

## Case Report

# Rehabilitation management in two siblings with Von Hippel-Lindau syndrome: A case series

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## Abstract

Von Hippel Lindau (VHL) is a hereditary multiple neoplasia syndrome. We report a case series of two siblings with Von Hippel Lindau (VHL) disease admitted to the rehabilitation department after surgical excision of Central Nervous System (CNS) haemangioblastomas. These clinical cases present rehabilitation challenges in VHL disease. We present a 39-year-old brother and his 45-year-old sister, with the diagnosis of incomplete spinal cord injury (SCI) associated with VHL syndrome lesions. The female patient was diagnosed with chronic motor incomplete cervical SCI and the male patient with acute motor incomplete thoracic SCI. Our target was to increase their functionality and improve their quality of life. Both underwent a comprehensive inpatient rehabilitation program. Programs were individualized as the female patient was admitted 15 years after her spinal cord surgical intervention, while the male patient's admission was after 4 months of his surgery.

**Keywords:** Haemangioblastoma, Rehabilitation, Siblings, Von Hippel-Lindau Syndrome

## Introduction

Von Hippel Lindau (VHL) is a hereditary disease that is associated with the development of cysts and tumors emerging throughout many distinct locations of the human body. It is inherited in an autosomal dominated pattern and is caused by a germline mutation in the VHL tumor suppression gene that is located on the chromosome 3p25-26<sup>1</sup>. There are also some sporadic cases (about 20%), associated with somatic mutations in the VHL gene with no family history<sup>2,3</sup>. VHL's incidence is about one case in 36.000 births and the penetrance is more than 9 out of 10 persons by 65 years old<sup>1,2,4</sup>.

The clinical manifestations of VHL disease include Central Nervous System (CNS) haemangioblastomas,

retinal haemangioblastomas, renal cysts and renal cell carcinoma (RCC), pheochromocytoma (PCC), pancreatic cysts and tumors, endolymphatic sac tumors, epididymal cystadenomas and broad ligament cystadenomas<sup>2,4,5</sup>. VHL syndrome is classified into Type 1 and Type 2 depending on genotype-phenotype correlations, the presence or absence of PCC and the frequency of developing other tumors<sup>2</sup>.

Haemangioblastomas, retinal and CNS, are the most common features of VHL disease<sup>5-7</sup>. Approximately, 7 out of 10 patients with VHL will develop haemangioblastoma in the CNS, mostly located in the cerebellum, spinal cord and brainstem<sup>7,8</sup>. According to other authors, VHL patients that develop craniospinal haemangioblastomas can be more than 8 out of 10<sup>6</sup>. Almost all of them, 9 out of 10, will develop multiple haemangioblastomas<sup>6,7</sup>.

In a major series of haemangioblastomas, 32% of the tumors were localized in the spinal canal and location distribution was 36%, 48% and 16%, in the cervical, thoracic and lumbar area, respectively<sup>9</sup>. CNS haemangioblastomas can cause significant symptoms and neurological deficits explained by their location<sup>6-8</sup>. Spinal cord tumors can cause pain, sensory deficits, spinal ataxia, incontinence and paresis<sup>10</sup>. Now days the risk of dying due to VHL has decreased; however, CNS haemangioblastoma is accounting

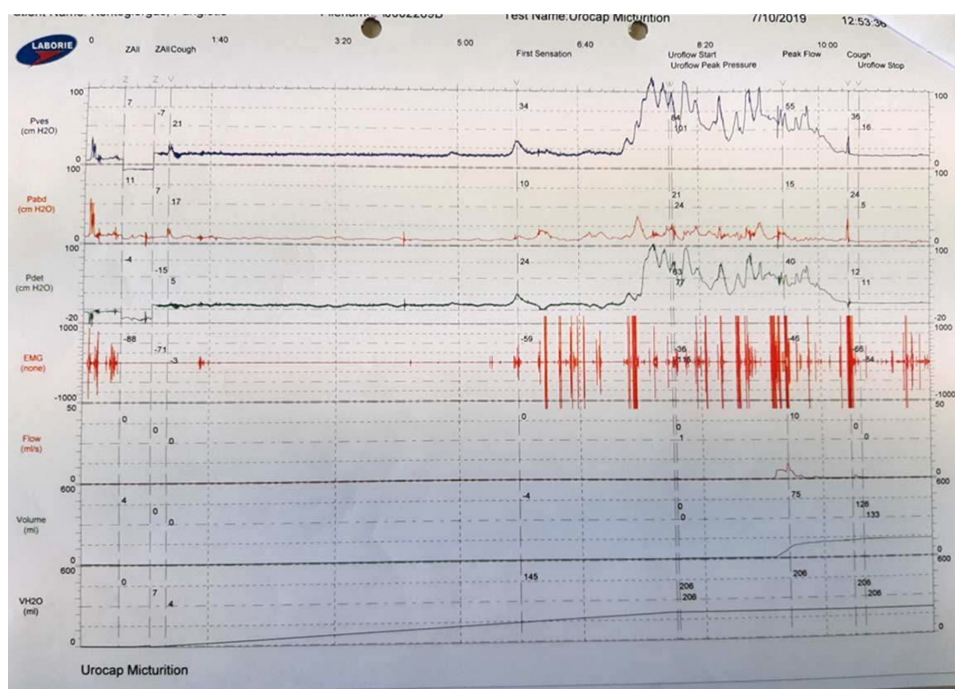
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**Figure 1.** Urodynamic study of the male subject: neurologic bladder dysfunction (detrusor overactivity (Pdet) and detrusor - external sphincter dyssynergia (EMG).

for almost 40% of deaths, and rates were higher in females<sup>11</sup>.

Surgery is the best treatment option for symptomatic tumors although it can be associated with morbidity due to postoperative neurological complications<sup>8</sup>. Neurological stability or improvement can occur after resection<sup>6</sup> but multiple surgeries can lead to neurological deterioration and surgical complications<sup>7</sup>. Due to this complex condition the management is complicated by the presence of neoplasms in various organs<sup>4</sup>. Complete surgical resection is usually feasible; however, the neurological impairments make these subjects good candidates for neurorehabilitation to diminish these sequelae<sup>12</sup>.

The present case study aimed to present the challenges in the rehabilitation treatment of patients with Von Hippel Lindau disease after surgical excision of CNS haemangioblastomas.

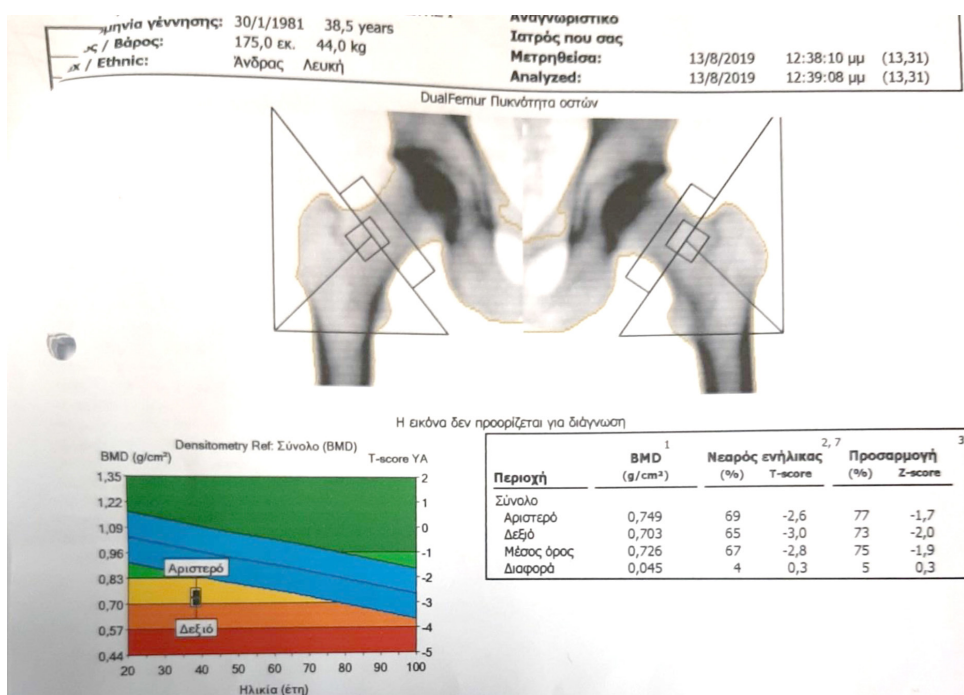
## Case 1

A 45-year-old female, was referred to the rehabilitation department after her last surgical intervention for the cerebellum's cystic lesion. She had diagnosed with VHL disease at the age of 27 years. Since her diagnosis she had undergone many surgical procedures including excision of intramedullary haemangioblastoma of cervical spinal cord and spinal fusion, excision of left cerebellum's haemangioblastoma with suboccipital craniectomy, revision of spinal fusion C3-C6 and somatectomy C4-C5/placement

of expandable cage, partial left nephrectomy due to clear cell renal cell carcinoma and 2<sup>nd</sup> excision of left cerebellum's node and cystic lesion (possible haemangioblastoma - pending histological confirmation).

Upon admission the neurological examination revealed bilateral pyramidal tract syndrome, worse on the left side of the body - motor incomplete cervical SCI, mild cognitive impairment (Mini Mental Score, MMS: 28/30, referred mild memory loss), signs of mild cerebellar dysfunction (dysmetria and bradykinesia), decreased range of motion of the left shoulder and left ankle joint, superficial sensory disturbances and proprioceptive dysfunction clinically equivalent to Brown-Sequard syndrome, limited left hand function, decreased muscle strength in both upper limbs, mainly in the left one. The motor assessment included examination of upper and lower limbs muscles. The Manual Muscle Test (MMT) in the supine position revealed that most muscles in her right upper limb were grade 4/5 or stronger and in her right lower limb were grade 5/5, whereas most muscles in her weaker left upper limb were grade 2/5 and in her left lower limb 4/5. She was classified according to American Spinal Injury Association (ASIA) impairment scale (AIS)/International Standards for Neurological Classification of SCI (ISNCSCI) as AIS D. She was able to stand and walk under supervision with no technical aids. Her Body Mass Index (BMI) was 20.2 Kg/m<sup>2</sup> (weight: 46 Kg, height: 1.51 m).

Blood examination revealed B12 and vitamin D deficiency,



**Figure 2.** Dual-energy X-ray absorptiometry (DXA). Male's total BMD (gr/cm<sup>2</sup>) and Z- score values measured at both hips (-1.7 left and -2 right), respectively.



**Figure 3.** X-ray of the knee region revealed osteoporotic bone image (right face and profile view).

B12: 168 picogram/milliliter (pg/mL), Vit D: 10 nanogram/milliliter (ng/mL) and hypercholesterolemia, LDL: 189 milligram/deciliter (mg/dL). Chest X-ray was normal, the cervical spine X-ray depicted the spinal fusion. The abdominal ultrasound revealed the partial nephrectomy (left) and multiple renal cysts in both kidneys (2 cysts on the right and 1 cyst on the left) causing no pelvicalyceal dilation. There were also many gallstones. No bladder dysfunction was detected (chronic case). Taking into consideration her risk of osteoporosis we measured her spine bone density with dual x-ray absorptiometry (DXA) which was found within normal range. The female patient was premenopausal and had a Z-score -1.4 at the lumbar spine. Calcium and vitamin D were prescribed according to DXA and lab results, based on current national guidelines for premenopausal women. She also had symptoms of isolated neck pain. To relieve pain we used cold and heat therapy, non-steroidal anti-inflammatory drugs (NSAIDs) and skeletal muscle relaxants. Due to depression she received venlafaxine 150 mg and alprazolam.

The patient attended an inpatient rehabilitation program which consisted of one 30-minute session of physical therapy and one 30-minute session of occupational therapy 5 days/week. The physiotherapist conducted a prescribed physical therapy program which included respiratory and active assisted range of motion exercises, stretching, strength and balance exercises and a walking plan. Occupational therapist focused on cognitive impairments, to correct positions for transfer, improve capabilities on self-care deficits: dressing, toileting and bathing etc.

After 2 months she was discharged home. Upon discharge she was able to walk independently and complete the daily tasks alone.

## Case 2

A 39-year-old male admitted with acute motor incomplete thoracic SCI (T3 level), with a known diagnosis of VHL syndrome. He underwent surgical procedures due to his disease including excision of haemangioblastomas of posterior cranial fossa and left nephrectomy. Also, he had a history of whole-body radiation therapy, ventriculoperitoneal (VP) shunt and surgical excision of haemangioblastoma T3 and patellectomy T2-T4.

The patient was referred to the rehabilitation department after his last surgical intervention for the spinal cord lesion. Upon admission the neurological examination revealed bilateral pyramidal tract syndrome, positive cerebellar signs, and urinary dysfunction (requiring a urethra indwelling catheter). He had no sitting balance. MMS examination was 30/30. Most muscles in his upper limbs were grade 4/5, whereas most muscles in his lower limbs were grade 3/5. According to ASIA/ISCoS International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) the patient was classified as AIS D<sup>13</sup>. Assessment of muscle tonus revealed spasticity grade 2 according to Ashworth scale in the lower limbs and presence of pyramidal signs

such as hyperreflexia (right>left), Babinski sign, and mild clonus at the right ankle. He had symptoms of generalized pain, mainly in the limbs. His pain was evaluated according to Visual Analogue Scale (VAS) as moderate (5/10). He also had symptoms of neurogenic bowel dysfunction (NBD), mostly constipation and a Foley catheter was placed due to patient's incontinence. His BMI was 14.67 Kg/m<sup>2</sup> (weight: 44 Kg, height: 1.75 m).

Blood examination revealed anemia (Hct: 31,3%) and vitamin D deficiency (6 ng/mL). The abdominal ultrasound revealed the left nephrectomy, the hypertrophy of the right kidney, multiple renal cysts in the right kidney and a cystic lesion, a tumor having echomorphology of angiomyolipoma, nephrolithiasis with no dilation of the pelvicalyceal system and a tumor in the adrenal gland. Chest x ray was normal. To evaluate his bone density we performed a DXA. Z-score values, measured at both hips, were in osteopenia range (-1.7 left and -2 right, respectively). However, knee X-ray revealed osteoporotic bone image. Vitamin D was prescribed according to DXA and lab results, based on current national guidelines for men. The urodynamic study revealed neurologic bladder dysfunction, detrusor overactivity and detrusor- external sphincter dyssynergia. That led to the need of performing intermittent self-catheterization. Limitation was the co-existing cerebellar syndrome, resulting in lack of coordination of the upper limbs' movements, as well as the absence of a carer.

His NBD was treated with bowel management program, suppositories and laxatives. For his pain we used opioids in combination with non-opioid analgesics with excellent results. Oral baclofen was used for the generalized spasticity with frequent assessment and dose adjustment. For depressive symptoms he received venlafaxine 150 mg and trazodone.

He attended an inpatient rehabilitation program which consisted of one 30-minute session of physical and one 30-minute session of occupational therapy 5 days/week. The physiotherapist conducted a prescribed physical therapy program which included gradually mobilization from supine in standing position using Tilt Table, bed side physiotherapy including respiratory exercises, active assisted range of motion exercises and stretching, and after re-education of sitting with graduated balance, and torso strengthening and respiratory exercises in sitting position, sitting on the bed with support, sitting on wheelchair, and later on mobilizing the patient early with knee ankle foot orthosis and standing – walking combined with balance and strengthening exercises in upright position. Occupational therapy department organized a plan to adapt to his functionality and good cognitive status to correct positions for transfer, improve capabilities on self-care deficits: dressing, toileting, bathing and mobility (ambulation with a wheelchair).

The patient was discharged home after 3 and half months of neurorehabilitation. Upon discharge he was able to perform therapeutic walking and was wheelchair bound. He performed activities of daily living independently.

## Discussion

Due to the progressive and high frequency of multiple tumors in various organ systems, rehabilitation of a certain lesion is complicated by the residual impairments from other tumors. A multidisciplinary rehabilitation team and an individualized neurorehabilitation program is needed for the optimum results in these patients<sup>4</sup>.

Our target was to improve individuals' functionality and quality of life to the maximum possible level through symptomatic treatment of the complications caused by the CNS lesions or by their surgical removal. CNS haemangioblastomas can lead to neurological deficits, especially when patients underwent multiple surgeries for removing lesions that reoccur<sup>7</sup>. Frequent signs and symptoms of patients with VHL who underwent resection are hypaesthesia (83%), weakness (65%), gait ataxia (65%), hyperreflexia (52%), pain (17%) and incontinence (14%)<sup>10</sup>.

In our cases the haemangioblastomas were located in the cervical and thoracic spinal cord area (in female and male, respectively), which are the most common sites<sup>14</sup>. Both our cases had undergone multiple surgeries to remove the brain and spinal cord haemangioblastomas and the male was admitted to the rehabilitation department during the fourth decade of his life. The occurrence of disabilities has been found to be more common between the third and the fourth decades of life in VHL patients<sup>15</sup>. During hospitalization in the rehabilitation department the patients participated in individualized physical and occupational therapy programs. A remarkable finding was the minor cognitive impairment in the female (chronic case) and the absence of any cognitive impairment in the male patient. Both were able to attend the rehabilitation program consistently. Patients were assessed clinically regularly, and their therapeutic program and medication were modified accordingly. Taking into consideration the possible risk of bone loss, we assessed early during their hospitalization their bone density with DXA, to determine the type of exercise program, the applied loading and the need to prescribe medications according to the results. Respiratory exercises to prevent complications during the acute care and rehabilitation, strength exercises to preserve and improve muscle strength, active assisted range of motion exercises and stretching to reduce stiffness, prevent contractures, manage spasticity and improve joints' range of motion. Patients who present with incomplete spinal cord lesions show additional benefits of standing associated with development of postural control, strengthening of antigravity muscles, improved balance reactions, maintenance of functional ranges of movement, skill acquisition in components of gait and decreased spasticity and pain<sup>16</sup>. However, mobilization to the upright position may trigger hemodynamic problems, including hypotension and syncope and caution is needed in patients with tetraplegia irrespective of whether their lesion was complete or incomplete<sup>17</sup>. Coordination exercises were used to improve upper limbs function and the accuracy of their movements. Balance exercises were used to improve stability and walking

was trained on smooth and on uneven terrain.

In the female person serum biochemical tests that revealed B12 deficiency and hypercholesterolemia may be explained by recent studies according to which vitamin B12 deficiency is associated with higher total cholesterol based on hypothesis of DNA methylation changes<sup>18</sup>. Low B12 levels may rather be a result of chronic malnutrition, which was suggested from her low BMI. On the contrary we did not find similar findings in the case of the male patient who was in the acute phase. However, both were vitamin D deficient as defined by levels of 25-OH Vitamin D <20 ng/ml. This is a common finding in neurodisabled persons. Possible reasons may be a combination of low dietary vitamin D intake, sun exposure avoidance due to depression or sun-sensitizing drugs, insufficient sun exposure due to hospitalizations and reduced mobility<sup>19</sup>.

Bone density with DXA was found to be within osteopenia limits in the two siblings. However, knee and pelvis X-ray revealed osteoporotic bone image in the male. BMI is a reliable predictor of knee osteoporosis in subjects with spinal cord injury and lower BMI was associated with increased risk of knee osteoporosis<sup>20</sup>. An exponential decrease of BMD around the knee, greater compared to hip, is found as a result of time after SCI. Both femur and tibia experience increased magnitude and bone loss rate, with reaching steady-state levels 1.2-3.6 years after injury<sup>21</sup>. A recent position statement of International Society of Clinical Densitometry recommends knee region for BMD testing in SCI<sup>22</sup>.

To relieve pain we may use cold and heat therapy, non-steroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants, whereas pregabalin is used for the neuropathic pain and oral baclofen for the generalized spasticity with frequent assessment and dose adjustment<sup>23</sup>. Incontinence is not so often, but urodynamic study may reveal detrusor overactivity and detrusor - external sphincter dyssynergia<sup>10</sup>. However, due to the co-existing cerebellar syndrome in this case the patient was not able to perform intermittent self-catheterization or even catheterization due to the lack of a carer. Both received medications for depression. It has been observed that there can be a level of distress in a part of VHL patients and their relatives or partners<sup>24,25</sup>. Not only patients but also their carers face depressive or anxiety symptoms<sup>26</sup>. Also, the need of surveillance in these patients has been found to affect negatively their quality of life<sup>24</sup>.

We are not aware of any other case study presenting brother and sister with von Hippel- Lindau disease. There was no evidence for retinal or pancreatic involvement in both siblings. However, others reported a case with identical twin sisters concluding that spontaneous mutation might be causal for VHL in their cases<sup>27</sup>.

The rehabilitation program helped both individuals to partially recover and manage most complications. Besides of reporting a rare presentation for hemangioblastomas in siblings, this article adds to the general knowledge because it presents complications during the rehabilitation program and comprehensive handling of these patients in the chronic and acute phase.

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