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Mini review article

HEREDITARY NEUROPATHIES CAUSED BY MUTATIONS IN THE GENE ENCODING PERIPHERAL MYELIN PROTEIN 22

HEREDITARNE NEUROPATIJE UZROKOVANE MUTACIJAMA U GENU KOJI KODIRA PERIFERNI MIJELINSKI PROTEIN 22

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Abstract

Mutations in the gene encoding peripheral myelin protein 22 (*PMP22*) can manifest as Charcot-Marie-Tooth neuropathy 1A (CMT1A), in case of duplication, or hereditary neuropathy with liability to pressure palsies (HNPP), in case of deletion. In rare cases, point mutations in the *PMP22* gene can occur, which can cause CMT1E and Déjerine-Sottas syndrome (DSS). Both CMT1A and HNPP represent the most common inherited neuropathies. The age of onset of CMT1A is manly in the first two decades, and the clinical features typically include atrophy and weakness of distal muscles with or without loss of sensation, foot deformities, such as *pes cavus* and "hammer" toe and reduced or absent muscle reflexes. Hereditary neuropathy with liability to pressure palsies most often begins in the adolescence and typically presents in the form of transient and recurrent focal mononeuropathies with motor and sensory symptoms and signs in the anatomical distribution of the affected nerve. Nerve conduction studies (NCS) show a uniform decrease in nerve conduction in CMT1A. These findings in HNPP show a diffuse, sensorimotor, demyelinating polyneuropathy with conduction blocks and temporal dispersion at the sites of compression (medial nerve in the carpal tunnel, ulnar nerve at the elbow and peroneal nerve at the fibular neck). Therapy of all hereditary neuropathies, including CMT1A, is limited to symptomatic therapy, thus, physical therapy, corrective surgical interventions, orthoses, and neuropathic pain therapy can be useful. The current approach to managing HNPP revolves around preventing damage to peripheral nerves caused by compression or stretching during prolonged activities and postures. Protective pads at the elbows or knees can be useful to prevent compression and nerve injury, while corticosteroids and physical therapy are indicated in the acute phase of the disease. The development of disease modifying therapies in CMT1A and HNPP is still ongoing.

Keywords:
hereditary neuropathy, *PMP22*, Charcot-Marie-Tooth neuropathy 1A, hereditary neuropathy with liability to pressure palsies

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Sažetak

Mutacije nastale u genu koji kodira periferni mijelinski protein 22 (*PMP22*) mogu se ispoljiti kao Šarko-Mari-Tutova (*Charcot-Marie-Tooth*) neuropatija 1A (CMT1A), u slučaju duplikacije ili hereditarna neuropatija sa sklonošću ka kompresivnim paralizama (HNPP), u slučaju delecije ovog gena. U retkim slučajevima dolazi do tačkastih mutatija u *PMP22* genu, pri čemu mogu nastati CMT1E i Dežerin-Sotasov (*Déjerine-Sottas*) sindrom (DSS). Najčešće nasledne neuropatije su CMT1A i HNPP. Šarko-Mari-Tutova neuropatija 1A najčešće počinje u prve dve decenije života, a u kliničkoj slici su tipično prisutni izražena hipotrofija i slabost distalnih mišića, sa ili bez ispada u senzibilitetu, deformacije stopala, poput ekskaviranog stopala (*pes cavus*) i „čekićastog" palca i sniženi ili odsutni mišićni refleksi. Hereditarna neuropatija sa sklonošću ka kompresivnim paralizama najčešće počinje između 20. i 30. godine života i ispoljava se u vidu tranzijentnih i rekurentnih fokalnih mononeuropatija sa motornim i senzitivnim simptomima i znacima u anatomskoj distribuciji zahvaćenog nerva. Elektromioneurografskim ispitivanjem (EMNG) dobija se uniformno sniženje nervne provodljivosti kod CMT1A. Nalaz EMNG kod HNPP ukazuje na difuznu, senzorimotornu, demijelinizacionu polineuropatiju, uz kondukcione blokove i temporalnu disperziju na mestima kompresije (medijalnog nerva u predelu ručja, ulnarnog nerva u predelu lakta i peronealnog nerva u predelu glave fibule). Terapija svih hereditarnih neuropatija, pa i CMT1A, uglavnom se svodi na simptomatsku terapiju, te od koristi mogu biti fizikalna terapija, korektivne hirurške intervencije, ortoze, kao i terapija neuropatskog bola. Terapija HNPP se uglavnom svodi na prevenciju kompresije nerva određenim aktivnostima i položajima tela. Zaštita laktova i kolena jastučićima može biti korisna kako bi se sprečila kompresija i povreda nerava, dok su u akutnoj fazi bolesti indikovani kortikosteroidna i fizikalna terapija. Razvoj terapija koje bi promenile tok bolesti i dalje je u toku.

Ključne reči:
hereditarne neuropatije, *PMP22*, Šarko-Mari-Tutova neuropatija 1A, hereditarna neuropatija sa sklonošću ka kompresivnim paralizama

Introduction

Primary hereditary neuropathies are inherited neuropathies in which neuropathy is the main clinical manifestation of the disease. They can be classified in various ways, and one approach is based on the type of nerve fibers affected and the mode of manifestation (**figure 1**). This classification includes four groups: hereditary motor and sensory neuropathies (HMSN or Charcot-Marie-Tooth group of neuropathies - CMT), distal hereditary motor neuropathies (dHMN), hereditary sensory and autonomic neuropathies (HSAN), and hereditary focal, recurrent neuropathies (such as hereditary neuropathy with liability to pressure palsies - HNPP and hereditary neuralgic amyotrophy - HNA) (**figure 1**). Based on electrophysiological criteria, CMT can be further divided into: demyelinating (CMT1 and CMT4), axonal (CMT2), and intermediate CMT (CMTX1) (1).

Hereditary neuropathies can be caused by mutations in various genes. These genes encode proteins that play crucial roles in maintaining the structure and function of peripheral nerves, such as myelin proteins, ion channel proteins, or proteins involved in axonal transport. So far, more than 100 genes have been discovered that are associated with CMT (2). Mutations occurring in the gene that encodes the peripheral myelin protein 22 (*PMP22*), located within the large chromosomal segment 17p11.2, can manifest in multiple clinical forms. Duplication of the *PMP22* gene is expressed as Charcot-Marie-Tooth neuropathy 1A (CMT1A), while deletion of this gene causes HNPP (1). Rarely, CMT1A and HNPP can be caused by point mutations in the *PMP22* gene (1, 3).

Very rare diseases such as CMT1E and Déjerine-Sottas syndrome (DSS) can also be caused by mutations in the *PMP22* gene (they will not be further discussed in this mini-review). The first form represents a demyelinating

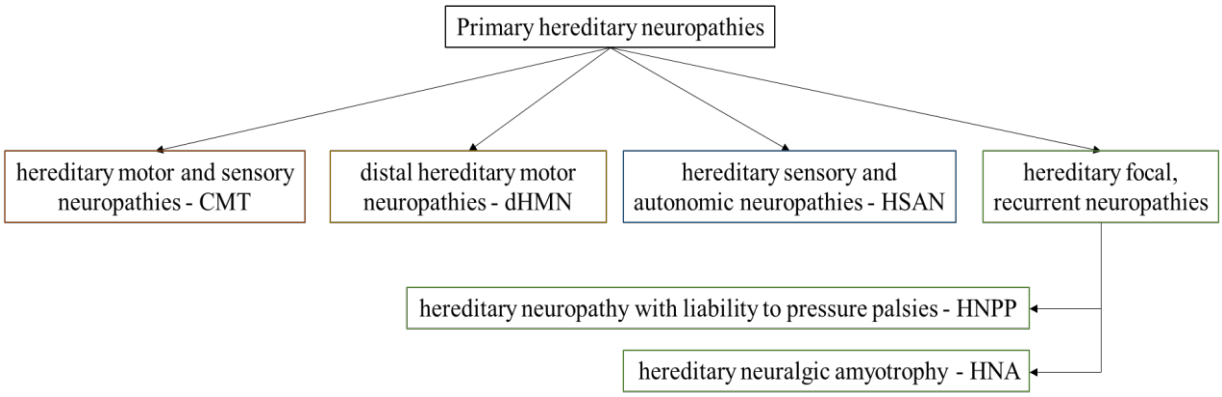

Figure 1. Classification of primary hereditary neuropathies based on the type of nerve fibers affected and the mode of manifestation

form of CMT due to point mutations in the *PMP22* gene and is histopathologically characterized by the presence of cellular aggregates of PMP22 protein. Second form, the DSS, is a demyelinating hereditary neuropathy that begins in the first two years of life. It is characterized by nerves with very thin myelin sheaths and consequently significantly reduced nerve conduction velocities (< 12 m/s) on nerve conduction studies (NCS), while nerve biopsies may reveal formations resembling onion bulbs. It can be caused by mutations in the *PMP22* or the *myelin protein zero* (*MPZ*) gene (4).

Epidemiology

The most common group of hereditary neuropathies and one of the most common neurogenetic disorders is CMT (5,6). The crude prevalence of CMT in Belgrade on December 31, 2007, was 9.7 per 100.000 for all CMT subtypes. This prevalence represents the lowest reported prevalence worldwide. The highest prevalence of CMT was described in Norway (82.3 per 100,000) (7), followed by Finland (34.6 per 100,000) (8).

Mutations in genes encoding the protein PMP22 (duplications and deletions), gap junction protein beta 1 (GJB1), myelin protein zero (MPZ), and mitofusin 2 (MFN2) are responsible for up to 90% of genetically confirmed CMT cases in Western countries (9). Epidemiological studies have shown that between 19.6% and 64.7% of patients with genetically confirmed CMT carry a duplication of the *PMP22* gene (7,10). This results in a calculated prevalence of CMT1A ranging from 1 per 3.800 to 1 per 12.500 (11).

The prevalence of HNPP is not well known (12). In Finland, a prevalence of 16 per 100,000 has been described (13). Foley et al. (10) described a prevalence of 7.3 per 100,000 in England. Finally, Ma et al. reported a prevalence of 6.08 per 100,000 in their recent meta-analysis (6). There is no available data on the prevalence of HNPP in Serbia.

Clinical manifestation

The clinical presentation of CMT1A can be highly variable, ranging from asymptomatic cases to severe forms of the disease. Nevertheless, the majority of CMT1A patients present with the "classic" CMT1 phenotype. Only a small number of patients exhibit a phenotype similar to DSS (14). By taking a thorough medical history in these patients, valuable information is often gathered regarding slower psychomotor development compared to their healthy peers, as well as difficulties with walking, running, and engaging in physical activities during their school years (14). The disease typically begins in the first two decades of life, although it can also manifest very early, between the ages of three and five (15). The clinical presentation usually includes pronounced atrophy and weakness of distal muscles, primarily affecting the muscles of the calves and feet, and later the muscles of the forearms and hands. The predominant weakness of the peroneal muscles leads to a "steppage gait" and "drop foot." Additionally, most patients also exhibit foot deformities such as *pes cavus* and "hammer" toe, giving the foot a characteristic appearance known as "Friedreich's foot." In later stages of the disease, the legs of CMT1A patients may exhibit an appearance resembling the "champagne bottle" or "inverted champagne bottle". Pronounced muscle atrophy in the hands typically occurs in severe forms of the disease and leads to hand deformities known as "claw hands." Muscle reflexes are reduced or absent, with Achilles tendon reflexes extinguishing first, followed by patellar reflexes. Axial and proximal muscles are usually spared, although in some patients, moderate proximal weakness and involvement of the phrenic nerve leading to respiratory insufficiency may occur (16). Cranial nerve involvement is rare in CMT1. The vestibulocochlear nerve is the most commonly affected cranial nerve and is associated with hearing loss, which may be present in approximately 5% of patients with CMT1A (17), as well as in some cases of point mutations in the *PMP22* gene (18,19).

Typically, HNPP manifests as transient and recurrent focal mononeuropathies with motor and sensory symptoms and signs in the anatomical distribution of the affected nerve (3,14,20). However, the disease can also present as mononeuritis multiplex (14). It typically starts between the ages of 20 and 30, although there have been reported cases with onset in the neonatal period and even as late as the 80th year of life (3,13,21). In the majority of cases (approximately 85%), the disease begins acutely and without pain (3,22). The most common sites of involvement are the median nerve in the carpal tunnel, the ulnar nerve at the elbow, the radial nerve in the upper arm, and the peroneal nerve at the knee (14). Isolated lesions of the brachial plexus can also occur (23). It is usually reported that the lesion of one or more nerves occurred following trivial nerve compression (such as sitting with legs crossed for a short period, sleeping on the arm, kneeling, leaning on elbows, and similar activities) (14). The signs of muscle weakness, atrophy, sensory deficits, and reduced muscle reflexes can be observed (3). Cranial nerves are rarely affected in HNPP (24). Transient paralysis of the facial nerve (25-27), trigeminal nerve (25,28), hypoglossal nerve (25,29) and recurrent laryngeal nerve have been described so far (30). Although not as common as in CMT1A, foot deformities such as *pes cavus* and "hammer" toe can also be observed in HNPP (3,14). Symptoms of acute mononeuropathy can last for weeks or months (14).

Nerve conduction studies

Motor conduction velocities in CMT1A are reduced and typically range around 25 m/s in the upper limbs (14,15), while distal motor latencies and F-wave latencies are prolonged. The electrodiagnostic findings indicate symmetric and uniform reduction in nerve conduction (15). CMT1A is characterized by a reduction in sensory and motor conduction velocities in most examined nerves, including those with normal clinical examination findings.

Although it is a demyelinating neuropathy, secondary axonal damage can occur, presenting as reduced compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) on NCS (31). The severity of CMT1A is not always correlated with nerve conduction velocities. On the other hand, the CMT1A severity directly correlates with reduced CMAP amplitudes and the absence of SNAP (32).

Despite the presence of focal neuropathy in the clinical presentation, NCS in patients with HNPP reveals a diffuse, sensorimotor, demyelinating polyneuropathy with conduction blocks and temporal dispersion at sites of compression (median nerve at the wrist, ulnar nerve at the elbow, and peroneal nerve at the fibular head) (3, 14). It has been shown that even in asymptomatic patients, some electrophysiological changes in the examined nerves can be seen (33).

Therapeutic approach

Symptomatic therapy

The treatment of all hereditary neuropathies, including CMT1A, primarily involves symptomatic therapy, as there is currently no disease-modifying therapy available. Physical activity is generwally advised. Various types of orthoses and specialized orthopedic shoes can be beneficial for maintaining joint stability in affected individuals. Corrective surgical interventions are mostly recommended for CMT1A patients with severe foot deformities (15). Patients should be advised to avoid toxic substances such as alcohol and certain medications, as they can further worsen the existing neuropathy. If a patient is diagnosed with neuropathic pain, standard treatment for neuropathic pain should be administered, which may include tricyclic antidepressants, pregabalin, gabapentin, and other appropriate treatments (14).

The symptomatic treatment of HNPP mainly focuses on preventing nerve compression. Activities and body positions that can cause nerve compression, such as sitting with legs crossed, sleeping on the arm, kneeling, leaning on elbows, and even rapid weight loss, should be avoided (3, 14, 34). Using pads to protect the elbows and knees can be beneficial in preventing nerve compression and injury (3). Currently, it is not known whether decompressive surgical intervention plays a significant role in the treatment of HNPP in patients with carpal tunnel syndrome and ulnar syndrome (35). In the acute phase of the disease, corticosteroid therapy and physical therapy are indicated (14). Heng et al. found that corticosteroid therapy can be beneficial in patients with HNPP with prolonged or incomplete recovery (36).

Development of disease modifying therapies

Substances such as ascorbic acid (37), progesterone antagonists (38), PXT3003 (a combination of baclofen, naltrexone, and D-sorbitol) (39), as well as antisense oligonucleotides (40), have been investigated in preclinical and clinical studies as potential therapeutic approaches that could modify the course of disease in CMT1A. Despite significant progress in understanding the pathogenesis and molecular basis of CMT1A, no disease modifying therapy has been approved in the treatment of CMT1A, so far.

Krauter et al. observed that inhibition of the PI3K/Akt/mTOR signaling pathway has positive effects in mice with HNPP phenotype. These effects include reducing excessive myelin growth, improving motor function, as well as electrophysiological (increased CMAP) and histopathological (reduced *tomacula* formation) parameters. These findings suggest that this signaling pathway could be a promising therapeutic target in the treatment of HNPP (41).

Conclusion

Both CMT1A and HNPP are isoallelic diseases caused by mutations in the *PMP22* gene, which exhibit significant clinical differences. They are also the most common hereditary neuropathies. Currently, there is no adequate therapy for CMT1A and HNPP, so treatment primarily focuses on alleviating existing symptoms. Further research and clinical studies are of great importance to better understand these diseases and find an appropriate therapeutic regimen.

Literature

1. Ramchandren S. Charcot-Marie-Tooth Disease and Other Genetic Polyneuropathies. Continuum (Minneap Minn). 2017; 23(5, Peripheral Nerve and Motor Neuron Disorders):1360-77.
2. Carroll AS, Burns J, Nicholson G, Kiernan MC, Vucic S. Inherited Neuropathies. Semin Neurol. 2019; 39(5):620-39.
3. Attarian S, Fatehi F, Rajabally YA, Pareyson D. Hereditary neuropathy with liability to pressure palsies. J Neurol. 2020; 267(8):2198-206.
4. Li J, Parker B, Martyn C, Natarajan C, Guo J. The PMP22 gene and its related diseases. Mol Neurobiol. 2013; 47(2):673-98.
5. Barreto LC, Oliveira FS, Nunes PS, de Franca Costa IM, Garcez CA, Goes GM, et al. Epidemiologic Study of Charcot-Marie-Tooth Disease: A Systematic Review. Neuroepidemiology. 2016; 46(3):157-65.
6. Ma M, Li Y, Dai S, Chu M, Sun L, Liu L, et al. A meta-analysis on the prevalence of Charcot-Marie-Tooth disease and related inherited peripheral neuropathies. J Neurol. 2023; 270(5):2468-82.
7. Braathen GJ, Sand JC, Lobato A, Hoyer H, Russell MB. Genetic epidemiology of Charcot-Marie-Tooth in the general population. Eur J Neurol. 2011; 18(1):39-48.
8. Marttila M, Kytovuori L, Helisalmi S, Kallio M, Laitinen M, Hiltunen M, et al. Molecular Epidemiology of Charcot-Marie-Tooth Disease in Northern Ostrobothnia, Finland: A Population-Based Study. Neuroepidemiology. 2017; 49(1-2):34-9.
9. Pisciotta C, Shy ME. Neuropathy. Handb Clin Neurol. 2018; 148:653-65.
10. Foley C, Schofield I, Eglon G, Bailey G, Chinnery PF, Horvath R. Charcot-Marie-Tooth disease in Northern England. J Neurol Neurosurg Psychiatry. 2012; 83(5):572-3.
11. Van Paassen BW, van der Kooi AJ, van Spaendonck-Zwarts KY, Verhamme C, Baas F, de Visser M. PMP22 related neuropathies: Charcot-Marie-Tooth disease type 1A and Hereditary Neuropathy with liability to Pressure Palsies. Orphanet J Rare Dis. 2014; 9:38.
12. Shy M, Lupski J, Chance P, Klein C, Dyck P. Hereditary Motor

and Sensory Neuropathies: An overview of Clinical, Genetic, Electrophysiologic, and Pathologic Features. In: PJ D, PK T, editors. Peripheral Neuropathy: Philadelphia: Elsevier Saunders; 2005. p.1623–58.
13. Meretoja P, Silander K, Kalimo H, Aula P, Meretoja A, Savontaus ML. Epidemiology of hereditary neuropathy with liability to pressure palsies (HNPP) in south western Finland. Neuromuscul Disord. 1997; 7(8):529-32.
14. Rakocević-Stojanović V. Nasledne neuropatije. In: Medicinski fakultet Univerziteta u Beogradu, urednici. Neuropatije Principi savremene dijagnostike i terapije. Beograd: Akademska misao; 2018. p.209-36.
15. Klein CJ. Charcot-Marie-Tooth Disease and Other Hereditary Neuropathies. Continuum (Minneap Minn). 2020; 26(5):1224-56.
16. McGrath MC. Charcot-Marie-Tooth 1A: A narrative review with clinical and anatomical perspectives. Clin Anat. 2016; 29(5):547-54.
17. Birouk N, Gouider R, Le Guern E, Gugenheim M, Tardieu S, Maisonobe T, et al. Charcot-Marie-Tooth disease type 1A with 17p11.2 duplication. Clinical and electrophysiological phenotype study and factors influencing disease severity in 119 cases. Brain. 1997; 120(5):813-23.
18. Kovach MJ, Lin JP, Boyadjiev S, Campbell K, Mazzeo L, Herman K, et al. A unique point mutation in the PMP22 gene is associated with Charcot-Marie-Tooth disease and deafness. Am J Hum Genet. 1999; 64(6):1580-93.
19. Sambuughin N, de Bantel A, McWilliams S, Sivakumar K. Deafness and CMT disease associated with a novel four amino acid deletion in the PMP22 gene. Neurology. 2003; 60(3):506-8.
20. Pareyson D, Scaioli V, Taroni F, Botti S, Lorenzetti D, Solari A, et al. Phenotypic heterogeneity in hereditary neuropathy with liability to pressure palsies associated with chromosome 17p11.2-12 deletion. Neurology. 1996; 46(4):1133-7.
21. Hardon WJ, Van Alfen N, Zwarts MJ, Rotteveel JJ. Hereditary neuropathy with liability to pressure palsies in a toddler. Neurology. 2002; 59(12):2008.
22. Paprocka J, Kajor M, Jamroz E, Jezela-Stanek A, Seeman P, Marszal E. Hereditary neuropathy with liability to pressure palsy. Folia Neuropathol. 2006; 44(4):290-4.
23. Orstavik K, Skard Heier M, Young P, Stogbauer F. Brachial plexus involvement as the only expression of hereditary neuropathy with liability to pressure palsies. Muscle Nerve. 2001; 24(8):1093-6.
24. Dubourg O, Mouton P, Brice A, LeGuern E, Bouche P. Guidelines for diagnosis of hereditary neuropathy with liability to pressure palsies. Neuromuscul Disord. 2000; 10(3):206-8.
25. Iwasaki Y, Iguchi H, Ikeda K, Kano O. CNS involvement in hereditary neuropathy with pressure palsies (HNPP). Neurology. 2007; 68(23):2046.
26. Poloni TE, Merlo IM, Alfonsi E, Marinou-Aktipi K, Botti S, Arrigo A, et al. Facial nerve is liable to pressure palsy. Neurology. 1998; 51(1):320-2.
27. Verhagen WI, Gabreels-Festen AA, van Wensen PJ, Joosten EM, Vingerhoets HM, Gabreels FJ, et al. Hereditary neuropathy with liability to pressure palsies: a clinical, electroneurophysiological and morphological study. J Neurol Sci. 1993; 116(2):176-84.
28. Davies DM. Recurrent peripheral nerve palsies in a family. Lancet. 1954; 267(6832):266-8.
29. Winter WC, Juel VC. Hypoglossal neuropathy in hereditary neuropathy with liability to pressure palsy. Neurology. 2003; 61(8):1154-5.
30. Ohkoshi N, Kohno Y, Hayashi A, Wada T, Shoji S. Acute vocal cord paralysis in hereditary neuropathy with liability to pressure palsies. Neurology. 2001; 56(10):1415.
31. Lewis RA, Sumner AJ, Shy ME. Electrophysiological features of inherited demyelinating neuropathies: A reappraisal in the era of molecular diagnosis. Muscle Nerve. 2000; 23(10):1472-87.
32. Pareyson D, Scaioli V, Laura M. Clinical and electrophysiological aspects of Charcot-Marie-Tooth disease. Neuromolecular Med. 2006 ;8(1-2):3-22.
33. Behse F, Buchthal F, Carlsen F, Knappeis GG. Hereditary neuropathy with liability to pressure palsies. Electrophysiological and histopathological aspects. Brain. 1972; 95(4):777-94.
34. Cruz-Martinez A, Arpa J, Palau F. Peroneal neuropathy after weight loss. J Peripher Nerv Syst. 2000; 5(2):101-5.
35. Earle N, Zochodne DW. Is carpal tunnel decompression warranted for HNPP? J Peripher Nerv Syst. 2013; 18(4):331-5.
36. Heng HS, Tang SS, Goyal S, Wraige EA, Lim MJ. Beneficial use of steroids in hereditary neuropathy with liability to pressure palsy. Dev Med Child Neurol. 2012; 54(2):183-6.
37. Passage E, Norreel JC, Noack-Fraissignes P, Sanguedolce V, Pizant J, Thirion X, et al. Ascorbic acid treatment corrects the phenotype of a mouse model of Charcot-Marie-Tooth disease. Nat Med. 2004; 10(4):396-401.
38. Meyer zu Horste G, Prukop T, Liebetanz D, Mobius W, Nave KA, Sereda MW. Antiprogesterone therapy uncouples axonal loss from demyelination in a transgenic rat model of CMT1A neuropathy. Ann Neurol. 2007; 61(1):61-72.
39. Attarian S, Young P, Brannagan TH, Adams D, Van Damme P, Thomas FP, et al. A double-blind, placebo-controlled, randomized trial of PXT3003 for the treatment of Charcot-Marie-Tooth type 1A. Orphanet J Rare Dis. 2021; 16(1):433.
40. Zhao HT, Damle S, Ikeda-Lee K, Kuntz S, Li J, Mohan A, et al. PMP22 antisense oligonucleotides reverse Charcot-Marie-Tooth disease type 1A features in rodent models. J Clin Invest. 2018;128(1): 359-68.
41. Krauter D, Ewers D, Hartmann TJ, Volkmann S, Kungl T, Fledrich R, et al. Inversely proportional myelin growth due to altered Pmp22 gene dosage identifies PI3K/Akt/mTOR signaling as a novel therapeutic target in HNPP. bioRxiv. 2021; p.2021-11.