REVIEW

Progress in the Diagnosis and Management of Chorea-acanthocytosis

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Abstract Chorea-acanthocytosis (ChAc) is the most common subtype of neuroacanthocytosis syndrome, characterized by the presence of acanthocytes and neurological disorders. It is thought to be caused by *VPS13A* mutations. Characteristic movement disorders in ChAc is choreiform movements affecting both trunk and extremities and prominent orolingual dyskinesia is pathognomonic. Acanthocytosis in peripheral blood smear, elevated serum creatine kinase and atrophy of heads of caudate nuclei and dilation of the anterior horn of the lateral ventricles in magnetic resonance imaging could assist the diagnosis of ChAc. Botulinum toxin injection is a possible treatment for the typical orofacial dystonia. Deep brain stimulation is a novel surgical treatment modality. Most cases chose globus pallidus internus as target. Patients with dystonia as a major manifestation will benefit more from high-frequency stimulation and those with major findings of chorea and dysarthria are suitable for low-frequency stimulation. More evidence of long-term outcomes is warranted.

CHOREA-ACANTHOCYTOSIS (ChAc) is an autosomal recessive hereditary disorder caused by the mutation of gene *VPS13A*. It is the most common subtype of neuroacanthocytosis (NA) syndromes. NA syndromes refer to group of syndromes characterized by the presence

of acanthocytes and neurological dysfunctions, which can be further classified into two major groups. First, the "core" NA syndromes present with basal ganglia degeneration, movement disorders, cognitive impairment and psychological symptoms. Based on various etiologies, there are four subtypes: ChAc, McLeod syndrome, Pantothenate kinase-associated neurodegeneration and Huntington's disease-like 2. The second major group of NA syndromes include abetalipoproteinemia (Bassen-Kornzweig syndrome) and familial hypobetalipoproteinemia, with peripheral neuropathy and sensory ataxia, but without movement disorders. In addition, several sporadic systemic diseases are also associated with acanthocytosis.¹ Despite that ChAc is the most common NA subtype, its prevalence is still

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exceedingly low, making comprehensive understanding of ChAc less feasible. Considering ChAc has a long clinical course with protean clinical manifestations, it is likely to be misdiagnosed at early phase. The management of ChAc, especially from a surgical perspective, has made substantial progress recently. This review focused on the epidemiology, clinical manifestations, diagnosis and treatment strategies of ChAc, aiming to improve physicians' understanding of this disorder.

ETIOLOGY AND PATHOGENESIS

The exact mechanism underlying ChAc remains elusive. Currently ChAc is thought to be caused by mutations on gene *VPS13A* (also called *CHAC*).²⁻³ *VPS13A*, located on chromosome 9q21, has 73 exons throughout the whole length. Its protein product, vacuolar protein sorting-associated protein 13A (VPS13A, also called chorein), is a member of VPS13 protein family. *VPS13A* mutations can result in either complete absence of⁴ or functionally-compromised⁵ VPS13A. Mammalian VPS13 protein family consists of VPS13A-VPS13D, each playing specific roles, and VPS13B-VPS13D cannot compensate the absence of VPS13A.⁶ Several researches have already unraveled some functions of VPS13A, while the exact pathophysiology of how VPS13A dysfunction can lead to the phenotype of ChAc remains unknown. A study of yeast VPS13p protein (homologue of mammalian VPS13) has demonstrated its role in maintaining normal mitochondrial function,⁷ and another report showed that VPS13A was involved in polymerization of actin and in lipid synthesis.⁸ Therefore, it was postulated that the abnormal spiky shape of erythrocytes in ChAc might be attributed to not only oxidative damage of membrane lipid secondary to mitochondrial dysfunction but also defected cell scaffold formation secondary to actin dysfunction. Besides, VPS13A was also involved in intracellular trafficking of vesicles.⁹ However, how these dysfunctions could translate into phenotypes still remains to be clarified. Moreover, considering ChAc has high phenotypic variation, patients could have quite different symptoms even in one family, suggesting possible epigenetic or environmental influence to be unraveled.¹⁰

EPIDEMIOLOGY

ChAc was a rare disease with only scattered re-

ports. Currently its actual prevalence was unknown. A relatively higher prevalence in Japan and some ethnic groups (such as French-Canadians¹¹) was reported, possibly due to founder effect.

CLINICAL FEATURES

ChAc generally has an onset in the age of twenties.¹ The key features of movement disorders in ChAc is choreiform movements affecting both trunk and extremities. Especially, prominent orolingual dyskinesia is thought to be pathognomonic in ChAc, which can cause self-mutilation such as lip- or tongue-biting.¹² Trunk instability with spasms (often called "rubber-man gait") can also be seen in patients with ChAc, while falls are uncommon (balance generally preserved).¹³ Rarely, patients can develop Parkinsonism in the late stage, which may be related with involvement of nigrostriatal pathways as disease progresses.¹⁴

Besides, behavioral, cognitive and psychiatric disturbances can also be seen in patients with ChAc, such as depression,¹⁵ schizophrenia-like behaviors¹⁶ and compulsive behaviors.¹⁷ Remarkably, psychiatric manifestations often precede movement disorders, leading to high risk of misdiagnosis sans thorough examination and continuous follow-up.

Finally, several clinical features are thought to be pathognomonic in ChAc. Seizures can present early in disease course, even before motor deficits.¹⁸⁻¹⁹ Other findings, such as peripheral neuropathy,²⁰ cardiac involvements²¹ (arrhythmia, cardiomyopathy), although more commonly seen in McLeod syndrome, can suggest a diagnosis of NA syndromes and be distinguished from other hyperkinetic disorders such as Huntington's disease.

ChAc is a highly disabling disease which slowly progresses for as long as 15 to 30 years. Orolingual dyskinesia and walking difficulty can be highly disturbing and debilitating. Swallowing problems can cause malnutrition and aspiration. Sudden death can result from choke, seizure attack or cardiac arrhythmia.

LABORATORY WORKUPS AND NEUROIMAGING

Several laboratory workups can assist the diagnosis of ChAc. Elevated serum creatine kinase can be seen in most patients with ChAc or McLeod syndrome.²² Acanthocytosis in peripheral blood smear

suggests ChAc, while it's very insensitive (positive rates as low as 5%-50%) and a number of patients need additional saline enhancing experiments or electron microscope scan after glutaraldehyde treatment to validate increased acanthocyte counts. Acanthocytosis can appear at late stage,²³ therefore a clear blood smear cannot rule out ChAc,²⁴ and a close monitoring is suggested when suspecting ChAc. Acanthocytes can also be found in people with heterozygous mutations of *VPS13A* (asymptomatic).²⁵

In neuroimaging, atrophy of heads of caudate nuclei and dilation of the anterior horn of the lateral ventricles in magnetic resonance imaging are typical signs of ChAc.²⁶ FDG-PET/CT also demonstrates impaired glucose metabolism in the basal ganglia.²⁷⁻²⁸ Besides, there were reports of striatal and pallidal iron accumulation.²⁹

DIAGNOSIS AND DIFFERENTIALS

To make a solid diagnosis, either *VPS13A* mutation confirmed by gene sequencing,³ or chorein deletion in red blood cells proven by Western blotting is required. However, only a small portion of ChAc patients reported in China were diagnosed at a gene/protein level.³⁰ Most diagnosis are made according to typical clinical manifestations, peripheral blood cells and radiological features.

Differential diagnosis includes: (1) Huntington disease (HD), an autosomal dominant inherited disorder associated with gene *IT15* mutation.³¹ HD has a common onset age of 35 to 45 years. Epileptic seizure and peripheral nerve impairments are rarely seen. Myopathy is not common and serum creatine kinase level is usually normal. Chorea symptoms of the limbs are more prominent in HD patients. Peripheral acanthocyte level is normal in most cases.^{27, 32} (2) Other types of NA syndromes such as McLeod syndrome. It is another extremely rare disease, which is X-linked recessive associated with gene *XK*. Most are male patients, with abnormal blood group antigen Kell. McLeod syndrome has an onset of 20 to 60 years of age. The symptoms of central nervous system and radiological features of ChAc and McLeod syndrome are not easy to distinguish. The latter has longer clinical course and higher prevalence of cardiac arrhythmia and dilated cardiomyopathy.¹

Due to the complexity of symptoms and the drastic changes throughout the whole course, there is cur-

rently no single uniform rating scale for ChAc. Rating scales for different types of movement disorders are applied, including Marsden-Schachter Chorea Rating Scale (MSCRS),³³ Unified Parkinson Disease Rating Scale (UPDRS), Unified Huntington Disease Rating Scale (UHDRS)³⁴ and Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), as well as other scales for cognitive, behavioral and psychological evaluations. It is still challenging to set up a unified evaluation system for ChAc.

MEDICAL MANAGEMENT

Botulinum toxin injection is a possible treatment for the typical orofacial dystonia of ChAc patients. However, there is not yet a uniform standard regarding the injection sites, dosage or methods. Botulinum toxin injections into the genioglossus muscle (125 units³⁵) relieve tongue protrusion dystonia. Paucar *et al*³⁶ performed ultrasound-guided botulinum toxin injection (10 units) into genioglossus, which significantly improved eating and speaking. Ortega *et al*³⁷ carried out electromyography-guided botulinum toxin application to the inferior head of the lateral pterygoid muscles (35 units) and masseters (15 units) of one ChAc patient, and managed to reduce severe teeth clenching and grinding. Concerning about the risk of suppression of other adjacent muscles associated with swallowing, physicians must be cautious about the application of local botulinum toxin injections. Tetrabenazine inhibits the synthesis and promotes the consumption of dopamine. It was reported to be effective in treating the tongue protrusion symptoms of ChAc patients,³⁸ but may exacerbate dysphagia.³⁹ Some patients choose to remove all their teeth in order to reduce tongue and cheek biting, or use an oral protective stick or towel to passively reduce injury.³⁸ Truncal and limb chorea and dystonia can be treated with classic anti-dystonia medications, including anticholinergics, benzodiazepines and baclofen.³⁸ Amantadine (200 mg/d) is also reported to be effective in treating chorea symptoms.⁴⁰ Parkinsonism is less commonly seen. Amantadine improves the gait of ChAc patients but levodopa was found to be weak.³⁹

SURGICAL MANAGEMENT

In 1997, Fujimoto reported a patient with ChAc undergoing bilateral pallidotomy, which was the ear-

liest attempt of managing ChAc surgically.⁴¹ Later on, with the introduction of deep brain stimulation (DBS) technique, more and more reports emerged regarding this novel treatment modality. Here we present a review of literature of ChAc treated by DBS (Table 1).

All of the present reports (Table 1) chose globes pallidus internus (GPi) as the target except for one

who selected ventral oral posterior nucleus.⁵¹ There are movement disorders which share some of the manifestations with ChAc can also be managed by stimulation of GPi, such as Huntington's disease⁵² and Gilles de la Tourette syndrome,⁵³ indicating a mutual neuromodulating effect on the pathophysiological basis. Considering that the number of the cases was limited,

Table 1. Cases reporting deep brain stimulation in treating chorea-acanthocytosis

References	Number of cases (n)	Acanthocyte count	MRI	VPS13 mutation	Disease course (yrs)	Frequency of stimulation	Functional outcomes
Fernandez-Pajorin <i>et al</i> ⁴²	1	7%	Asymmetric lateral ventricles	(+)	13	low (60 Hz)	UHDRS (motor) [preop. 39 to 13 (1 year postop.)]
Lee <i>et al</i> ⁴³	1	21%	Bilateral atrophy of caudate nuclei and putamen	(+)	3	high (130 Hz)	UHDRS (motor) [preop. 59 to 36 (2 months postop.) and to 34 (1 year postop.)]
Lim <i>et al</i> ^{44, b}	1	↑	Asymmetric atrophy of caudate nuclei and putamen	N/A	6	low (60 Hz)	AIMS [preop. 20 to 12 (2 months postop.) and to 10 (8 months postop.)]
Miquel <i>et al</i> ^{34, a}	3	↑	2 with caudate nuclei atrophy, 1 with normal MRI	1 case (+), 2 cases N/A	6-7	high (140-185 Hz)	UHDRS (motor) (a mean improvement of 50% from 1 to 5 months postop. and 40% improvement for >6 months postop.)
Kefalopoulou <i>et al</i> ^{45, c}	2	↑	Caudate nuclei atrophy	N/A	N/A	high (130 Hz)	UHDRS (motor) (case 1 from 40 to 23, case 2 from 74 to 50), (chorea sub-score: case 1 from 8 to 1, case 2 from 24 to 8)
Shin <i>et al</i> ⁴⁶	1	20%	Bilateral atrophy of caudate nuclei and putamen	(+)	4	high (130 Hz)	UHDRS (motor) [preop. 44 to 13 (2 months postop.)]
Li <i>et al</i> ^{47, b}	2	6%	Bilateral caudate nuclei atrophy	N/A	12	low (60 Hz)	UHDRS (motor) (case 1 from 36 to 13, case 2 from 53 to 26)
Ruiz <i>et al</i> ^{48, b}	1	20%	Bilateral dilation of lateral ventricles and atrophy of caudate nuclei	N/A	11	high (130 Hz)	UHDRS (motor) [preop. 24 to 14 (2 months postop.)]
Wihl <i>et al</i> ^{49, d}	1	25%	Bilateral dilation of lateral ventricles and atrophy of caudate nuclei	N/A	3	low (10-50 Hz) & high (130-1000 Hz)	No improvements
Guehl <i>et al</i> ⁵⁰	1	10%	N/A	(+)	8	low (40 Hz) & high (130 Hz)	UHDRS (motor) [preop. 13.5 to 9.5 (low frequency) and 18 (high frequency) postop.]
Burbaud <i>et al</i> ⁵¹	1	↑	Bilateral atrophy of caudate nuclei and putamen	(+)	12	high (160 Hz)	MSCRS [preop. 54 to 34 (3 months postop.)]

UHDRS: Unified Huntington Disease Rating Scale; AIMS: Abnormal Involuntary Movement Scale; MSCRS: Marsden-Schachter Chorea Rating Scale; N/A: not available. ^aThis study was a multi-center retrospective analysis with 15 patients, of which 3 were from the center that study was carried out (as demonstrated in the table) and 12 were from previous reports (also shown in the table). ^bGenetic analysis was carried out to rule out Huntington's disease. ^cNo band of chorein was found in Western Blotting. ^dA phenotypic analysis of Kell antigen was carried out to rule out McLeod syndrome, and a genetic analysis was done ruling out Huntington's disease and Dentatorubral-pallidolucyan atrophy.

no agreement was achieved regarding the stimulation parameters. For patients receiving high-frequency stimulation,^{45-46, 48} some had evident improvements of symptoms especially orofacial and axial dystonia, chorea was also improved, but the symptoms of dysarthria didn't seem to respond well. For patients receiving low-frequency stimulation,^{47, 5} improvements were mainly in chorea and dystonia, some of which even had symptoms exacerbation (such as chorea and dysarthria) under high-frequency stimulation. Generally, it seems that patients with dystonia as a major manifestation will benefit more from high-frequency stimulation and those with major findings of chorea and dysarthria are suitable for low-frequency stimulation. However, as present cases were all very limited in number and highly heterogeneous in surgery and protocols for motor function evaluation, a single-center or multi-center protocol-guided perspective study is strongly warranted for evidences of higher level.

Currently, there are only limited literature assessing the short-term and long-term outcomes for ChAc treated with GPi-DBS. Miquel *et al*³⁴ retrospectively analyzed 15 cases of ChAc from multiple centers treated with bilateral GPi-DBS. As for symptoms, there were major improvements in chorea, and also improvements of varied degrees regarding dystonia and gait disturbance, but dysarthria didn't seem to respond to the treatment well. As for motor function, a mean improvement of UHDRS reached 54.3% from 1 month to 5 months postoperatively, and reaching 44.1% 6 months postoperatively. Some patients had symptoms recurred after 6 months postoperatively, which indicates that a maximum benefit might be achieved around 6 months after the surgery, after which close follow-ups should be carried out for evaluation of symptoms and adjustment of stimulation parameters in order to optimize the effect.

There are still many questions to answer in the diagnosis and management of ChAc. As an orphan disease, the number of patients with ChAc is highly limited. To make things worse, the long disease courses and high heterogeneity of manifestations further adds to the problem of misdiagnosis. Both limited patient number and the issue of misdiagnosis make it a challenge to maintain a constantly functional database for patient data collection and follow-ups, and furthermore, to establish a unified rating scale for evaluation. Current there are no

agreements for the selection of treatment regimen of ChAc, and surgical interventions (such as DBS) is primarily for patients refractory to medications. It remains unexplored whether an early DBS will help to improve the total outcome. Finally, the initial programming and adjustment of stimulation parameters for ChAc are also to be studied.

Conflicts of interest statement

The authors have no conflicts of interest to disclose.

REFERENCES

1. Jung HH, Danek A, Walker RH. Neuroacanthocytosis syndromes. *Orphanet J Rare Dis* 2011; 6:68. doi: 10.1186/1750-1172-6-68.
2. Ueno S, Maruki Y, Nakamura M, et al. The gene encoding a newly discovered protein, chorein, is mutated in chorea-acanthocytosis. *Nat Genet* 2001; 28(2):121-2. doi: 10.1038/88825.
3. Rampoldi L, Dobson-Stone C, Rubio JP, et al. A conserved sorting-associated protein is mutant in chorea-acanthocytosis. *Nat Genet* 2001; 28(2):119-20. doi: 10.1038/88821.
4. Tomiyasu A, Nakamura M, Ichiba M, et al. Novel pathogenic mutations and copy number variations in the VPS13A Gene in patients with chorea-acanthocytosis. *Am J Med Genet B Neuropsychiatr Genet* 2011; 156(5):620-31. doi: 10.1002/ajmg.b.31206.
5. Rzepnikowska W, Flis K, Kaminska J, et al. Amino acid substitution equivalent to human chorea-acanthocytosis I2771R in yeast Vps13 protein affects its binding to phosphatidylinositol 3-phosphate. *Hum Mol Genet* 2017; 26(8):1497-510. doi: 10.1093/hmg/ddx054.
6. Kurano Y, Nakamura M, Ichiba M, et al. *In vivo* distribution and localization of chorein. *Biochem Biophys Res Commun* 2007; 353(2):431-5. doi: 10.1016/j.bbrc.2006.12.059.
7. Park JS, Thorsness MK, Policastro R, et al. Yeast Vps13 promotes mitochondrial function and is localized at membrane contact sites. *Mol Biol Cell* 2016; 27(15):2435-49. doi: 10.1091/mbc.E16-02-0112.
8. Pappas SS, Bonifacio J, Danek A, et al. Eighth International Chorea-Acanthocytosis Symposium: Summary of Workshop Discussion and Action Points. *Tremor Other Hyperkinet Mov (NY)* 2017; 7:428. doi:10.7916/D8XD127W.
9. Park JS, Neiman AM. VPS13 regulates membrane morphogenesis during sporulation in *Saccharomyces*

- cerevisiae. *J Cell Sci* 2012; 125(Pt 12):3004-11. doi: 10.1242/jcs.105114.
10. Lossos A, Dobson-Stone C, Monaco AP, et al. Early clinical heterogeneity in choreoacanthocytosis. *Arch Neurol* 2005; 62(4):611-4. doi: 10.1001/archneur.62.4.611.
 11. Dobson-Stone C, Velayos-Baeza A, Jansen A, et al. Identification of a VPS13A founder mutation in French Canadian families with chorea-acanthocytosis. *Neurogenetics* 2005; 6(3):151-8. doi: 10.1007/s10048-005-0220-9.
 12. Gooneratne IK, Weeratunga PN, Gamage R. Teaching video neuroimages: orofacial dyskinesia and oral ulceration due to involuntary biting in neuroacanthocytosis. *Neurology* 2014; 82(8):e70. doi: 10.1212/WNL.0000000000000144.
 13. Schneider SA, Lang AE, Moro E, et al. Characteristic head drops and axial extension in advanced chorea-acanthocytosis. *Mov Disord* 2010; 25(10):1487-91.
 14. Bostantjopoulou S, Katsarou Z, Kazis A, et al. Neuroacanthocytosis presenting as parkinsonism. *Mov Disord* 2000; 15(6):1271-3.
 15. Balhara YP, Varghese ST, Kayal M. Neuroacanthocytosis: presenting with depression. *J Neuropsychiatry Clin Neurosci* 2006; 18(3):426. doi: 10.1176/jnp.2006.18.3.426.
 16. Yamada H, Ohji T, Sakurai S, et al. Chorea-acanthocytosis presenting with schizophrenia symptoms as first symptoms. *Psychiatry Clin Neurosci* 2009; 63(2):253-4. doi: 10.1111/j.1440-1819.2008.01915.x.
 17. Walker RH, Liu Q, Ichiba M, et al. Self-mutilation in chorea-acanthocytosis: manifestation of movement disorder or psychopathology? *Mov Disord* 2006; 21(12):2268-9. doi: 10.1002/mds.21156.
 18. Al-Asmi A, Jansen AC, Badhwar A, et al. Familial temporal lobe epilepsy as a presenting feature of choreoacanthocytosis. *Epilepsia* 2005; 46(8):1256-63. doi: 10.1111/j.1528-1167.2005.65804.x.
 19. Doghmi N, Elkoundi A, Meskine A, et al. Epilepsy revealing chorea-acanthocytosis: about a case. *Pan Afr Med J* 2016; 24:172. doi: 10.11604/pamj.2016.24.172.9686.
 20. Vita G, Serra S, Dattola R, et al. Peripheral neuropathy in amyotrophic chorea-acanthocytosis. *Ann Neurol* 1989; 26(4):583-7. doi: 10.1002/ana.410260415.
 21. Kageyama Y, Matsumoto K, Ichikawa K, et al. A new phenotype of chorea-acanthocytosis with dilated cardiomyopathy and myopathy. *Mov Disord* 2007; 22(11):1669-70. doi: 10.1002/mds.21556.
 22. Saiki S, Sakai K, Murata KY, et al. Primary skeletal muscle involvement in chorea-acanthocytosis. *Mov Disord* 2007; 22(6):848-52. doi: 10.1002/mds.21437.
 23. Sorrentino G, De Renzo A, Miniello S, et al. Late appearance of acanthocytes during the course of chorea-acanthocytosis. *J Neurol Sci* 1999; 163(2):175-8.
 24. Storch A, Kornhass M, Schwarz J. Testing for acanthocytosis A prospective reader-blinded study in movement disorder patients. *J Neurol* 2005; 252(1):84-90. doi: 10.1007/s00415-005-0616-3.
 25. Critchley EM, Clark DB, Wikler A. Acanthocytosis and neurological disorder without betalipoproteinemia. *Arch Neurol* 1968; 18(2):134-40.
 26. Henkel K, Danek A, Grafman J, et al. Head of the caudate nucleus is most vulnerable in chorea-acanthocytosis: a voxel-based morphometry study. *Mov Disord* 2006; 21(10):1728-31. doi: 10.1002/mds.21046.
 27. Zhou X, Guan H, Shi X, et al. Clinical, laboratory and neuroimaging characteristics of neuroacanthocytosis. *Clin J Neurol* 2014; 45(2):112-5.
 28. Cui R, You H, Niu N, et al. FDG PET brain scan demonstrated glucose hypometabolism of bilateral caudate nuclei and putamina in a patient with chorea-acanthocytosis. *Clin Nucl Med* 2015; 40(12):979-80. doi: 10.1097/RLU.0000000000000968.
 29. Kaul B, Goyal V, Shukla G, et al. Mineral deposition on magnetic resonance imaging in chorea-acanthocytosis: a pathogenic link with pantothenate kinase-associated neurodegeneration? *Neurol India* 2013; 61(2):169-70. doi: 10.4103/0028-3886.111129.
 30. Liu J, Bader B, Danek A. Neuroacanthocytosis in China: a review of published reports. *Tremor Other Hyperkinet Mov (NY)* 2014; 4:248. doi: 10.7916/D8Q23XDX.
 31. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nat Rev Neurol* 2014; 10(4):204-16. doi: 10.1038/nrneurol.2014.24.
 32. Su F, Zeng Y, Pei Z, et al. The clinical analysis of Huntington disease: a case study from 12 genetic diagnosis families. *Chin J Nerv Ment Dis* 2016; 42(1):6-10. doi: 10.3969/j.issn.1002-0152.2016.01.002.
 33. Marsden CD, Schachter M. Assessment of extrapyramidal disorders. *Br J Clin Pharmacol* 1981; 11(2):129-51.
 34. Miquel M, Spampinato U, Latxague C, et al. Short and long term outcome of bilateral pallidal stimulation in chorea-acanthocytosis. *PLoS One* 2013;

- 8(11):e79241. doi: 10.1371/journal.pone.0079241.
35. Schneider SA, Aggarwal A, Bhatt M, et al. Severe tongue protrusion dystonia: clinical syndromes and possible treatment. *Neurology* 2006; 67(6):940-3. doi: 10.1212/01.wnl.0000237446.06971.72.
36. Paucar M, Lindestad PA, Walker RH, et al. Teaching video neuroimages: feeding dystonia in chorea-acanthocytosis. *Neurology* 2015; 85(19):e143-4. doi: 10.1212/WNL.0000000000002108.
37. Ortega MC, Skarmeta NP, Diaz YJ. Management of oromandibular dystonia in a chorea acanthocytosis: a brief review of the literature and a clinical case. *Cranio* 2016; 34(5):332-7. doi: 10.1179/2151090315Y.00000000027.
38. Walker RH. Management of neuroacanthocytosis syndromes. *Tremor Other Hyperkinet Mov (NY)* 2015; 5:346. doi: 10.7916/D8W66K48.
39. Ong B, Devathanan G, Chong PN. Choreoacanthocytosis in a Chinese patient—a case report. *Singapore Med J* 1989; 30(5):506-8.
40. Arango GJ, Tenorio M, Marulanda E. Neuroacanthocytosis: clinico-pathological study of a family with different phenotypes. *Mov Disord* 2002; 17:S237-S8.
41. Fujimoto Y, Iozaki E, Yokochi F, et al. A case of chorea-acanthocytosis successfully treated with posteroventral pallidotomy. *Rinsho Shinkeigaku* 1997; 37(10):891-4.
42. Fernandez-Pajarin G, Sesar A, Ares B, et al. Deep brain bilateral pallidal stimulation in chorea-acanthocytosis caused by a homozygous VPS13A mutation. *Eur J Neurol* 2016; 23(1):e4-5. doi: 10.1111/ene.12833.
43. Lee JH, Cho WH, Cha SH, et al. Globus pallidus interna deep brain stimulation for chorea-acanthocytosis. *J Korean Neurosurg Soc* 2015; 57(2):143-6. doi: 10.3340/jkns.2015.57.2.143.
44. Lim TT, Fernandez HH, Cooper S, et al. Successful deep brain stimulation surgery with intraoperative magnetic resonance imaging on a difficult neuroacanthocytosis case: case report. *Neurosurgery* 2013; 73(1):E184-7; discussion E188. doi: 10.1227/01.neu.0000429852.45073.73.
45. Kefalopoulou Z, Zrinzo L, Aviles-Olmos I, et al. Deep brain stimulation as a treatment for chorea-acanthocytosis. *J Neurol* 2013; 260(1):303-5. doi: 10.1007/s00415-012-6714-0.
46. Shin H, Ki CS, Cho AR, et al. Globus pallidus interna deep brain stimulation improves chorea and functional status in a patient with chorea-acanthocytosis. *Stereotact Funct Neurosurg* 2012; 90(4):273-7. doi: 10.1159/000338216.
47. Li P, Huang R, Song W, et al. Deep brain stimulation of the globus pallidus interna improves symptoms of chorea-acanthocytosis. *Neurol Sci* 2012; 33(2):269-74. doi: 10.1007/s10072-011-0741-y.
48. Ruiz PJ, Ayerbe J, Bader B, et al. Deep brain stimulation in chorea acanthocytosis. *Mov Disord* 2009; 24(10):1546-7. doi: 10.1002/mds.22592.
49. Wihl G, Volkmann J, Allert N, et al. Deep brain stimulation of the internal pallidum did not improve chorea in a patient with neuro-acanthocytosis. *Mov Disord* 2001; 16(3):572-5.
50. Guehl D, Cuny E, Tison F, et al. Deep brain pallidal stimulation for movement disorders in neuroacanthocytosis. *Neurology* 2007; 68(2):160-1. doi: 10.1212/01.wnl.0000250536.81426.1a.
51. Burbaud P, Rougier A, Ferrer X, et al. Improvement of severe trunk spasms by bilateral high-frequency stimulation of the motor thalamus in a patient with chorea-acanthocytosis. *Mov Disord* 2002; 17(1):204-7.
52. Biolsi B, Cif L, Fertit HE, et al. Long-term follow-up of Huntington disease treated by bilateral deep brain stimulation of the internal globus pallidus. *J Neurosurg* 2008; 109(1):130-2. doi: 10.3171/JNS/2008/109/7/0130.
53. Zhang JG, Ge Y, Stead M, et al. Long-term outcome of globus pallidus internus deep brain stimulation in patients with Tourette syndrome. *Mayo Clin Proc* 2014; 89(11):1506-14. doi: 10.1016/j.mayocp.2014.05.019.