NO IMPROVEMENT OF PHYSICAL CAPACITY DURING CARDIAC REHABILITATION IN A PATIENT WITH ELEVATED IGF-1 AND NORMAL PRESSURE HYDROCEPHALUS

Brak poprawy wydolności fizycznej w trakcie rehabilitacji kardiologicznej u pacjenta z podwyższonym IGF-1 i wodogłowiem normotensyjnym

Zuzanna Janicka, Małgorzata Kurpaska, Katarzyna Piotrowicz, Marzena Kubiak, Paweł Krzesiński

Military Institute of Medicine – National Research Institute, Department of Cardiology and Internal Diseases, Poland

Zuzanna Janicka – 0009-0007-6856-045X

Abstract

Introduction and objectives: Multimorbidity (type 2 diabetes, hyperlipidaemia, arterial hypertension, obesity, limited exercise tolerance) is a common challenge during cardiac rehabilitation in patients with chronic coronary syndrome. **Materials and methods:** A 54-year-old man after percutaneous coronary angioplasty followed a cardiac rehabilitation programme. He presented with generalised muscle weakness, phenotypic signs of acromegaly, as well as elevated serum creatine kinase and insulin-like growth factor 1. The qualification for rehabilitation was based on multiparametric assessment of physical exercise using ergospirometry combined with comprehensive physiotherapy examination. Kinesitherapy programme was developed on the basis of heart rate at the anaerobic threshold and then divided into 24 sessions of telemonitoring-guided cycle ergometer interval-training, which was continued for 5 weeks. **Results:** Worsening of muscle strength was observed after the second stage of cardiac rehabilitation, which led to extension of diagnosis. Acromegaly was excluded due to inhibition of growth hormone secretion in oral glucose tolerance test. Normal pressure hydrocephalus was detected on head magnetic resonance imaging. The patient was eventually diagnosed with Hakim syndrome. **Conclusions:** Patients with chronic coronary syndrome require implementation of cardiac rehabilitation as soon as possible after coronary intervention. Attention needs to be paid to every alarming abnormality during examination, therapeutic failures in particular. This allows for quick interventions, further diagnosis or treatment. Physiotherapy examination along with exercise tests is an indispensable element of planning kinesitherapy as part of cardiac rehabilitation and can contribute to individualisation of therapeutic approach.

Streszczenie

Wprowadzenie i cele: Wielochorobowość (cukrzyca typu 2, hiperlipidemia, nadciśnienie tętnicze, otyłość, ograniczenie tolerancji wysiłku) stanowią powszechne wyzwanie podczas rehabilitacji kardiologicznej pacjentów z przewlekłym zespołem wieńcowym. **Materiały i metody:** U 54-letniego mężczyzny po angioplastyce wieńcowej wdrożono program rehabilitacji kardiologicznej. Pacjent prezentował uogólnione osłabienie siły mięśniowej i cechy fenotypowe akromegalii oraz podwyższone stężenie kinazy kreatynowej i insulinopodobnego czynnika wzrostu 1. W kwalifikacji do rehabilitacji wykorzystano wieloparametryczną ocenę wysiłku podczas ergospirometrii w połączeniu z całościowym badaniem fizjoterapeutycznym. Program kinezyterapii opracowano na podstawie tętna osiąganego na progu beztlenowym i podzielono go na 24 sesje treningu interwałowego na cykloergometrze z telemonitoringiem w ciągu 5 tygodni. **Wyniki:** Po drugim etapie rehabilitacji kardiologicznej obserwowano pogorszenie siły mięśniowej, w związku z czym zdecydowano o poszerzeniu diagnostyki. Na podstawie hamowania wydzielania hormonu wzrostu w teście doustnego obciążenia glukozą wykluczono akromegalię. W badaniu rezonansu magnetycznego głowy uwidoczniono wodogłowie normotensyjne, w związku z czym rozpoznano zespół Hakima. **Wnioski:** Pacjenci z przewlekłym zespołem wieńcowym wymagają wdrożenia rehabilitacji kardiologicznej możliwie jak najszybciej po interwencji. W trakcie postępowania należy zwracać uwagę na wszelkie niepokojące nieprawidłowości, a zwłaszcza niepowodzenie stosowanych procedur, aby możliwie szybko i właściwie skierować pacjenta na dalszą diagnostykę i leczenie. Badanie fizjoterapeutyczne wraz z testami wysiłkowymi jest nieodzownym elementem planowania i prowadzenia kinezyterapii w ramach rehabilitacji kardiologicznej, aby zindywidualizować podejście terapeutyczne.

Keywords: exercise test, muscle strength, insulin-like growth factor 1, acromegaly, normal pressure hydrocephalus

Słowa kluczowe: test wysiłkowy, siła mięśniowa, insulinopodobny czynnik wzrostu 1, akromegalia, wodogłowie normotensyjne

DOI 10.53301/lw/175141

Received: 17.10.2023

Accepted: 13.11.2023

Corresponding author:
Zuzanna Janicka
Military Institute of Medicine – National Research Institute, Department of Cardiology and Internal Diseases, Warsaw
e-mail: z.janicka1310@gmail.com

Case report

A 54-year-old male patient with chronic coronary syndrome (CCS) was admitted to the Department of Cardiology and Internal Diseases for the second stage of cardiac rehabilitation two weeks after percutaneous coronary intervention (PCI) of the anterior descending artery (ADA) with drug-eluting stent implantation. The patient was also diagnosed with type 2 diabetes mellitus (DM2), hyperlipidaemia, arterial hypertension, abdominal obesity and single ventricular arrhythmia. After PCI, the patient was qualified for conservative treatment of coronary artery disease (CAD). Despite reporting reduced exercise tolerance and more rapid fatigue, he jogged recreationally. Home measurements showed normal blood pressure control. Echocardiography indicated normal myocardial contractility, a left ventricular ejection fraction of 65%, low mitral and tricuspid regurgitation and signs of impaired left ventricular muscle relaxation. Physical examination revealed obesity (BMI: 32 kg/m^2), limited lumbar spine mobility, bilateral flat feet, valgus knees and generalised muscle weakness (Lovett score of 4.5). No focal nervous system damage or other neurological symptoms (e.g. urinary incontinence, myoclonus) were found. Additionally, phenotypic features of acromegaly, such as frontal bossing, large auricles, large tongue, widened interdental spaces, prominent mandible, low voice and hoarseness, were notable. Laboratory investigations showed increased creatine kinase (CK) activity (325 U/L, with reference values up to 171 U/L) and elevated insulin-like growth factor-1 (IGF-1) (227.5 ng/mL, with reference values up to 196 ng/mL). Also, a tendency towards nocturnal hypertension was noted during 24-hour monitoring. Typical treatment of CAD with statin, hypotensive therapy and oral hypoglycaemics were administered.

A 6-Minute Walk Test (6MWT) and cardiopulmonary exercise test (CPET) were performed in order to plan an individual rehabilitation programme. These tests showed significantly reduced physical capacity, impaired muscle strength and normal chronotropic and tension response (tab.). Furthermore, an abnormal haemodynamic profile in the form of reduced stroke volume (SV) after reaching the anaerobic threshold (AT), with no ECG ischemic changes in ST segment or T-wave, or chest pain, assessed by impedance cardiography, was noteworthy.

As part of rehabilitation, respiratory gymnastics, upper and lower limb active exercises and interval cycle ergometer training with telemonitoring in a progressive scheme were implemented. The patient received education on the principles of physical activity undertaken, and a training heart rate at AT ± 5% (93 ± 4/min) was recommended. The patient performed 5 cycle ergometer training sessions during hospital stay. Then, due to his low risk of exercise-induced cardiovascular events (CVEs), he was qualified for home telerehabilitation. Over the course of the next 5 weeks, he completed 24 stationary bike training sessions (3 sets of 5–8 minutes each), including 9 at the training HR, rated at 3/10 on the Borg scale (83% of workouts). During home training sessions, the patient reported improved exercise tolerance, denied angina symptoms, and had normal blood pressure control.

During the telerehabilitation follow-up visit, a decrease in physical capacity and increasing muscle weakness were recorded. Follow-up laboratory workup showed low-density lipoprotein (LDL) at 43 mg/dL, with CK levels below twice the upper limit of normal, prompting a reduction in the statin dose. Considering CPET results, the recommended training HR was reduced to 85 bpm. Due to the observed muscle weakness on physical examination, typical features of endocrinopathy along with elevated CK and IGF-1 levels, the patient was referred to the Department of Endocrinology. Biochemical/hormonal tests were run two months after telerehabilitation, confirming elevated IGF-1 levels (215.7 ng/mL, with reference values up to 204 ng/mL) and showing growth hormone (GH) suppression by oral glucose, thus excluding acromegaly. Head MRI revealed four-ventricular hydrocephalus.

Due to the presence of the Hakim–Adams triad (disorders of gait, dementia and urinary incontinence), the patient underwent endoscopic third ventriculostomy (ETV) five months after completing telerehabilitation, resulting in improvement in gait, concentration, and vision. Normal pressure hydrocephalus was diagnosed.

Discussion

As set out in the guidelines for patients with CAD after PCI [1], regular moderate physical activity is recommended, with an emphasis on aerobic endurance exercises, as well as resistance exercises within the range of 30–50% of maximum muscle strength, repeated 2–3 times per week. An individual training programme was developed for our patient based on the anaerobic threshold HR obtained from CPET [2, 3]. Performing CPET as part of the qualification for cardiac rehabilitation not only allows for the precise determination of training HR in a safe, aero-

Table. CPET findings at baseline vs. follow-up

Parameter	Baseline	Follow-up	Difference
6MWT [m]; [% pred.]	556; 83%	584; 86%	+28; +3%
Borg's score	6/10	7/10	+1
Load [W]	155	128	−27
Load [% pred.]	57	48	−9
RER	1,09	1,00	−0,09
VO_2 [mL/min/kg]	16	15	−1
VO_2 [% pred.]	65	58	−7
HR max [min^{-1}]	117	106	−11
% max HR limit	80	73	−7
HR in AT [min^{-1}]	93	85	−8
O_2 Pulse [mL/beat]	17	16	−1
O_2 Pulse [% pred.]	81	80	−1
VE [L/min]	72,8	64,1	−8,7
BR [%]	89	75	−14
BF [min^{-1}]	29	29	0
VE/VCO_2 slope	31,6	34,8	+3,2
OUES	2,3	1,8	−0,5

% pred. – percent of predicted value; 6MWT – 6-minute walk test; AT – anaerobic threshold; BF – breathing frequency; BR – breathing reserve; HR – heart rate; OUES –oxygen uptake efficiency slope; O_2 Pulse – oxygen pulse; RER – respiratory exchange ratio; VE – minute ventilation; VO_2 – oxygen uptake at peak exercise; VE/VCO_2 slope –ventilation efficiency

bic range [3], but also provides a reliable assessment of physical capacity , as well as chronotropic and tension responses, an analysis of potential myocardial ischemia in ECG, risk stratification, and diagnosis of non-cardiac causes of reduced exercise tolerance [4, 5].

The patient exhibited a significant decrease in physical fitness [5] (peak oxygen uptake, VO_{2peak} 16 mL/min/kg, 65% of predicted value) of multifactorial aetiology. The CPET result did not indicate any specific cause of dyspnoea. The involvement of CAD, microvascular disease in particular, was considered. It is worth emphasising that the patient had fully patent coronary arteries, was qualified for conservative treatment, reported no angina symptoms, and presented with no ECG ST-segment changes or T-wave abnormalities typical of ischemia. However, the sensitivity and specificity of exercise ECG in diagnosing CAD are estimated at 68% and 77%, respectively [6].

Borderline low absolute values of O_2 Pulse and a reduction in SV values during exercise after reaching the AT supported the diagnosis of ischemic heart disease [4, 7–9]. The inability to maintain an appropriate SV during exercise after reaching AT, along with an abnormal systemic vascular resistance index (SVRI) response, indicates significant vascular stiffness [2], resulting in impaired tissue extraction of oxygen. Additionally, slightly elevated values of ventilation efficiency (VE/VCO_2 slope) were noted, directing the diagnosis towards heart failure. No abnormalities were found in ventilation or gas exchange. During the qualification for cardiac rehabilitation, muscle weakness was pronounced, as indicated by consistently low workload at peak exercise (57% predicted) and oxygen uptake efficiency slope (OUES) reduced to 2.3 (normal 3.06) [10]. Lower OUES values are associated with reduced muscle mass, disturbances in intramuscular blood flow, impaired oxygen extraction and utilisation by muscles, and rapid development of lactic acidosis [11]. The OUES index can be applied during submaximal efforts [3, 12], which is significant in the case of muscle weakness.

Changes in myocardial function and structure (left ventricular diastolic dysfunction, arterial hypertension, vascular stiffness, and progression of atherosclerosis) [13], respiratory system disorders, impaired respiratory muscle function in particular [14, 15], as well as myopathy [16], manifesting as muscle and joint pain [17], and overall fatigue [2, 16, 18] were considered due to elevated IGF-1 levels and clinical suspicion of acromegaly as the cause of low tolerance of physical exercise. Myopathy may result from the direct impact of excess IGF-1 on muscles and from the involvement of accompanying metabolic disorders (e.g. diabetes) [16, 19, 20]. Hypertrophy of type 1 fibres, atrophy of type 2A fibres [16, 21] and increased intramuscular fat content [22] play an important role in its etiopathogenesis. Hypertrophic peripheral skeletal muscles are functionally weaker both in terms of strength and endurance [19, 20, 23, 24]. Sarcopenia may manifest with elevated CK levels [16, 25], as observed in the presented patient. It is worth noting that the patient was treated with rosuvastatin, whose spectrum of adverse effects includes myopathy. However, the downward trend in CK levels (325 U/L followed by 218 U/L within a few days), despite no modification of pharmacotherapy, rather excludes the involvement of this factor.

The patient's muscle weakness was also attributed to chronic normotensive hydrocephalus and the associated damage to the pyramidal system (the corticospinal tract in particular) [26], which, among other things, regulates muscle tone. During cardiac rehabilitation, no classical Hakim–Adams triad of clinical findings (urinary incontinence and cognitive deficits) were seen, and no evident signs of dyskinesia, athetosis, tremors, or myoclonus were found. It was expected that at least reduced muscle

function would be maintained at a similar level following the rehabilitation cycle, rather than the progression of myopathy over a short 6-week period. Increasing, typically hypokinetic gait disturbances, characterised by a slow wide-based gait, drew attention and prompted further diagnostic evaluation [27].

The presented case suggests considering an individual approach to cardiac rehabilitation for patients with generalised muscle weakness. On one hand, chronic elevation of IGF-1 levels significantly increases CV risk, leading to a predicted average reduction in life expectancy of 10 years [14]. On the other hand, progressive musculoskeletal dysfunction results in reduced functionality and activity, necessitating individually tailored kinesiotherapy programmes [19]. Furthermore, hydrocephalus-induced damage to the pyramidal system results in generalised muscle weakness requiring neurosurgical intervention.

Based on the conducted diagnostic workup, the risk of exercise-induced CV events was assessed as low, and the patient was classified for hybrid telerehabilitation. Unfortunately, despite the individually tailored aerobic training cycle, a decrease in physical performance and increasing muscle weakness were observed, along with lowering peak VO_2, workload, and OUES. CAD progression was not suspected due to the absence of ECG changes or angina, and improvement in hemodynamic profile, expressed by reduced SVRI. However, workload lower by 27 W and a decrease in OUES value by 0.5 indicate progressive myopathy. It is noteworthy that the patient showed less engagement in the follow-up exercise test, as he did not reach the target respiratory exchange ratio (RER) at peak exertion, which is ≥1.05.

Limitation of resistance exercises, which are believed to play the main role in preventing sarcopenia, seems to be the reason for the failure of therapy in the presented patient, who was unable to perform high-intensity resistance training (6 times a week for 40–60 minutes), recommended for older individuals to reverse frailty syndrome [14]. This does not imply, however, that this level of exertion is not recommended for such patients. Previous studies have shown that strength and endurance training should be implemented in patients with elevated IGF-1 levels as early as possible [28] due to the increasing reduction in muscle mass and increasing proximal muscle weakness [19, 24]. Various exercise programmes have been utilised in such patients, encompassing warm-up, endurance, resistance, balance, and stretching exercises, performed three times a week for 60–75 minutes [19, 28, 29]. A reduction in overall fatigue level and improvement in physical endurance, quadriceps muscle strength, and balance were observed following these programmes. On the other hand, the cause of muscle weakness in the presented case was not solely due to elevated IGF-1 levels, but also due to progressive central and peripheral neuropathy. Furthermore, the observed change in IGF-1 levels could have been secondary to hydrocephalus [30]. Neurosurgical intervention involving the creation of an alternative route for cerebrospinal fluid circulation through ventriculocisternostomy, leading to the resolution of clinical symptoms, is the treatment of choice for normotensive hydrocephalus [31]. Therefore, the use of kinesiotherapy did not yield the expected clinical effects.

Conclusions

We presented a case of a patient undergoing cardiac rehabilitation due to one of the most common indications. The initial clinical presentation did not distinguish the patient from other patients with a similar multimorbidity profile. The follow-up of the rehabilitation process and its limited therapeutic efficacy prompted us to expand the diagnostic process to identify non-cardiological causes of reported exercise intolerance and weakness. Non-standard additional tests and individualised therapeutic approaches may be needed in some patients qualified for cardiac rehabilitation.

References

1. Piotrowicz R, Jegier A, Szalewska D, et al. Rekomendacje w zakresie realizacji kompleksowej rehabilitacji kardiologicznej. Stanowisko Ekspertów Sekcji Rehabilitacji Kardiologicznej i Fizjologii Wysiłku Polskiego Towarzystwa Kardiologicznego. AsteriaMed, Gdańsk 2017
2. Michalski ADC, Ferreira AS, Kasuki L, et al. Clinical and functional variables can predict general fatigue in patients with acromegaly: an explanatory model approach. Arch Endocrinol Metab, 2019; 63: 235–240. doi: 10.20945/2359-3997000000127
3. StraburzyńskaMigaj E. Testy spiroergometryczne w praktyce klinicznej. Warszawa, Wydawnictwo Lekarskie PZWL, 2010
4. SmarżK, Jaxa-ChamiecT, ChwyczkoT, et al. Cardiopulmonary exercise testing in adult cardiology: expert opinion of the Working Group of Cardiac Rehabilitation and Exercise Physiology of the Polish Cardiac Society. Kardiol Pol, 2019; 77: 730–756. doi: 10.33963/KP.14889
5. Glaab T, Taube C. Practical guide to cardiopulmonary exercise testing in adults. Respir Res, 2022; 23: 9. doi: 10.1186/s12931-021-01895-6
6. Bourque JM, Beller GA. Value of exercise ECG for risk stratification in suspected or known CAD in the era of advanced imaging technologies. JACC Cardiovasc Imaging, 2015; 8: 1309–1321. doi: 10.1016/j.jcmg.2015.09.006
7. Chaudhry S, Arena R, Bhatt DL, et al. A practical clinical approach to utilize cardiopulmonary exercise testing in the evaluation and management of coronary artery disease: a primer for cardiologists. Curr Opin Cardiol, 2018; 33: 168–177. doi: 10.1097/HCO.0000000000000494
8. Sperling MP, Caruso FC, Mendes RG, et al. Relationship between non-invasive haemodynamic responses and cardiopulmonary exercise testing in patients with coronary artery disease. Clin Physiol Funct Imaging, 2016; 36: 92–98. doi: 10.1111/cpf.12197
9. Goldkorn R, Naimushin A, Rozen E, et al. Early post-stress decrease in cardiac performance by impedance cardiography and its relationship to the severity and extent of ischemia by myocardial perfusion imaging. BMC Cardiovasc Disord, 2020; 20: 354. oi: 10.1186/s12872-020-01639-2
10. Williamson W, Fuld J, Westgate K, et al. Validity of reporting oxygen uptake efficiency slope from submaximal exercise using respiratory exchange ratio as secondary criterion. Pulm Med, 2012; 2012: 874020. doi: 10.1155/2012/874020
11. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol, 2000; 36: 194–201. doi: 10.1016/s0735-1097(00)00691-4

12. Baba R, Nagashima M, Goto M, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. J Am Coll Cardiol, 1996; 28: 1567–1572. doi: 10.1016/s0735-1097(96)00412-3
13. Giustina A, Boni E, Romanelli G, et al. Cardiopulmonary performance during exercise in acromegaly, and the effects of acute suppression of growth hormone hypersecretion with octreotide. Am J Cardiol, 1995; 75: 1042–1047. doi: 10.1016/s0002-9149(99)80721-8
14. Hergott CG, Lovins J. The impact of functional exercise on the reversal of acromegaly induced frailty: a case report. Physiother Theory Pract, 2022; 38: 471–480. doi: 10.1080/09593985.2020.1768456
15. Lopes AJ, Guedes da Silva DP, Ferreira Ade S, et al. What is the effect of peripheral muscle fatigue, pulmonary function, and body composition on functional exercise capacity in acromegalic patients? J Phys Ther Sci, 2015; 27: 719–724. doi: 10.1589/jpts.27.719
16. McNab TL, Khandwala HM. Acromegaly as an endocrine form of myopathy: case report and review of literature. Endocr Pract, 2005; 11: 18–22. doi: 10.4158/EP.11.1.18
17. Biagetti B, Simó R. GH/IGF-1 abnormalities and muscle impairment: from basic research to clinical practice. Int J Mol Sci, 2021; 22: 415. doi: 10.3390/ijms22010415
18. Thomas SG, Woodhouse LJ, Pagura SM, et al. Ventilation threshold as a measure of impaired physical performance in adults with growth hormone excess. Clin Endocrinol (Oxf), 2002; 56: 351–358. doi: 10.1046/j.1365-2265.2002.01476.x
19. Lima TRL, Kasuki L, Gadelha MR, et al. The effectiveness of a therapist-oriented home rehabilitation program for a patient with acromegaly: a case study. J Bodyw Mov Ther, 2019; 23: 634–642. doi: 10.1016/j.jbmt.2019.01.006
20. Woodhouse LJ, Mukherjee A, Shalet SM, et al. The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. Endocr Rev, 2006; 27: 287–317. doi: 10.1210/er.2004-0022
21. Nagulesparen M, Trickey R, Davies MJ, et al. Muscle changes in acromegaly. Br Med J, 1976; 2: 914–915. doi: 10.1136/bmj.2.6041.914
22. Martel-Duguech L, Alonso-Pérez J, Bascuñana H, et al. Intramuscular fatty infiltration and physical function in controlled acromegaly. Eur J Endocrinol, 2021; 185: 167–177. doi: 10.1530/EJE-21-0209. Erratum in: Eur J Endocrinol, 2021;185: X3
23. Guedes da Silva DP, Guimarães FS, Dias CM, et al. On the functional capacity and quality of life of patients with acromegaly: are they candidates for rehabilitation programs? J Phys Ther Sci, 2013; 25: 1497–1501. doi: 10.1589/jpts.25.1497
24. Füchtbauer L, Olsson DS, Bengtsson BÅ, et al. Muscle strength in patients with acromegaly at diagnosis and during long-term follow-up. Eur J Endocrinol, 2017; 177: 217–226. doi: 10.1530/EJE-17-0120
25. Mizera Ł, Halupczok-Żyła J, Kolačkov K, et al. Myokines in acromegaly: an altered irisin profile. Front Endocrinol (Lausanne), 2021; 12: 728734. doi: 10.3389/fendo.2021.728734
26. Sarica A, Quattrone A, Mechelli A, et al. Corticospinal tract abnormalities and ventricular dilatation: a transdiagnostic comparative tractography study. Neuroimage Clin, 2021; 32: 102862. doi: 10.1016/j.nicl.2021.102862
27. Kot-Bryćko K, Kot M, Pudlo R. Wodogłowie normotensyjne – zapomniane, ale groźne. Psychiatr Dypl, 2014; 11: 31–34. doi: 10.3389/fendo.2021.728734
28. Lima TRL, Kasuki L, Gadelha M, et al. Physical exercise improves functional capacity and quality of life in patients with acromegaly: a 12-week follow-up study. Endocrine, 2019; 66: 301–309. doi: 10.1007/s12020-019-02011-x
29. Hatipoglu E, Topsakal N, Erkut Atilgan O, et al. Physical and cardiovascular performance in cases with acromegaly after regular short-term exercise. Clin Endocrinol (Oxf), 2015; 83: 91–97. doi: 10.1111/cen.12708
30. Yang Y, Landin-Wilhelmsen K, Zetterberg H, et al. Serum IGF-1 is higher in patients with idiopathic normal pressure hydrocephalus than in the population. Growth Horm IGF Res, 2015; 25: 269–273. doi: 10.1016/j.ghir.2015.10.001
31. Shprecher D, Schwalb J, Kurlan R. Normal pressure hydrocephalus: diagnosis and treatment. Curr Neurol Neurosci Rep, 2008; 8: 371–376. doi: 10.1007/s11910-008-0058-2. doi: 10.1007/s11910-008-0058-2