



EMG CASE No. 59, January 2003

Presenting Symptom(s): Swelling of the left knee for 3 months

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Appropriate Audience: Residents and practicing physicians

Learning Objectives: After completing this educational activity, participants will be able 1) Formulate a relevant list of differential diagnoses for childhood sensory polyneuropathies, 2) Recall and interpret clinical features and electrodiagnostic data consistent with Hereditary Sensory Neuropathies, and 3) Understand the genetic basis of HSAN IV and the social and developmental implications for children with this disorder.

This case is no longer available for CME credit.

History

A 13-year-old African American boy was admitted to the hospital for swelling of the left knee. This started 3 months earlier after having jumped from the second story of a building. There was a significant delay in seeking medical attention.

He had been in foster care for the last 11 years for reported neglect, physical and sexual abuse on several occasions. The child had a longstanding history of behavioral problems and self-mutilation. His medical history consisted of numerous injuries including electrical burns and scalds on the hands, face, torso, and lower extremities, some of which required skin grafting. Around the age of 3 years, he developed ataxia and an occipital headache. An MRI revealed Arnold-Chiari Type I malformation. He was treated with a suboccipital craniectomy and C1 laminectomy.

- *Prior to continuing, please develop a differential diagnosis and list each possible diagnosis in order of likelihood.*
- *Is there any additional information regarding the clinical history that might be helpful in clarifying your differential list or changing its order of priority?*

Commentary I

The differential diagnosis is quite broad at this stage and includes; syringomyelia, Friedreich's Ataxia, spinocerebellar degeneration, ataxia-telangiectasia, gluten enteropathy (nontropical sprue neuropathy), nutritional (vitamins E and B6 deficiency), abetalipoproteinemia, idiopathic sensory neuropathy, autoimmune disorders such as; systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome, infectious (including HIV), Hereditary Sensory Autonomic Neuropathies (HSAN) Type I-II-III-IV-V, toxic/heavy metal exposure, child abuse, and neglect.

A history of arthritis, skin rashes, recurrent fever, constipation, cold intolerance and failure to thrive should be elicited. Past hospitalizations and HIV status should be ascertained. A detailed dietary history should be obtained. It is important to determine whether the child has any motor symptoms, such as focal weakness or fatigue. Autonomic symptoms should also be inquired about. These include the excessive or diminished sweating, pattern of bowel habits, and symptoms suggestive of postural hypotension. Developmental delays and



school performance should be documented to determine whether cognitive development is appropriate for the chronological age. A family history is often helpful in determining the mode of inheritance of monogenic disorders.

History, continued

On detailed questioning the child denied a history of recurrent joint pain, swelling, or skin rash. He denied constipation, change in the stool color, and cold intolerance. His voice was not hoarse. He had no history of bowel or bladder incontinence. He admitted that he felt dizzy upon standing up at times. He also stated that he sweats very little, even when he engaged in vigorous exercise. He denied mouth and eye dryness as well as fatigue, frequent falls, and clumsiness. The patient has consanguineous parents and 3 siblings, none of them with similar complaints. He has had problems in school. Having repeated the fourth grade, he now attends a school for children with learning disabilities. A dietary history indicated a balanced nutritional intake, with no exposure to lead or other heavy metals.

- *If necessary, revise your differential diagnosis based on the additional clinical history.*
- *On which details of the physical examination should you focus at this point?*

Commentary II

Autoimmune diseases such as juvenile rheumatoid arthritis, SLE, and Sjogren's syndrome are less likely, given the negative history of skin rash, dryness of the eyes and mouth, arthralgia, and arthritis. A review of his past medical records did not show a history of recurrent opportunistic infections or HIV positive serology.

Motor examination should include careful manual muscle testing in all four extremities which will help to exclude focal mononeuropathies, as may be seen in lead poisoning. Sensory examination should include evaluation of pinprick, light touch, and proprioception. It is important to determine the extent of sensory neuropathy and involvement of dorsal column fibers versus spinothalamic involvement.

Given the past history of Arnold-Chiari type I malformation, syringomyelia is a possibility. Both sensory and motor symptoms, which are restricted to the involved segments, correlate with the location and extent of the syringomyelia. Given the child's low socioeconomic status, exposure to heavy metals including lead may account for a progressive sensory motor neuropathy. Failure to thrive, mental retardation, anemia, abdominal pain and focal mononeuropathies often occur with lead poisoning. Other considerations include nutritional deficiencies such as hypovitaminosis of vitamin E or B6.

It is also possible that the child's problems may be attributable to psychiatric disturbances secondary to a prolonged history of physical and sexual abuse. However, this should be a diagnosis of exclusion, after all organic disorders have been ruled out. Given the fact that the child has consanguineous parents, an inherited/genetic disorder, especially autosomal recessive disorders, may be more likely.

Physical Examination

Physical examination showed a lean 13-year-old African American boy with several old scars over the hands, face, torso, and lower extremities. The child appeared drowsy, and was



otherwise comfortable and cooperative. His speech was appropriate and intelligible. His cranial nerve examination was normal. Musculoskeletal examination revealed effusion on the left knee without erythema or warmth to touch. No pain was elicited during range of motion on the left knee. However, there was a 10-degree extension lag and 110 degrees of flexion. Otherwise, full range of motion was noted in all 4 extremities. Muscle strength was 5/5 in all 4 extremities proximally and distally. Reflexes were 1+ throughout. Babinski sign was absent bilaterally, and there was no clonus. Romberg test was negative. Light touch sensation and proprioception were intact. He stated that he did not perceive pinprick as a sharp stimulus, particularly over the distal lower extremities. Skin temperature over the dorsum of both feet was 280 deg (normal 320 deg). His skin was dry, especially in the extremities, and nails were brittle.

- *At this point, review your differential diagnosis and revise as appropriate.*
- *Are there additional observations on physical examination that might be helpful in narrowing your differential list?*

Commentary III

In the light of intact proprioception, negative Romberg test, and the absence of frequent falls, generalized clumsiness, and ataxia the following diagnoses can be ruled out: Friedreich's Ataxia, spinocerebellar degeneration, Ataxia-Telangiectasia, abetalipoproteinemia, and gluten enteropathy (nontropical sprue neuropathy), vitamin E and vitamin B6 deficiency. Syringomyelia is less likely, since there was no band type sensory loss or motor weakness.

Based on the available history and physical findings, it appears that the child has impairment of pain and temperature sensation. The diagnostic consideration would be Hereditary Sensory Autonomic Neuropathy. Pressure over the nail beds is a useful way of determining pain sensitivity. The appearance of the tongue can help distinguish between HSAN III and HSAN IV. In HSAN III, patients have a smooth tongue whereas in HSAN IV, the fungiform papillae are visible. According to the mother and foster caregivers, the child had an elevated pain threshold, which was noticed when the child was 1 year old.

Physical Examination, continued

Pressure over the nail beds in all four limbs was not perceived painful by him. The fungiform papillae were clearly visible on the tongue. Hyperkeratosis was noted on both palmar and plantar surfaces.

- *If necessary, revise your differential diagnosis based on the additional physical findings.*
- *Design your approach to the electrophysiologic examination based on the existing data.*

Commentary IV

The workup of this patient will help to rule out all reversible and treatable causes that may contribute to a syndrome of peripheral sensory neuropathy with loss of nociception. Therefore, routine complete blood count, chemistries, vitamin levels, TSH, and lead level were obtained. These studies were all negative, making a hereditary/congenital disorder more likely to be the cause of his symptoms. An MRI of the brain showed no abnormalities



in the brain parenchyma and ventricular system. A pseudomeningocele formation was present in the midline of the posterior fossa, due to prior surgical procedure.

Physical exam indicates that the child has a syndrome involving generalized loss of nociception and anhidrosis. This presentation is most consistent with HSAN. There are 5 subtypes of HSAN, the clinical features of which are described in Table I.

HSAN	Age of Onset	Clinical features	Genetics
I	Early childhood-3 rd decade	Leg pain, foot ulcers, pes cavus finally leading to peroneal atrophy and distal autoamputation	Chr 9q22 locus Mainly AD, some AR Mutations in the serine palmitoyl transferase gene
II	Early childhood	Loss of pain, temperature, tactile sensation with mutilation of fingers and toes	AR and AD
III (Riley-Day syndrome)	Early childhood	Absent reflexes, orthostatic hypotension, GI/bladder dysmotility, anhidrosis, smooth tongue, short stature, kyphoscoliosis	9q31 locus AR found in Ashkenazi Jews Mutations in I kappa B kinase complex associated gene
IV	Early childhood	Profound decrease in pain sensitivity, anhidrosis, episodic fever, ability to produce tears present, fungiform papillae present on tongue	AR Mutations in the NTRK1 gene
V	Early childhood	Decreased pain and temperature sensation only with normal nerve conduction velocity	AR

Given the information to date, the child most likely has either HSAN IV or V. The electrodiagnostic testing will be helpful at this stage. The presence of normal nerve conduction velocity will suggest HSAN V whereas delayed NCV will be in favor of HSAN IV. HSAN III is unlikely given the presence of fungiform papillae and ability to produce tears in the child. A sweat test with iodine/starch is indicated in order to confirm anhidrosis. Intradermal histamine challenge may show either impaired wheal and flare reaction or the absence of pain and pruritis following injection.

Electrophysiologic Data

SENSORY NERVE CONDUCTION STUDIES							
NERVE	SIDE	STIM SITE	RECORD	cm	AMPL	LAT	CV
Sural	Left	ankle			Absent SNAP		



Sural	Right	ankle			Absent SNAP		
Ulnar	Right	wrist			13mV	3.5msec	

MOTOR NERVE CONDUCTION STUDIES							
NERVE	SIDE	STIM SITE	RECORD	cm	AMPL	LAT	CV
Tibial	Left	ankle			4.3 mV	6 msec	-
		knee			4.1 mV	15 msec	39m/s
Tibial	Right	ankle			5.2 mV	6 msec	-
		knee			4.7 mV	16.2 msec	37 m/s
Ulnar	Right	wrist			8.7 mV	3.6 msec	-
		elbow			7.6 mV	8.6 msec	49 m/s

NEEDLE ELECTROMYOGRAPHY									
INSERTional activity: N, sust, unsust									
FIB: 0, 1+, 2+, 3+, 4+									
OTHer: 0 or fascic, myotonia, myokymia									
EFFort: N, decr									
RECRuitment: N, inc or dec 1+, 2+, 3+, 4+									
AMPliitude: N, inc or dec 1+, 2+, 3+, 4+									
DURation: N, inc or dec 1+, 2+, 3+, 4+									
POLyphasia: N, inc or dec 1+, 2+, 3+, 4+									
R/L	MUSCLE	INSER	FIB	OTH	EFF	REC	AMP	DUR	POL
R	APB	NL	0	0	0		NL	NL	none
R	ADM	NL	0	0	0		NL	NL	none
R	EHL	NL	0	0	0		NL	NL	none



R	Tib. Ant.	NL	0	0	0		NL	NL	none
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- *On the basis of both the clinical and electrophysiologic evaluations, formulate your diagnostic impression. List the most likely diagnosis first and follow in order with the other possibilities that are not excluded by the data. Eliminate those diagnoses not supported by the data.*
- *Are there additional electrophysiologic data that you feel would further delineate the diagnosis? (Remember, collecting data that are not needed for the diagnosis is costly and uncomfortable for the patient.)*

Electrophysiologic Data, continued

- *Make the final revisions of your diagnostic impression(s).*

Diagnostic Impression

Nerve conduction studies showed absent sural sensory nerve potentials bilaterally, with borderline right ulnar sensory nerve evoked amplitude. Borderline low tibial compound motor action potential amplitude and delay in distal latencies bilaterally are also noted. Motor nerve conduction velocities were all borderline slow. Electromyography was essentially normal.

The electrodiagnostic impression: Predominantly sensory axonal polyneuropathy with some evidence of motor involvement, axonal and demyelinating in nature.

- *What other diagnostic procedures (laboratory tests, etc.), if any, are needed?*
- *What treatment would you recommend?*

Commentary V

Hereditary Sensory Autonomic Neuropathy IV (HSAN IV) is also called Congenital Insensitivity to Pain and Anhidrosis (CIPA). It is an extremely rare disorder. Rosenberg et al. reported the largest series of 32 patients in 1994. It is an autosomal recessive disorder characterized with insensitivity to painful stimuli and absence of sweating. Anhidrosis contributes to defective thermoregulation, often causing episodic fevers in patients with CIPA. However, this feature was absent in our patient. The absence of pain and temperature sensation allows the individuals to inflict injury upon themselves, without resulting pain. Therefore they never develop aversion to recurrent external trauma and frequent burns/scalds, as seen in our patient. His skin biopsy demonstrated the absence of cutaneous nociceptive afferents and sympathetic efferents to eccrine sweat glands suggesting autonomic fiber loss. There were no "C" fibers seen innervating the follicles or sweat glands. Under E-microscope the sural nerve biopsy revealed subtle mixed axonal degenerative neuropathy with fiber loss, sprouting, collagen pockets, and a demyelinating neuropathy. Additional electrodiagnostic testing of sympathetic skin response (SSR) would have been helpful to evaluate sympathetic fiber function. We could not test SSR on our patient since he was discharged from the hospital. Mental retardation is another feature of the CIPA syndrome, with a small number of patients being microcephalic. The patient has mild mental retardation with an IQ level 50-55 by using Wechsler Intelligence Scale for Children-Third Edition. The presentation of a child with a history of multiple burns, traumatic injuries and self-mutilation should alert one to the possibility of physical abuse. However, the diagnosis of an HSAN IV (CIPA) should also be explored, given an adequate history and physical examination.



Management involves conservative measures such as minimizing injury from blunt trauma, and supervision during bathing to avoid scalds from excessively hot water. Careful foot and hand monitoring to avoid trauma is essential. Visceral pain perception is also impaired. One should be mindful of a possible intraabdominal process, which would not be easily diagnosed in patients with CIPA. The diagnosis must also be shared with others because these children can be separated from their parents with the suspicion of child abuse and neglect, thus compounding the physical and emotional impairments that they suffer. Recent advances in positional cloning have resulted in the identification of TRKA (NTRK1) gene mutations, which are causative for CIPA. This gene is located on chromosome 1. The TRKA gene encodes a tyrosine kinase associated with the receptor for nerve growth factor (NGF). Upon activation of the NGF receptor, the TRKA protein is autophosphorylated, triggering a downstream cell-signaling cascade. Thus, a disruption of the normal function of TRKA results in the death of NGF dependent neurons. Patient's skin biopsy was forwarded to a cytogenetic laboratory to determine the mutations on tyrosine kinase gene.

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