# Clinical Reasoning: A 26-Year-Old Woman With Recurrent Pain, Weakness, and Atrophy in Bilateral Upper Limbs During Pregnancy and Puerperium

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## Abstract

We present the case of a 26-year-old woman with recurrent episodes of severe pain, weakness, and atrophy in her bilateral upper extremities during pregnancy and puerperium. She reported 2 similar episodes at ages 5 and 10 years, after which she fully recovered. On examination, we observed significant atrophy in her bilateral upper extremity muscles with decreased strength. Needle electromyography (EMG) revealed neurogenic damage in her bilateral upper limbs. The patient's clinical manifestations and auxiliary examination suggested a brachial plexopathy. Metabolic and immune factors that may occur during pregnancy and puerperium were evaluated. We also screened for paraneoplastic, neoplastic, and genetic factors. Finally, a hereditary form of disease was considered. This case emphasizes the importance of early diagnosis and avoidance of triggers.

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## Section 1

A 26-year-old woman developed tingling in her right upper limb during the second month of pregnancy that progressed to her left upper limb within several days. The pain, which first appeared at night, worsened during cold weather and improved when it was hot. Two weeks later, she developed proximal weakness in her right more than left arm. She also noticed progressive difficulty lifting her arms, using chopsticks, and buttoning clothes. There was no history of antecedent trauma, infection, or vaccination. The patient did not take any medication and was referred for rehabilitation therapy. The pain gradually resolved 3 months later, and the weakness in both arms slowly improved. She was eventually able to manage her daily activities without assistance, but had mild residual weakness.

One week after giving birth, the patient experienced another attack. She developed severe pain in the left shoulder and arm, numbness in the left hand, and could not raise her left arm. After a few days, she developed weakness and pain in both upper limbs. No neck pain, bowel/bladder dysfunction, or muscle fasciculations were reported. She denied weakness or sensory change in her lower limbs. She reported having 2 similar episodes at ages 5 and 10 years, after which she fully recovered. Regarding family history, her mother also reported a similar single episode that started with muscle weakness in the right upper extremity 1 month after parturition, from which she recovered 8 months later.

On examination, mental status was normal and cranial nerves were intact. Strength in the upper extremities was decreased (Figure, A). The patient had normal strength in the lower extremities. Tone was decreased in the arms and normal in the legs. Significant atrophy of bilateral infraspinatus, teres minor, and deltoid muscles were observed in addition to decreased sensation to pinprick along the radial aspect of the forearms. No fasciculations were noted. Deep tendon reflexes (DTRs) were 1+ in the upper limbs and 2+ in the lower limbs. No pathologic reflexes were found. The patient had a similar facial appearance as her mother because both had hypotelorism (measured pupil-to-pupil with a ruler) (Figure, B).

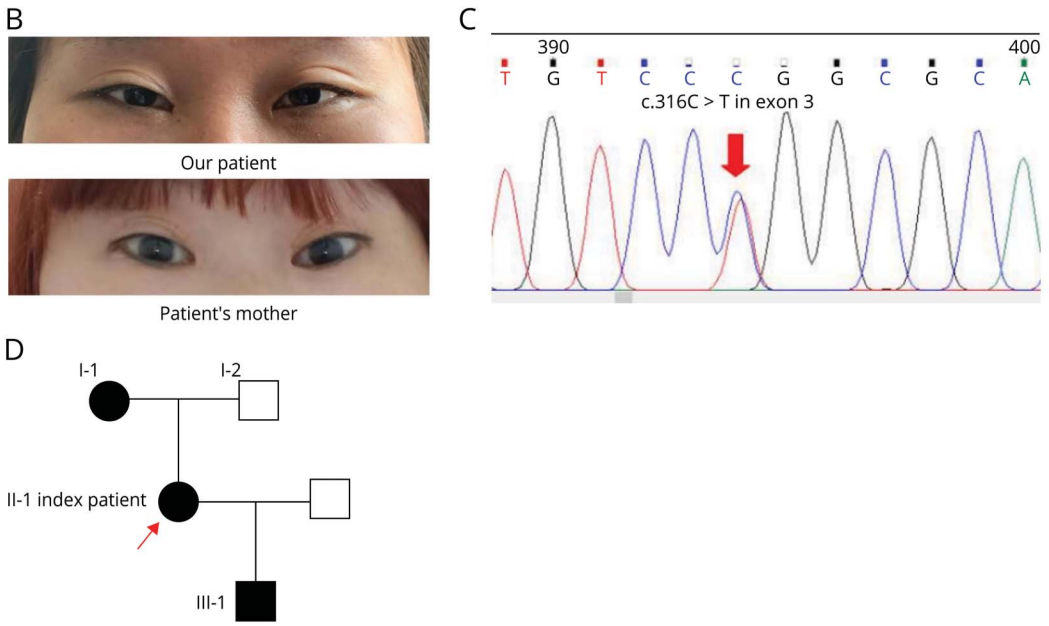
### Question for Consideration:

1. Where would you localize the lesion?

**Figure** Clinical and Gene Findings

A

| | Shoulder abduction | Shoulder external rotation | Elbow flexion and extension | Forearm supination | Wrist extension and flexion | Finger flexion | Finger abducation |
|---|---|---|---|---|---|---|---|
| Right | 2 | 3 | 3 | 3 | 3 | 3 | 2 |
| Left | 2 | 2 | 3 | 3- | 2 | 3- | 2- |




(**A**) Strength in the upper extremities (Medical Research Council); (**B**) Dysmorphic features; (**C**) A heterozygous single nucleotide change c.316C > T in exon 3 of the *SEPT9* gene, resulting in the amino acid change p.Rl06W; (**D**) Pedigree: Female individuals are shown as circles, male individuals as squares. Filled symbols represent affected individuals with an exon 3 missense variation of the *SEPT9* gene. Open symbols indicate nonaffected individuals and a slanting arrow the index patient. III-1 is without attack so far.

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## Section 2

The severe pain, numbness, and weakness with focal muscle atrophy in the bilateral upper limbs and depressed reflexes suggest involvement of the peripheral nervous system. The CNS is less likely involved in the absence of upper motor neuron signs. Therefore, we considered a multilevel radicular process involving multiple nerve roots (C5-T1), brachial plexopathy, or neuropathy (radial, median, axillary, suprascapular, and musculocutaneous nerves). The patient also experienced significant pain during each attack. The differential diagnosis based on localization might involve the following:

1. Radiculopathy, which can be caused by trauma or various inflammatory or neoplastic disorders but does not typically involve the bilateral upper extremities simultaneously.
2. Plexopathy, such as Parsonage-Turner syndrome or diabetic radiculoplexus neuropathies, which can be associated with severe pain at the onset of weakness.
3. Multiple mononeuropathies, which can be caused by vasculitis, inflammation, or diabetic neuropathy and result in neuropathic pain.

### Question for Consideration:

1. What is the most appropriate next step in this patient's workup?

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## Section 3

Needle electromyography (EMG) and nerve conduction studies (NCS) were performed after the fourth attack. EMG revealed neurogenic damage in the bilateral upper limbs. Sensory nerve conduction studies also showed a low-amplitude right radial nerve sensory nerve action potential (SNAP) and slow sensory conduction velocity of the right median nerve and bilateral radial nerves. The motor nerve conduction testing showed decreased compound muscle action potential (CMAP) amplitudes elicited bilaterally from the axillary, radial, and musculocutaneous nerves and right median nerve (Table). The abovementioned findings revealed dysfunction in the middle and upper trunci of the bilateral brachial plexus.

The patient's clinical manifestations and auxiliary examination suggested a brachial plexus neuropathy; however, she had no history of recent infection, trauma, vaccination, cancer, toxic exposure, diabetes, or radiation therapy. Laboratory tests, including erythrocyte sedimentation rate, antinuclear antibodies, and antineutrophil cytoplasmic antibodies, were within normal limits. CSF tests were normal. Immunologic testing for antiganglioside and anti-Hu paraneoplastic antibodies showed negative results. Contrast-enhanced MRI of the brachial plexus and cervical spine was normal. Considering the high rate of recurrence, family history, and presence of dysmorphic features, a hereditary disease was suspected.

### Questions for Consideration:

1. What hereditary disease could account for patient's symptoms?
2. What testing is required for definitive diagnosis?

**Table** Nerve Conduction Studies and EMG

| CMAP | Stimulation site | Recording site | Latency, ms | Amplitude (motor mV, sensory μV) | Conduction velocity, m/s |
|---|---|---|---|---|---|
| **R median** | Wrist | APB | 3.80 (<4) | 0.7 (>5) | |
| | Elbow | APB | 7.81 | 0.4 (>5) | 54 (>50) |
| **L median** | Wrist | APB | 2.50 (<4) | 6.4 (>5) | |
| | Elbow | APB | 5.52 | 5.5 (>5) | 73 (>50) |
| **R ulnar** | Wrist | ADM | 1.88 (<3.8) | 7.1 (>5) | |
| | Below elbow | ADM | 5.00 | 8.2 (>5) | 74 (>50) |
| **L ulnar** | Wrist | ADM | 2.24 (<3.8) | 11.2 (>5) | |
| | Below elbow | ADM | 5.05 | 9.4 (>5) | 82 (>50) |
| **R radial** | Forearm | EIP | 4.06 | 0.3 (>8) | — |
| **L radial** | Forearm | EIP | 4.38 | 0.3 (>8) | — |
| **R musculocutaneous nerve** | Erb's | Biceps | 5.99 | 1.4 (>6) | — |
| **L musculocutaneous nerve** | Erb's | Biceps | 4.84 | 1.2 (>6) | — |
| **R axillary nerve** | Erb's | Deltoid | 3.23 | 1.2 (>6) | — |
| **L axillary nerve** | Erb's | Deltoid | 4.48 | 3.0 (>6) | — |
| **R tibial** | Ankle | AH | 2.71 (<5) | 18.0 (>4) | |
| **L peroneal** | Ankle | EDB | 3.80 (<5) | 6.3 (>3) | |
| **SNAP** | | | | | |
| **R median** | Wrist | Digit II | 5.94 | 43.7 (>10) | 26 (>50) |
| **L median** | Wrist | Digit II | 2.45 | 65.0 (>10) | 65 (>50) |
| **R ulnar** | Wrist | Digit V | 2.34 | 56.3 (>10) | 58 (>50) |
| **L ulnar** | Wrist | Digit V | 2.19 | 32.0 (>10) | 60 (>50) |
| **R radial** | Forearm | Anatomical snuff box | 2.97 | 2.90 (>10) | 45 (>50) |
| **L radial** | Forearm | Anatomical snuff box | 2.92 | 20.5 (>10) | 45 (>50) |

| | Spontaneous activity | | Motor unit morphology | | |
|---|---|---|---|---|---|
| **EMG** | **Fibs/PSWs** | **Fasciculation** | **Amplitude** | **Duration** | **Recruitment** |
| **L deltoid** | 3+ | — | No units | No units | No units |

Continued

**Table** Nerve Conduction Studies and EMG *(continued)*

| | Spontaneous activity | | Motor unit morphology | | |
|---|---|---|---|---|---|
| **EMG** | **Fibs/PSWs** | **Fasciculation** | **Amplitude** | **Duration** | **Recruitment** |
| **L biceps** | 1+ | — | Normal | Normal | Decreased |
| **L EDC** | 2+ | — | No units | No units | No units |
| **L APB** | 1+ | — | No units | No units | No units |
| **R deltoid** | 2+ | — | Normal | Normal | No units |
| **R biceps** | 2+ | — | Increased | Increased | Decreased |
| **R EDC** | 3+ | — | Increased | Increased | No units |
| **R APB** | 3+ | — | No units | No units | No units |
| **L tibialis anterior** | — | — | Normal | Normal | Normal |
| **R vastus medialis** | — | — | Normal | Normal | Normal |

Abbreviations: ADM = abductor digiti minimi; AH = abductor hallucis; APB = abductor pollicis brevis; CMAP = compound muscle action potential; EDB = extensor digitorum brevis; EDC = extensor digitorum communis; EIP = extensor indicis proprius; EMG = Needle electromyography; Fibs/PSWs = fibrillation potentials or positive sharp waves; SNAP = sensory nerve action potential.
Annotation: The values in parentheses are reference normal values.

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## Section 4

When evaluating patients for a genetic disease involving the brachial plexus, hereditary neuralgic amyotrophy (HNA) should be considered. Gene analyses were performed for HNA. We identified a heterozygous single nucleotide change c.316C > T in exon 3 of the *SEPT9* gene (GRCh37/hg19 chr17:75398380), resulting in the amino acid change p.R106W (Figure, C). This variation was also found in the patient's mother and son (Figure, D). The son was 2 months old during genetic testing.

## Discussion

Neuralgic amyotrophy (NA) is clinically characterized by the sudden onset of extreme neuropathic pain in the upper limbs, followed by weakness and atrophy of the affected muscles and occasional sensory deficits, with slow recovery over months to years.[1] Neuralgic amyotrophy has an idiopathic form (INA, also called Parsonage-Turner syndrome) and an autosomal dominant hereditary form (HNA). Compared with INA, HNA is much rarer.[2,3] Single HNA episodes strongly resemble INA. The striking similarities include pain, predilection for the arm plexus, and provocation by the same triggers.[4] Distinguishing features include family history, earlier age at onset, a higher rate of recurrence, and the presence of dysmorphic features in HNA, which are noteworthy in our case.

The European CMT Consortium developed the first diagnostic guidelines for HNA.[5] Subsequently, Alfen et al.[6] supplemented the characteristics of HNA. They proposed core features of HNA, which are as follows: (1) acute, unilateral, or bilateral brachial plexopathy; (2) severe pain precedes onset of weakness by days to few weeks; (3) predominantly motor deficits; (4) number of episodes variable (1–20); and (5) precipitating factors: infections, immunizations, surgery, pregnancy, parturition, unusually strenuous exercise of the affected limb, and exposure to cold. In our study, the patient suffered from attacks during pregnancy and after delivery. The onset of HNA usually occurs in the second or third decade of life, though earlier and later onset is possible. HNA can run 2 distinct courses: a relapsing/remitting course with symptom-free intervals or incomplete recovery, characterized by persistent neurologic deficits after repeated attacks in the same limb.[6,7]

Several authors have also noted minor dysmorphic features associated with HNA. These include a long, narrow face, small mouth, hypotelorism (close-set eyes), shortened palpebral fissures, epicanthal folds, cleft palate, minor syndactyly, circular skin creases, long nasal bridge, and short stature.[8,9] Both our patient and her mother have mild dysmorphic features, such as hypotelorism, which can help differentiate HNA from INA.[5]

Regarding genetics, HNA (Online Mendelian Inheritance in Man catalog, OMIM 162100) is an autosomal dominant disorder associated with pathogenic variations in the *SEPT9* gene on chromosome *17q25.3*.[10, 11] To date, 3 point variations (c.-131G > C, c.262C > T, and c.278C > T) and a genetic founder haplotype have been identified in HNA pedigrees supporting a critical role for the *SEPT9* gene.[8,12,13] In general, HNA is genetically heterogeneous and has been linked to a variation or duplication in the *SEPT9* gene in only 55% of affected families.[14] One or more unknown genes may also be associated with HNA.[3]

So far, sequence analysis of *SEPT9* in larger cohorts of HNA families has not identified any additional variations beyond those previously reported.[11,14] In this study, our patient had an unusual heterozygous variation with typical HNA symptoms, NM_001113491.1p.R106W (c.316C > T), located on exon 3 of the *SEPT9* gene. Genetic analyses suggested a heterozygous variation in the *SEPT9* gene in 3 generations, the patient, her mother, and her son.

Currently, there is no standardized approach for treatment. Some case series suggest that early corticosteroid therapy or i.v. immunoglobulin may benefit patients in the acute phase of NA.[15] This case emphasizes the importance of early diagnosis and avoidance of triggers. HNA should be highly suspected when a patient presents with severe pain followed by weakness and atrophy of the upper extremities. Although we found a gene locus that might be responsible for HNA, the significance of this finding should be verified in subsequent studies.


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## Appendix *(continued)*

| Name | Location | Contribution |
|---|---|---|
| **Dan-Dan Xie, MD** | Department of Neurology, Cheng Du Second People's Hospital, Chengdu, China | Analysis or interpretation of data |
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