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Thevenard's Disease - a hereditary sensory and autonomic neuropathy type I

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VERSITA

Abstract

Thevenard's Disease is a rare, hereditary sensory and autonomic neuropathy which leads to hyperkeratotyc and ulcerative lesions of the feet. We present two patients, a father and son, 39 and 18 years of age, in whom the disease first manifested in adolescence. Plantar hyperkeratosis and trophic, painless ulcerations occurred first, with subsequent feet deformities. Neurological and radiological findings pointed to chronic demyelination, polyneuropathy with damage to sensory fibers. Differential diagnosis and treatment options are discussed.

Hereditary sensory and autonomic neuropathy type I (HSAN I), i.e. Thevenard's disease, is a dominant hereditary sensorimotor, axonal neuropathy which usually develops in the second (rarely later) decade of life, without autonomic disorder. It may be classified both as a genetic and a clinical heterogeneous disease with sensory dysfunction. Type I HSAN was firstly described by Nelaton (1) in 1852, and by Thevenard (2) in "L'acropathie ulcero-mutilante familiale" that is familial ulcerative mutilating acropathy, a name used up to now. We present two patients (a father, and son) with HSAN I.

Case 1

A 39-year-old man was admitted due to a painless ulceration on the right plantar foot (Figure 1). The onset of the disease occurred at the age of 17, with hyperkeratosis on the right plantar foot at the level of metatarsophalengeal (MTP) joints. Due to hammer-like toe deformities and aggravated walking ability when the patient was 18, amputation of the 2nd and 3rd toes of the right foot, including pertaining methatharsal bones, was performed, while at the age of 20, the great toe distal phalanges were amputated. The following year distal phalanges of the 1st, and 2nd toe of the left foot were amputated. The disease progressed with a reduced pain and loss of temperature sensation, foot edema, formation of hallux on both sides, and a painless ulceration on the right foot sole. On two occasions, when the patient was 33 and 34-years old, a reconstructive surgery using a rotation flap was attempted to

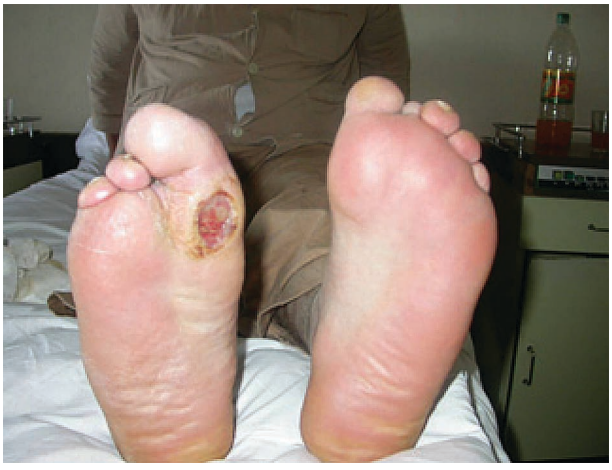

Figure 1. Right plantar foot ulceration

manage the ulcer, but without success. Routine laboratory tests showed that all the examined parameters were within the range of normal, including glucose, ESR 14 mm/h. Serology for lues was negative. Radiography of the feet revealed visible amputation of the middle and distal phalanges of the 2nd toe and distal phalange of the great toe of the left foot; amputation of the 2nd and 3rd toes of the right foot including a part of the pertaining methatharsal bones (Figure 2). Doppler ultrasonography of the lower extremities showed a normal finding for the arteries and deep veins, while valvular stenosis of the left greater saphenous vein was observed. The neurophysiologic examination (EMNG) suggested a chronic, axonal, sensomotoric, medium severe polyneuropathy.

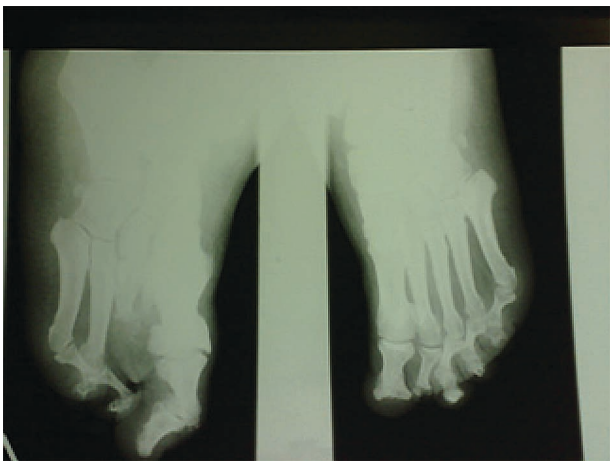

Figure 2. Radiography of the feet: amputation of the middle and distal phalanges of the 2nd toe and distal phalange of the great toe of the left foot. Right: amputation of the 2nd and 3rd toes of the right foot, including and pertaining phalanges of both toes

Case 2

The son of the above patient, aged 18, was also admitted due to plantar ulcer. The onset of the disease occurred when the patient was 17, with hyperkeratosis on the left foot sole at the level of MTP I joint, where a deep painless ulceration developed (Figure 3). At the age of 19, resection of the 2nd methatharsal bone bulb releasing the

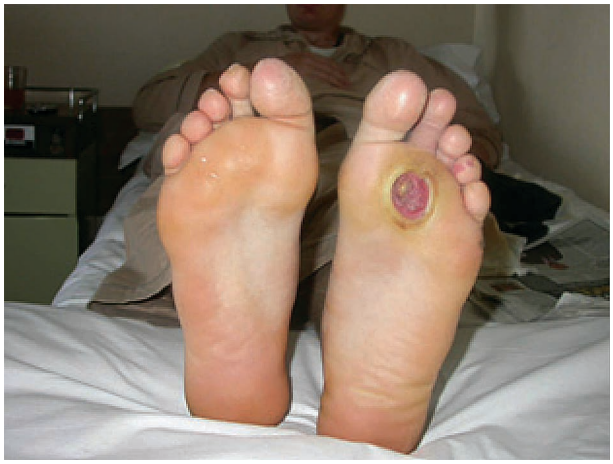

Figure 3. Left foot sole deep ulceration

tendon due to the flexion finger contour was done, as well as ulcer reconstruction, but this was ineffective and chronic ulcer developed again.

Laboratory findings showed no pathology, ESR 16 mm/h, VDRL and TPHA were negative. Radiography of the feet revealed normal bone structures. Doppler ultrasonography of the lower extremities showed normal findings except for a decreased blood flow through the arteries of both feet soles. EMNG examination revealed absence of sensory action in both tibial, median, and ulnar nerves to the right.

Discussion

Hypersensitive sensory and autonomic neuropathies (HSANs) or hypersensitive sensory neuropathies (HSNs) are genetically defined neuropathies which are classified into five types (HSAN I-V) (3). Type I is the most common form where sensory neurons and their small fibers are primarily affected (4). The disease is caused by the mutation of the gene SPTLC 1, which codes a long strain of a basic subunit 1 serine palmitoyl transferase (SPTLC 1) at the chromosome 9q 22.1 - q 22.3 (5). Patients show rise of *de novo* synthesis of glycosylceramidase in lymphoblasts that results in abnormal neuronal apoptosis (6-8). Some more recent studies suggest that this mechanism is not present in every patient, as well

as that the development of the disease is affected by gene expression, so that the clinical presentation may be less severe and the disease may occur later in life (9). The disease usually manifests in the second or third decade of life. Sensory alterations cause consequential hypekeratosis, mutilating acropathy, and painless plantar ulcerations. Except for the loss of pain sensation, temperature sensation is also damaged. Achilles reflex is weak or absent. Motor dysfunction of various degrees may be present (10). The anal sphincter function and sexual ability are preserved. The disease progresses with frequent episodes of osteomyelitis, sequestrations, acroosteolysis leading to sole mutilation (10).

By phenotype, HSAN I is similar to Charcot-Marie-Tooth (CMT) 2B, a disease mediated by RAB 7 gene mutation, and with more pronounced motoric disorders (11). Recently a new form has been described, namely the so-called HSAN I B which, besides neuropathy, includes a frequent occurrence of cough and gastroesophageal reflux (12).

HSAN II is an autosomal, recessive, hereditary disease. It starts in early childhood, affects extremities, and it is characterised by loos of sensory functions, ulcerations, spontaneous amputation, atrophy, hyporeflexia (11,13). It is a consequence of HSN2 gene mutation at the chromosome 12q 13.33 (14,15).

HSAN III (familial dysautonomia, Riley-Day syndrome) is an autosomal recessive hereditary disease frequently associated with the Eastern Europe Ashkenazi Jews. It presents at birth with insensitivity to pain and temperature, cardiovascular damage, pneumonia, vomiting, gastrointestinal truct dysfunction with frequent episodes of hypertension. Diagnostic criteria include absence of fungiform papillae on the tip of the tongue and pathologic histamine test. The disease is a consequence of IKBKAP gene mutation at the chromosome 9q 31 (16,17).

HSAN IV is also an autosomal recessive hereditary disease associated with NTRK1 gene mutation at the chromosome 1q 21 – q 22. The affected patients have an innate insensitivity to pain, anhidrosis, mental retardation, frequent febrile episodes (11,18).

In these patients, eccrine sweat glands are not innervated (19). Early death happens in approximately 20% of children.

HSAN V (20) is similar to the type IV, the major difference being in less pronounced anhidrosis and absence of mental retardation (11). A possible pathogenic mechanism is a mutation of the gene that codes the beta nerve growth factor (BNGF) at the chromosome 1p 11.2 - p 13.2. We also took into consideration a special disease (maybe a new type of HSAN VI) already presented in elderly Japanese siblings (in three of six family members), including anosmia, anhidrosis and loss of sensoric functions, orthostatic hypotension, but without ulcerations (21).

In differential diagnosis, leprosy, syringomyelia, hereditary motoric and sensory neuropathy (HMSN) must be considered, which are predominantly motoric neuropathies of slow and rapid progression, as weel as Fabry's Disease, and Lesch Nyhan's Syndrome, porphyria (primarily motoric neuropathy) (22). Also, acquired ulceromutilational acropathy may be considered when caused by alcoholism, cigarette smoking and it usually develops later in life. Luetic neuropathy (dorsalis tebis), diabetic polyneuropathy and acropathy were also excluded.

We presented two patients with a rare disease, in whom the diagnosis was made based on the anamnesis, clinical presentation, slow progression of the disease and neurophysiologic findings. The therapy is symptomatic. Attention should be paid to the care of the feet and wearing comfortable, anatomic footwear. Also, corrective surgery is advised in advanced cases.

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Thevenardova bolest - nasledna, senzorna i autonomna neuropatija tipa I

Sažetak

Uvod: Nasledna neuropatija tip I, Thevenardova bolest predstavlja dominantno naslednu aksonsku (senzornu i autonomnu) neuropatiju koja se najčešće javlja u drugoj deceniji života. Na osnovu etiopatogenetskih i kliničkih karakteristika, ubraja se u heterogenu grupu bolesti koju karakterišu senzorni (disfunkcionalni) poremećaji. Nelaton je 1850. godine prvi opisao ovu bolest. Thevenard je bolest okarakterisao kao hereditarnu ulceromutilantnu akropatiju, te se ona i danas opisuje pod tim nazivom.

Prikaz slučaja: U radu su prikazana dva slučaja porodičnog javljanja ovog oboljenja. Kod oca, tridesetdevetogodišnjeg muškarca, bolest se javila

u sedamnaestoj godini života u vidu hiperkeratoze na tabanu levog stopala i to u nivou metatarzo-falangealnih zglobova. Već u osamnaestoj godini amputiran mu je drugi i treći prst na desnom stopalu uključujući i odgovarajuće metatarzalne kosti. Bolest je poprimila progresivan tok, pa je u dvadesetoj godini amputirana distalna falanga na palcu desnog stopala. Navedene promene su oteževale još više hod, prsti na stopalu su poprimali izgled čekića, ulceracija na tabanu se povećavala kao i otok čitavog stopala. Senzorne funkcije u smislu percepcije bola i temperature su se smanjivale do potpunog gubitka. U dva navrata, tokom četvrte decenije života, na pacijentu je izvršena rekonstruktivna hirurška intervencija sa rotacionim režnjem radi sanacije ulkusa na tabanu desnog stopala. Na prijemu, svi laboratorijski nalazi bili su u granicama normale, uključujući i serološke reakcije na sifilis. Radiografskim snimkom utvrđeno je: odsustvo srednje i distalne falange drugog prsta i distalne falange palca na levom stopalu; nedostatak drugog i trećeg prsta desnog stopala uključujući i deo metatarzalnih kostiju. Ultrasonografski je isključeno postojanje insuficijencije arterijskih krvnih sudova kao i dubokih vena na donjim ekstremitetima. Elektromioneurografija je ukazala na postojanje hronične, aksonske senzorno-motorne polineuropatije srednjeg stepena težine.

U drugom prikazanom slučaju, kod sina prethodno opisanog pacijenta, bolest je počela u sedamnaestoj godini života. Kao osamnaestogodišnji mladić, primljen je prvi put na bolničko lečenje da bi se sanirala ulceracija koja se razvila iz hiperkeratotičnog zadebljanja na levom stopalu. Već u devetnaestoj godini kod njega je urađena resekcija na nivou druge metatarzalne kosti sa oslobađanjem tetive (fleksiona kontraktura prsta), kao i rekonstrukcija postojeće ulceracije. Sprovedena terapija nije urodila plodom, s obzirom da se u daljem periodu ponovo razvila hronična ulceracija na istom mestu. Objektivnim pregledom, uočena je duboka bezbolna ulceracija na nivou baze prvog metatarzo-falangealnog zgloba na levom stopalu. Svi laboratorijski nalazi su bili u granicama normale. Radiografija stopala je otkrila očuvanost strukture koštanog tkiva. Ultrazvučni pregled je ukazivao na usporenu arterijsku cirkulaciju na nivou oba stopala. Elektromioneurografskim pregledom uočeno je senzorno oštećenje na nivou: n. *tibialis* obostrano, n. *medianus* desno i n. *ulnaris* desno.

Diskusija: Pod hipersenzitivnim senzornim i autonomnim neuropatijama podrazumeva se heterogena grupa naslednih neuropatija koje su iz didaktičkih razloga klasifikovane u pet fenotipova. Prvi tip je najčešći i u njemu su primarno izmenjeni senzorni neuroni. Do oštećenja senzornih neurona dolazi usled mutacije gena SPTLC 1 (eng. *serine palmitoyl transferase-long chain*) koji je smešten na 9q 22.1 - q 22.3 i koji je odgovoran za sintezu serin-palmitoil transferaze. Posledično dolazi do *de novo* sinteze glikozilceramida i do proliferacije limfoblasta koji su odgovorni za apoptozu neurona. Novija istraživanja ukazuju da je stepen ekspresivnosti genetskog poremećaja odgovoran za čitav dijapazon različitih kliničkih manifestacija. Senzorni poremećaji rezultuju hiperkeratozom, mutilacionom akropatijom i bezbolnim plantarnim ulceracijama. Dolazi do oštećenja osećaja toplote, do smanjenja ili potpunog odsustva Ahilovih refleksa, kao i do disfunkcijskih motornih poremećaja različitog stepena. Funkcija sfinktera i seksualna aktivnost ostaju očuvani. Bolest pokazuje progredijentan tok pa se često razvijaju osteomijelitis sa sekvestracijom koštanog tkiva i akroosteolizom, koja vodi ka teškim mutilacijama stopala.

Diferencijalna dijagnoza: U diferencijalnoj dijagnozi treba uzeti u obzir *Charcot-Marie-Tooth* bolest, do koje dolazi usled mutacije na RAB 7 genu i kod koje su motorni poremećaji značajno jače izraženi. U odnosu na ostala četiri fenotipa (II-V), diferencijalno-dijagnostički drugi tip koji se nasleđuje autozomno recesivno (mutacija na

HSN2genu, smeštenom na hromozomu 12q 13.33) karakterišu poremećaji koji se javljaju već u ranom detinjstvu a mogu da zahvataju bilo koji ekstremitet. U trećem tipu (autozomno recesivni *Riley-Day* sindrom) promene su prisutne već na rođenju. Pored oslabljenog osećaja bola i temperature, postoje poremećaji kardiovaskularnog i gastrointestinalnog sistema sa epizodama hipertenzije, povraćanja, čestih pneumonija. Patognomonično je odsustvo filiformnih papila na jeziku i histaminski test. Za nastale promene odgovorna je mutacija na IKBKAP genu smeštenom na hromozomu 9q31. Četvrti fenotipski tip (autozomno recesivna nasledna mutacija na genu NRTK 1, smeštenom na hromozomu 1q 21 – q 22) karakteriše i prisustvo anhidroze, mentalna retardacija i česte febrilne epizode. Usled odsustva inervacije ekrinih znojnih žlezda, kod 20% obolele dece dolazi do smrtnog ishoda. Peti fenotipski tip (verovatno mutacija gena koji kodira sintezu neurogenog faktora rasta ß-smeštenog na hromozomu 1p 11.2 - p 13.2) klinički se razlikuje od prethodnog po odsustvu mentalne retardacije i manje izraženoj anhidrozi. Takođe, diferencijalno-dijagnostički, treba pomišljati i na bolest (šesti fenotip?) koja je opisana kod Japanaca, i to kod tri od šest članova jedne porodice, u vidu prisustva funkcionalnih senzornih poremećaja, anosmije, anhidroze, ortostatske hipotenzije - ali bez ulceracija. Diferencijalno-dijagnostički treba isključiti i lepru, siringomijeliju, druge nasledne senzorne neuropatije, ali i često prisutne faktore rizika za stečene mutilantne akropatije kao što su alkoholizam (promene se javljaju kasnije u životu), lues (*tabes dorsalis*) i dijabetesna polineuropatija i akropatija.

Zaključak: Prikazom obolelih stiče se uvid u jednu retku naslednu neurokutanu genodermatozu, čija diferencijalna dijagnoza obuhvata širok spektar senzornih, motornih i disfunkcijskih poremećaja neurovegetativnog sistema. Za sada, u terapiji na raspolaganju stoje samo higijensko-dijetetske mere (anatomski prilagođena komforna obuća), kao i korektivne hirurške mere u uznapredovalim slučajevima.