were evaluated and treated by Mayo Clinic neurologists and anesthesiologists from January 1, 1996 to December 31, 2009. The diagnosis was accepted in persons who suffered brachial neuritis attacks with known mutations in *SEPT9*, attack(s) with family history confirmed in a first degree relative, or multiple recurrent attacks without other explanation regardless of family history. The neurological, surgical or obstetrical, and anesthetic records of identified patients were reviewed. Details regarding perioperative corticosteroid administration or other immunotherapies were noted. A periprocedural attack was defined to occur within 30 days of the procedure.

Clinical characteristics of HBPN patients suffering attacks

The neurological records were reviewed in detail regarding the precipitating events, history of prior attacks, family history, *SEPT9* genetic testing, and neurological exam. Available surgical and anesthetic records were reviewed. A structured evaluation of neurologic deficit allowed for calculation of neuropathy impairment score (NIS) summing the motor, sensory and reflex deficits (0 to 244), with 0 signifying no neurologic deficits and 244 representing a patient with areflexia, paretic extremities and bulbar areas, and no sensation.[15] We also determined a neurologic peripheral neuropathy disability score (Dyck Score) ranking from 0-8. Zero is normal without signs or symptoms of neuropathy, and 8 is symptomatic neuropathy requiring constant care in an intensive care setting.[16] An NIS score of 25–50 often correlates with a Dyck Score of 3-4. An NIS score > 50 correlates with Dyck Scores ≥ 5 and precludes most vocations. Details regarding NIS and Dyck assessment tools are provided (Supplemental images).

SEPT9 DNA analysis

All *SEPT9* coding exons were sequenced using dye termination chemistry (Applied Biosystems, Carlsbad, California). PCR primer sets were designed using the web-based design tool Primer3 (http://frodo.wi.mit.edu). Intronic primers were designed at least 30 bp away from intron/exon boundaries. The cleaned products were mixed with 5 picomoles of the forward or reverse PCR primers for sequencing. DNA sequence variants were identified using Mutation Surveyor Analysis Software (Soft Genetics, State College, Pennsylvania,

USA). *SEPT9* copy number was evaluated by custom-designed Agilent oligo array-based Comparative Genomic Hybridization (aCGH) (Agilent Technologies, Santa Clara, California, USA) to profile DNA copy number variations at *SEPT9* chromosome region. The probes on Agilent aCGH microarrays are 60-mer oligonucleotides and were overlapped or spaced along chromosomal regions of *SEPT9* at high density. Analysis of the copy-number variants was performed according to the manufacturer's instructions and software.

Results

Findings of postoperative or postpartum attacks

Seventeen HBPN patients who suffered postoperative or partum attacks were identified; they suffered 20 total attacks, including 13 postsurgical and 7 postpartum attacks (Supplementary Table 1& 2). Patients #2, #3 and #4 had multiple attacks that were evaluated at our institution. The median age at attack was 31 (range 15-65) years. The postsurgical or postpartum attack was the first manifestation of HBPN in 5 patients. Five patients had positive *SEPT9* genetic testing. Among 11 patients who suffered postsurgical attacks, 10 had a family history of HBPN, and 1 patient had repeated attacks without family history. All 6 patients who suffered postpartum attacks had a family history of HBPN.

We also identified 8 HBPN patients who had 21 total surgical procedures at our institution, but they did not suffer attacks after procedures and did not receive any prophylactic treatment. Thus, among the 25 HBPN patients who had 48 total surgical or childbirth procedures, 17 (68%) had postprocedural or postpartum attacks; the occurrence rate of HBPN attacks was 42% (20 out of 48).

Surgical and anesthetic characteristics preceding attacks

Six attacks occurred following surgery on the affected limb. Three involved exploration of affected peripheral nerves in an initial attempt to treat and/or diagnose the problem, but there were subsequent more widespread brachial involvements post surgery beyond where the nerves were explored (Supplementary Tables 1& 2). Eleven attacks involved general anesthetics preceding the procedures. Two postsurgical attacks utilized only local anesthetic infiltration of the surgical area (lidocaine or equivalent injection). Postpartum attacks occurred following 3 normal vaginal deliveries, 2 Caesarean sections, and 2 deliveries where delivery route and anesthetic were not documented.

Clinical features of attacks

Details related to clinical features of the attack are summarized (Supplementary Tables 1& 2). The median Dyck Score was 4 (range 2-5) at initial evaluation, while the median NIS score was 22 (range 2-43). The Dyck Score is consistent with definite clinical neuropathy that impairs skills of daily living including working. The degree of disability indicated by the Dyck Score is greater than what is predicted from the NIS scores.[16] This discrepancy occurs, because the overall NIS score does not specify which extremity is involved. Notably, HBPN attacks frequently lead to weakness of critical shoulder and hand grasp muscles, and an extended area including the arm and hand is often affected by severe pain. All patients had significant pain, and in most cases, pain was characterized as the "worst in their life". Most patients developed weakness after onset of pain, and only 1 patient developed weakness before pain started.

The median onset time following surgery or childbirth was 3 (range 0-30) days. Characteristic upper extremity attacks affected multifocal localizations, including the brachial plexus (upper trunk predominant) and the subserved nerves including within the shoulder (axillary, suprascapular), arm, forearm and hand (radial, musculoskeletal, median,

ulnar). Two attacks affected other nerves. Patient # 3 had recurrent laryngeal nerve involvement following a breast biopsy performed under masked anesthesia without airway instrumentation. Patient # 7 had bilateral phrenic nerve involvement following lumbar spine surgery.

Treatment and Symptom Resolution

Median follow up was 11 (range 3- 48) months. All except 1 (Patient #3) had significant improvement or complete recovery from pain at last follow up, The median Dyck Score improved by 3 points. Seven patients were treated with corticosteroids, and 2 also had intravenous immunoglobulin. Pain dramatically improved with initiation of steroids in all but 2 patients. Other pain therapies included acetaminophen, nonsteroidal antiinflammatory drugs, opioids, gabapentin, and antidepressants with varied but generally less effect compared to corticosteroids. No overt rapid improvement in weakness occurred with steroids, and in 2 of 7 treated patients weakness progressed despite steroids being initiated (Patient #14 second attack, 1 gram IV methylprednisolone; Patient #2 1st attack, oral and 1 gram IV methylprednisolone). Physical therapy was employed to address weakness and range of motion, and contractures were not noted in any patients at follow up.

Prophylactic Treatment for HBPN

Three HBPN patients identified prospectively with previous surgical or postpartum attacks were followed by us longitudinally and were given periprocedural immunotherapy as prophylaxis to prevent a subsequent attack with childbirth or surgery (Table).

Patient #14—A 34-year old woman (165 cm, 70.5 kg), the subject of our earlier report (and presented in the Table and Supplementary Tables 1 & 2),[6] had suffered 2 postpartum attacks and was pregnant with her third child. Ten out of 12 of her HBPN affected relatives had suffered postpartum attacks with each of their deliveries. Her genetic testing revealed a *SEPT9* gene mutation duplication. She suffered a postpartum attack following her first delivery by vaginal route. For her 2nd pregnancy, we recommended Caesarian delivery to reduce strain on the brachial plexus from pushing and hoped to prevent an attack. Unfortunately she had an attack within hours of delivery, indicating that parturition rather than the route of delivery triggered the attack. In an attempt to prevent another attack for the 3rd delivery, she underwent elective Caesarian section and was given preoperative IV methylprednisolone, 1 gm, and 6 daily postpartum infusions of immunoglobulin beginning the day after delivery. She did not suffer an attack.

Patient # 18—A 30-year old woman (164 cm, 87 kg) presented for thyroidectomy for papillary thyroid carcinoma. Five months previously she had her first attack after a normal vaginal delivery. Her father, paternal grandfather, and sister all had HBPN confirmed by *SEPT9* duplication mutation. Oral prednisone, 30 mg daily, was used to treat attack symptoms, and she had gradual improvement of pain and weakness. The dose was increased to 60 mg daily for 1 week prior to surgery. For surgery, she was kept awake, and the upper extremities were positioned with slight flexion at the elbows, as pain and paresthesias occurred with full elbow extension. She reported no symptoms with final positioning. Dexamethasone was administered prior to surgical incision. General endotracheal anesthesia was induced with careful direct laryngoscopy to avoid extending the neck. After surgery, she denied worsening of symptoms and was tapered off prednisone. Six weeks later she continued to do well and only had pre-existing bilateral wrist drop which continued to improve over subsequent months.

Patient # 19—A 66-year old man (184 cm, 107 kg) was diagnosed with HBPN and had a history 5 attacks of brachial neuritis and recurrent laryngeal neuritis without alternative

explanation despite extensive clinical workup. Family history evaluation was limited by the small size of his family, and he had negative *SEPT9* mutation analysis. He experienced his first attack during high-school after dental work, and 4 additional attacks occurred at ages 18, 28, 31, and 47 years. Two additional attacks also occurred after dental work under local anesthesia, and 1 attack followed spine surgery, each with terrible pain. The attack at age 47 years occurred following cervical laminectomy from C3–C7 performed in the sitting position. The surgery lasted 7 hours and 30 minutes. Attack symptoms began on the day of surgery; they were characterized by multiple upper extremity mononeuropathies and progressed over 1 week. He was treated with oral prednisone and physical therapy and recovered gradually over many months.

When he presented recently for lumbar laminectomy, in an effort to prevent another attack, he was given methylprednisolone, 1 gm IV, the day preceding, the day of, and the day following surgery. For surgical exposure he was positioned *prone*, and all pressure points were padded carefully. Total anesthesia time was 225 minutes. Uncharacteristically, he did not experience a postsurgical HBPN attack.

Discussion

The occurrence of surgery or labor-induced attacks of brachial plexus neuropathy provides a unique avenue of investigation for HBPN. In this HBPN series, we observed an overall 68% occurrence rate for surgical and postpartum attacks. For many HBPN patients, family history is not known until kindred evaluation is conducted.[17] In this series, 5 patients had periprocedural attacks as their first manifestation of HBPN. For patients who have a first attack, family history should be investigated. However, a negative family history need not exclude the diagnosis, and we previously reported 1 patient who had recurrent attacks without family history and was later found to carry a *SEPT9* duplication abnormality.[13] Mutation of the *SEPT9* gene can help establish the diagnosis of HBPN,[12,13,11] but as is evident in this cohort and earlier studies[12,11,13] it need not be present to make the diagnosis. Specifically, we found infrequently persons who carry the *SEPT9* mutation despite a clear family history and recurrent attacks.

The HBPN patients reported here underwent multiple types of surgical and anesthetic procedures or different routes of childbirth. The locations of surgeries leading to their attacks varied widely, and no correlation was found with type of surgery or anesthetic. In several cases, attacks occurred in areas remote from the surgical procedure, suggesting direct trauma is not the only trigger for attacks. Procedural attacks suffered by HBPN patients were severe; they resulted in disabilities that interfered with work and daily activities, which is typical of brachial neuritis attacks in general.[3] Pain typically resolved over several months, while weakness could take more than a year to resolve, which is also consistent with other reports of brachial neuritis.[7] We found steroids were helpful in treating pain for most patients and were generally more effective than other traditional pain regimens i.e. narcotics or antiepileptic medication. However, progression of weakness still occurred in some patients despite the introduction of steroids.

Among our HBPN cohort, 3 patients were treated with prophylactic immunosuppression and did not suffer attacks following surgery or child birth. The absence of attacks following surgery and parturition was uncharacteristic of their prior histories. One of these patients (patient #14) had an earlier nerve biopsy that confirmed an inflammatory component during her 2nd postpartum attack, and such attacks occurred in nearly every woman in her family after each of their deliveries. She and case #18 both had *SEPT9* duplication mutations. The main rationale for our prophylactic attempt to prevent the attacks is based on our observation that the biopsy of affected nerves is characterized by the disruptive

inflammatory mononuclear infiltrates in nerve brachial plexus microvessels, including vessel walls.[6] Prophylactic steroids could also potentially reduce the physiologic reaction from surgery, such as increased cytokine release, which may be important in the triggering of these attacks. Prophylactic therapy in patients who are diagnosed with idiopathic brachial plexus neuropathy (Parsonage-Turner syndrome) will require future investigation and might be supported by one large series which suggested recurrent attacks occur in as many as 26.1% of patients.[7]

To our knowledge, this prophylactic immunotherapy/corticosteroid treatment approach has not been reported previously, and its success should be interpreted carefully. These patients were highly selected, as they had demonstrated great proclivity to post-surgical or postpartum attacks. Although immunotherapy has associated risks to the patient and unborn, these patients were willing to assume the risks, given the severity and frequency of their earlier attacks. Additionally, both steroids and IVIG have relative safety profiles during pregnancy and surgery for other conditions including such as is described in acute inflammatory demyelinating polyradiculoneuropathy (Guillaine-Barré syndrome).[19]

In summary, HBPN attacks occurring after the physical stresses of surgery or childbirth appear comparable to other brachial neuritis attacks. Prophylactic corticosteroids may prevent postprocedural attacks in selected individuals who have known recurrent postprocedural attacks. Among some HBPN patients the risks and rationale of such prophylaxis are justified when considering the frequency of attacks, severity of the disabling attacks, pathologic descriptions and the relative safety profile of short course corticosteroids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Acronyms or Abbreviations

HBPN	hereditary brachial plexus neuropathy
HNA	hereditary neuralgic amyotrophy
SEPT9	Septin-9
NIS	neuropathy impairment score
DXS	Dexamethasone
MPS	Methylprednisolone
IVIG	Intravenous immunoglobulin
PRED	Oral prednisone

Table

HBPN patients prophylactically treated with corticosteroid

Patient #	Age (y) & Gender	Age at first Attack (yr)	Family history	*SEPT9* Mutation*	Surgery type	Anesthetic	Perioperative Steroids and Immunosuppressants
14	34 F	19	Y	Y	Caesarean section	Epidural	24 hours prior to induced delivery had MPS 1000 mg Postpartum IVIG 0.4 gm/kg/day × 6 days beginning post delivery day 1
18	30 F	30	Y	Y	Thyroid resection	General	PRED 60 mg/day 1 week prior to surgery During surgery 8 mg IV DXS
19	66 M	17	N	N	Lumbar spine surgery	General	IV MPS 1000 mg day preceding, day of, and day after surgery

*All *SEPT9* mutations were gene duplications including the 645 base pair exon.

Abbreviations; M=male; F=female; Y=yes; N=No; DXS=Dexamethasone; MPS=Methylprednisolone; IVIG= Intravenous immunoglobulin; PRED=Oral prednisone.