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Abducens Nerve Palsy - A Rare Complication of Spinal Cord Stimulator Insertion: Case Report and Literature Review

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Background: Spinal cord stimulation (SCS) is an emerging therapeutic intervention for intractable chronic pain. However, SCS surgery is not exempt from complications such as lead migration, infections, hardware malfunction and neurological deficits.

Case Report: We present this case report on bilateral abducens nerve palsy, as a rare iatrogenic complication of SCS system insertion in a 65-year-old man with intractable chronic pain. After failing conservative treatment and explant, he underwent corrective strabismus surgery and achieved symptom control.

Conclusion: The case presents a diagnostic and management challenge due to the nature of his presentation, neuroimaging pitfalls and limited high-quality evidence for management. We recognise cranial nerve palsy as a potential, yet real, complication of SCS surgery, of which abducens nerve palsy presents significant detriment to patients lives. As SCS continues to expand in clinical practice, inevitably, so will its iatrogenic sequela signalling the need for greater recognition and formation high-quality evidence for efficacious management.

Key words: Spinal cord stimulation insertion, abducens nerve palsy, chronic pain, case report

BACKGROUND

Although spinal cord stimulator (SCS) insertion for neuromodulation is a safe and effective procedure for treatment of a variety of chronic pain syndromes, complications of this intervention have been reported (1). These have been attributed to device-related complications, including lead migration, lead fracture, implantable pulse generator (IPG) site pain, or surgical complications, which include postdural puncture headache, infection, and hematoma (1). In this report, we present a case of the bilateral abducens nerve (CNVI) palsy as a potentially rare complication associated with SCS insertion. Informed consent was obtained from the patient.

CASE PRESENTATION

We present a 65-year-old man with progressive chronic back pain secondary to bilateral radiculopathy over his 4-decade-long career as a nurse. His past medical history includes hypertension, type-2 diabetes mellitus, hypercholesterolemia, bile acid malabsorption, anxiety, depression, and eustachian tube dysfunction. Potential

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surgical targets for treatment were not demonstrated on magnetic resonance imaging (MRI) spine and SCS insertion was recommended for neuromodulatory management of his pain.

The patient underwent SCS insertion, in July 2021, where dual lead electrodes were fluoroscopically placed posteriorly up to the T8 level, with direct implantation of the IPG as per the current guidelines from the Neuromodulation Society of the United Kingdom and Ireland. There were no obvious complications during and immediately after the procedure, leading to discharge.

Two days postprocedure, the patient developed bilateral hearing loss and tinnitus accompanied by episodes of severe headache, nausea, and vomiting. He represented to hospital on day 3 with blurred vision, diplopia, bilateral ocular abduction deficits worse on right eye, and right esotropia with left dominant fixation (Fig. 1). He also experienced severe vertigo and unsteadiness. His headaches were postural, worse when upright, sitting or standing, and improved with recumbence. The SCS remained unprogrammed during the onset of his symptoms.

In approaching diagnostic differentials, a full neurological examination was conducted to determine the presence of neurological deficits that may assist in localization. Examination revealed no signs of ataxia, hemisensory, or hemiparesis deficits. COVID-19 testing was negative.

Ophthalmological examination for intraocular pressure and fundoscopy were normal. External examination was unremarkable without features of proptosis, chemosis, lid swelling, or ptosis, making extraocular muscle pathology, such as thyroid eye disease or idiopathic orbital inflammation, unlikely. Characteristic clinical manifestations associated with myasthenia gravis, including Cogan's lid twitch sign (i.e., overshoot twitch of lid retraction following eye return of primary position from downgaze) and fatigability, and temporal arteritis, including temporal tenderness, jaw claudication, and scalp tenderness, were not observed. There were no pathologies identified in the other cranial nerves (CNs).

The patient was diagnosed with isolated bilateral ocular abduction deficits and esotropia, which was most likely attributed to bilateral CNVI palsies. The disease pattern can be represented by a lesion anywhere from the nerve's origin to the lateral rectus muscle, suggesting the potential role of several pathological mechanisms along the neuroanatomical course of the nerve itself.

As the SCS was MRI conditional, MRI brain and whole spine were performed 20 days postprocedure. MRI brain demonstrated no features suggestive of intracranial hypotension. There was also no evidence of subdural collections, brain stem sagging, or pituitary bulging. In keeping with mild-to-moderate small-vessel disease, the brain parenchyma contained multiple foci of fluid-attenuated inversion recovery (FLAIR) hyperintensities predominantly within the cerebral cortex, deep white matter, and pons. There was also a high T2/FLAIR signal in the dorsal pons without corresponding restricted diffusion. T2 hyperintensity in the dorsal pons coinciding with low-pressure headaches may suggest relation to intracranial hypotension though other salient features were not clearly visualized on MRI. The progressive evolution of his symptoms over 24 hours and bilateral involvement of CNVI was unlikely to be attributable to stroke.

Of note, MRI did demonstrate an incidental pseudomeningocele, which was characterized as a localized left dorsal subcutaneous fluid collection at the IPG site. Intraspinally, the dorsal epidural space was largely obscured by artifacts from the SCS. However, no significant epidural collection was visualized. A lumbar puncture was not carried out, due to the exacerbatory risk of further complications, on suspicion that his diplopia was possibly caused by an inadvertent dural tear during the procedure.

Management

Conservative treatment measures, including rest, hydration, and analgesia, were first implemented, fol-

Fig. 1. Twenty-six days post-operation. Physical examination demonstrating motility of both eyes when looking left (a), forward (b), and right (c).

lowed by application of an eye patch to mitigate against diplopia. The SCS was explanted, and alterations were made to the patient's prescription glasses with optometry. His symptoms continued to persist, and his recovery timeline and prognosis were unclear. He underwent strabismus surgery for visual correction at 6 months, which resulted in resolution of his visual symptoms. His diplopia, tinnitus, and low-pressure headaches have since resolved.

DISCUSSION

CNVI palsy is a common cause of acquired horizontal diplopia with abduction impairment and an esotropia ipsilateral to injury (2). However, CNVI palsy following SCS insertion is a rare phenomenon. There is only one other case report (3) that describes transient CNVI palsy following SCS insertion, where there was a comparable description of prodromal tinnitus and headache. We propose that the underlying etiology in this case was a subclinical leak of cerebrospinal fluid (CSF) at the location of epidural fixation of the IPG leading to intracranial hypotension (3,4).

Literature stemming back to the 1900s has reported cases of isolated CNVI palsy as a rare complication following various CSF diversion procedures, such as lumbar puncture, lumbar drain, spinal anesthesia, myelography, ventriculoperitoneal shunting, and spinal surgery (Tables 1 and 2). The gauge size of spinal needles may play a role in the occurrence of this phenomenon, thereby the development of smaller needles may have decreased the incidence of this complication (4). Although uncommon in general, CN dysfunction following dural puncture has been reported and includes CNIII, CNIV, CNV, CNVII, CNVIII, CNIX, and CNX, with impairment to CNVI being most common (4).

Other less specific signs preceding CNVI palsy, such as postural headache, nausea, and vomiting, as seen in this case, are common in similar literature and indicate CSF depletion. It has been theorized that the progressive decrease in CSF pressure with subsequent sagging of the intracranial contents may be responsible for disturbances of the CNs, especially CNVI (4).

The neuroanatomical course of CNVI makes it susceptible to injury at several distinct locations, resulting in unique clinical patterns. Damage to the pons in the context of the CNVI may present as ipsilateral horizontal gaze palsy, contralateral weakness, and internuclear ophthalmoplegia. Inflammation or trauma to the petrous bone may cause decreased hearing, hemo-

Table 1. Literature findings of Abducens nerve palsy following spinal surgery.

Age	Gender	Procedure	Needle gauge	Type	CNVI palsy	Preceding symptoms	Post-operative Onset (days)	Symptom duration (days)	Primary Management	Secondary Management	Reference (x)	Year
65	M	Surgical - SCS	14		Bilateral		2	180	Surgical (Strabismus surgery), EBP	Conservative, Orthoptics (eye patch)	Current case	2021
47	F	Surgical - Discectomy	-	-	Left	Headache	12	34	Surgical (dural repair), chest drain	Orthoptics, Conservative (bed rest)	Sandon et al., 2016 (8)	2016
48	M	Surgical - Discectomy	-	-	Right	Headache	14	11	Surgical (dural repair)	-	Joo et al., 2013 (9)	2013
48	M	Surgical - Discectomy	-	-	-	-	21	91	Surgical (revision thoracotomy and dural repair), chest drain	-	Khurana et al., 2013 (10)	2013
46	M	Surgical - Vertebrectomy	-	-	Bilateral	Headache	-	152	-	-	Khurana et al., 2013 (10)	2013
36	M	Surgical - Vertebrectomy	-	-	Left	Headache	10	30	-	-	Sudhakar et al., 2013 (11)	2013

Table 1 cont. Literature findings of Abducens nerve palsy following spinal surgery.

Age	Gender	Procedure	Needle gauge	Type	CNVI palsy	Preceding symptoms	Post-operative Onset (days)	Symptom duration (days)	Primary Management	Secondary Management	Reference (x)	Year
53	M	Surgical - Discectomy	-	-	Left	Headache	42	28	Surgical (dural repair)	-	Thomas et al., 2012 (12)	2012
61	M	Surgical - Spinal Fusion	-	-	Right	Headache	4	35	-	Medical (Hydration, Analgesia (NSAIDs)), Conservative (bed rest)	Cho et al., 2009 (13)	2009
22	F	Surgical - Tumour resection C1/C2	-	-	Right	-	3	28	-	-	Nakagawa et al., 2003 (14)	2003
56	M	Surgical - SCS	-	-	Left	Headache	5	90	-	Conservative (bed rest)	Wolfensberger and Borruat, 2000 (3)	2000
59	M	Surgical - Decompression, spinal fusion	-	-	Right	-	0	183	-	Orthoptics (Eye patch)	Barsoum et al., 1999 (15)	1999
67	M	Surgical - VPS	-	-	Bilateral	Headache, nausea and vomiting	14	77	-	-	Espinosa et al., 1993 (16)	1993
69	M	Surgical - VAS	-	-	Right	Headache	9	63	-	-	Espinosa et al., 1993	1993
69	M	Surgical - VPS	-	-	Bilateral	Headache	7	-	Surgical (extraocular muscle surgery)	-	Espinosa et al., 1993	1993
70	F	Surgical - VAS	-	-	Right	Hearing loss	7	60	-	-	Black et al., 1981 (1)7	1981
72	F	Surgical - VAS	-	-	Bilateral	Headache, nausea and vomiting	8	84	Surgical - Shunt revision, insertion of antisiphon device	-	Black et al., 1981	1981

SCS: Spinal cord stimulator; VPS: Ventriculoperitoneal Shunt; VAS: Ventriculoatrial Shunt

Table 2. Literature findings of Abducens nerve palsy following cerebrospinal fluid shunting procedures.

Age	Gender	Procedure	Needle gauge (G)	Type	CNVI palsy	Preceding symptoms	Post-operative Onset (days)	Symptom duration (days)	Primary Management	Secondary Management	Reference (x)	Year
36	F	SA	27	Whitacre	Right, CNXII	Headache	730	91	EBP	Medical (Hydration, Analgesia, Caffeine), Conservative (bed rest)	Pirbudak, 2020 (18)	2020
37	F	EC	-	-	Right	Headache, nausea and vomiting, neck and shoulder pain/stiffness	7	-	EBP	Medical (Hydration, Analgesia (paracetamol), Barbiturate, and Caffeine)	Wardhan & Wrazidlo, 2020 (19)	2020
62	F	LPS	-	-	Bilateral	Headache	5	90	Removal of LP shunt	Orthoptics (Eye patch), Medical (Steroids (dexamethasone))	Alhalal, Al-Salman & Anazi, 2018 (20)	2018
32	F	EC	-	Tuohy	Left	Headache	6	75	EBP	Orthoptics, Supportive (Hydration, Analgesia (paracetamol), Caffeine), Conservative (bed rest)	Cluff et al.,, 2016 (21)	2016
25	F	EA	-	-	Bilateral	Headache, neck pain, numbness and tingling in her arms	3				Mahulikar et al., 2016 (22)	2016
32	F	EA	-	-	Left, CNV, CNVII	Numbness on left side of face	2	90		Steroids, antiviral	Gilca et al., 2015 (23)	2015
29	F	SA	22	Quincke	Right	Headache, nausea and vomiting, neck and shoulder pain/stiffness , opthalmalgia	3	28	EBP	Conservative (bed rest)	Adakli et al., 2014 (24)	2014
27	M	SA	-	-	Bilateral		4			Conservative	Duran et al., 2014 (25)	2014

Table 2 cont. Literature findings of Abducens nerve palsy following cerebrospinal fluid shunting procedures.

Age	Gender	Procedure	Needle gauge (G)	Type	CNVI palsy	Preceding symptoms	Post-operative Onset (days)	Symptom duration (days)	Primary Management	Secondary Management	Reference (x)	Year
32	M	SA	22	Quincke	Bilateral	-	1	7	-	Medical (Caffeine, Theophylline)	Basaranoglu and Saidoglu, 2013 (26)	2013
28	F	SA	26	Atraucan	Left	-	5	61	-	Medical (Hydration, Caffeine, Analgesia (NSAIDs), Steroids)	Saracoglu et al., 2013 (27)	2013
21	F	EA	-	-	Left	Headache	-	-	EBP	-	Sudhakar et al., 2013 (10)	2013
71	F	EC	-	-	Bilateral	-	14	60	-	-	Sudhakar et al., 2013	2013
38	F	EC	-	-	Left	Headache, neck and shoulder pain/stiffness	6	150	-	-	Sudhakar et al., 2013	2013
22	M	EC	-	-	Right	-	9	14	-	-	Sudhakar et al., 2013	2013
35	F	EC	-	-	Bilateral	Headache, nausea and vomiting, neck and shoulder pain/stiffness	6	60	EBP	Medical (Analgesia (opioids))	Sudhakar et al., 2013	2013
65	F	LD	14	Tuohy	Left	-	0	91	-	Orthoptics (Eye patch, Fresnel prism), Medical (Steroids (dexamethasone))	Cain et al., 2012 (28)	2012
28	F	EA	18	Tuohy	-	Headache	7	90	EBP	Medical (Hydration, Analgesia (paracetamol), Theophylline)	Fiala et al., 2012 (29)	2012
25	F	SA	-	-	Left	-	14	-	Surgical - craniotomy with evacuation of bilateral SDH	-	Hassen and Kalantari, 2012 (30)	2012

Table 2 cont. Literature findings of Abducens nerve palsy following cerebrospinal fluid shunting procedures.

Age	Gender	Procedure	Needle gauge (G)	Type	CNVI palsy	Preceding symptoms	Post-operative Onset (days)	Symptom duration (days)	Primary Management	Secondary Management	Reference (x)	Year
31	F	SA	26	Quincke	-	Headache	3	15	-	Medical (Hydration, Analgesia (paracetamol, NSAIDs (aspirin, ibuprofen)) caffeine, mannitol)	Amini-Saman et al., 2011 (31)	2011
41	F	LP	15	Tuohy	Right	Headache, Vomiting	42	120	Surgical (Evacuation of subdural hematoma)	Baclofen	Magro et al., 2011 (32)	2011
26	F	EC	18	Tuohy	Right	Headache	5	50	EBP	Medical (Hydration, Analgesia (paracetamol), Caffeine) Conservative (bed rest)	Corbonnois et al., 2010 (33)	2010
46	M	EA	18	Tuohy	-	Headache	6	21	EBP	Medical (Hydration, Analgesia (paracetamol), Caffeine)	Schober et al., 2010 (34)	2010
53	F	LP	14	-	Left	Headache	0	183	-	Medical (Hydration, Analgesia (NSAIDs)), Conservative (bed rest)	Yaman et al., 2010 (35)	2010
22	F	EC	-	-	Right	Headache	6	14	EBP, anticoagulation, acetazolamide – treatment of cortical thromboses		Bial et al., 2009 (36)	2009
40	M	LP	-	-	Left	Headache	4	28	-	-	Anwar et al., 2008 (37)	2008
60	M	IT	17	Tuohy	Left	Headache	7	60	-	Medical (Hydration), Conservative (Bed rest)	Gibbins et al., 2008 (38)	2008

Table 2 cont. Literature findings of Abducens nerve palsy following cerebrospinal fluid shunting procedures.

Age	Gender	Procedure	Needle gauge (G)	Type	CNVI palsy	Preceding symptoms	Post-operative Onset (days)	Symptom duration (days)	Primary Management	Secondary Management	Reference (x)	Year
31	M	LD	-	-	-	Headache, neck and shoulder pain/stiffness, fever	7	14	EBP	Orthoptics (Eye patch), Medical (Hydration, Caffeine, Analgesia)	Mannes et al., 2008 (39)	2008
-	F	EA	18	-	-	Headache	7	28	EBP	-	Yatziv et al., 2008 (40)	2008
45	F	LP	22	Quincke	Bilateral	Headache	5	639	EBP	Orthoptics (Eye patch, Prism glass)	Béchard et al., 2007 (41)	2007
43	M	LP	-	-	Left	Headache, neck and shoulder pain/stiffness	12	61	EBP	-	Khemka and Mearza, 2006 (42)	2006
35	M	EA			Left	Headache	11			Medical (antihypertensive therapy)	Thurtell et al., 2006 (43)	2006
38	M	SA	22	Quincke	Bilateral	Headache, nausea and vomiting	4	183	-	Medical (Steroids (prednisolone), Analgesia (NSAIDs))	Kose et al., 2005 (44)	2005
40	F	EC	17	Tuohy	Bilateral	Headache, nausea and vomiting	10	36	EBP	-	Arcand et al., 2004 (45)	2004
41	F	LD	14	Tuohy	Right	Headache	1	22	Lumbar drain removal	-	Cheung et al., 2003 (46)	2003
27	F	EC	25	Sprotte	Left	Headache	5	91	EBP	-	Chohan et al., 2003 (47)	2003
38	F	SA	25	Quincke	Bilateral	Headache, neck and shoulder pain/stiffness, photophobia	14	14	Surgical (burr hole evacuation of hematoma)	Medical (Analgesia, Steroids), Conservative (bed rest)	Slowinski et al., 2003 (48)	2003
43	M	LP	20	Yale	Left	Headache	4	122	-	Orthoptics (Glass prism)	Niedermüller et al., 2002 (49)	2002
37	M	LP	-	-	Left, CNIV	Headache	5	608	EBP	Orthoptics	Follens et al., 2001 (50)	2001
33	M	LP	22	-	Bilateral	Headache	9	213	-	-	Thomke et al., 2000 (50)	2000
61	M	LP	22	-	Right	-	7	122	-	-	Thomke et al., 2000	2000

Table 2 cont. Literature findings of Abducens nerve palsy following cerebrospinal fluid shunting procedures.

Age	Gender	Procedure	Needle gauge (G)	Type	CNVI palsy	Preceding symptoms	Post-operative Onset (days)	Symptom duration (days)	Primary Management	Secondary Management	Reference (x)	Year
58	M	IT	14	Tuohy	Left	Headache	6	14	EBP	Medical (Hydration, Analgesia (opioids, paracetamol)), Conservative (bed rest)	Velarde et al., 2000 (52)	2000
13	F	EC	18	Tuohy	Left, CNIII	-	1	1	Cessation of epidural infusion	-	Haughton and Chalkiadis, 1999 (53)	1999
32	F	EA	17	Tuohy	Left	Headache	6	56	EBP	Orthoptics (Eye patch)	Szokol and Falleroni, 1999 (54)	1999
38	F	IT	-	-	Right	Headache, nausea and vomiting, dizziness	8	122	EBP	Medical (Hydration, Analgesia, Steroids)	Dumont et al., 1998 (55)	1998
32	F	EA	16	Tuohy	Left	Headache	10	365	EBP, Surgical (extraocular muscle surgery)	-	Johnson et al., 1998 (56)	1998
47	F	MY	-	-	Right	Headache, nausea and vomiting, dizziness	6	122	-	Orthoptics (Fresnel prism)	Dinakaran et al., 1995 (57)	1995
33	F	MY	-	-	Left	Headache, opthalmalgia	1	14	-	-	Bell et al., 1994 (58)	1994
39	F	MY	-	-	Left	Headache, nausea and vomiting, dizziness	10	183	-	-	Bell et al., 1994	1994
41	F	MY	-	-	Left	Headache	7	91	-	-	Bell et al., 1994	1994
47	F	MY	-	-	Left	Headache	5	91	-	-	Bell et al., 1994	1994
46	F	MY	-	-	Right	Headache	12	122	-	-	Bell et al., 1994	1994
26	F	EC	17	-	-	Headache	8	91	EBP	-	Dunbar and Katz, 1994 (59)	1994
31	M	LP	20	-	Bilateral	Headache, neck and shoulder pain/stiffness, opthalmalgia	10	122	EBP	-	Dunbar and Katz, 1994	1994

SA: Spinal Anaesthesia; EC: Epidural Catheter; LPS: Lumbar Puncture Shunt; LP: Lumbar Shunt; LD: Lumbar Drain; EA: Epidural Anesthesia; IT: Intrathecal Injection; MY: Myelography; CSA: Continuous Spinal Anaesthesia. Reports prior to 1994 on abducens nerve palsy following CSF diversion procedures can be found in Nishio et al (2004)'s review article (60).

tympanum or facial numbness, and pain. Masses and lesions in the cavernous sinus or superior orbital fissure can result in Horner's syndrome or other accompanying CN palsies, while CNVI palsy accompanied by proptosis or conjunctivitis may point to a local pathology in the ipsilateral orbit (2). CNVI is particularly predisposed to injury secondary to alterations in intracranial pressure, where it may experience structural displacement and resultant nerve injury. This is exemplified where the nerve curves at an almost right angle over the angular apex of the petrous bone. Caudal displacement of the brain stem, typically seen in intracranial hypotension, results in the stretching of CNVI into Dorello's canal. Its course also puts it in positions of direct compression from the clivus, basilar artery, and anterior inferior cerebellar artery.

Generally, a presentation of isolated CNVI palsy warrants a medical workup, including erythrocyte sediment rate, metabolic and biochemistry profiles, and a full blood count. MRI brain with contrast and diffusion-weighted imaging should be performed to exclude intracranial masses, acute brain stem ischemia, and assess for CNVI enhancement. If MRI fails to capture the source of impairment, a lumbar puncture for CSF analysis and opening pressure measurement can be done. Additionally, immunological studies, such as acetylcholine receptor antibody testing, should be considered with appropriate clinical suspicion.

Our patient presented with bilateral diplopia in the absence of other neurological deficits, ocular pain, and papilledema. Combined with prodromal tinnitus, postural headache, vomiting, and nausea, his clinical picture strongly corresponded to intracranial hypotension, most likely a secondary inadvertent intraprocedural dural puncture resulting in subclinical CSF leak (4). This is substantiated by the presence of a spinal pseudomeningocele following SCS insertion as seen on MRI.

Pseudomeningoceles are typically asymptomatic but can become symptomatic, usually presenting with delayed onset. Symptoms can be broadly grouped as direct or indirect symptoms, where direct symptoms are sac-related spinal symptoms, while indirect symptoms refer to localized swelling, lumbar pain, myelopathy, and radiculopathy. D'Esneval et al (6) described spinal pseudomeningocele as a complication following accidental dural puncture in spinal procedures and has a particularly high incidence in revision spinal surgery as opposed to primary spinal surgery due to epidural fibrosis. Epidural fibrosis is a possible contributing factor in our patient, given his extensive history of spinal procedures for pain management.

While our hypothesis primarily revolves around intracranial hypotension, it is important to note that modest and temporary increases in intracranial pressure (ICP) can also be associated with pseudomeningoceles (6). In this context, Bosscher (7) demonstrated via mathematical modelling, how changes in epidural, subarachnoid, and intracranial pressures and volumes can lead to neurological complications. ICP fluctuations or the occurrence of large variation pressure waves can contribute to the stretching or compression of CNs, thereby resulting in direct axonal and vascular damage. This damage can lead to CN dysfunction as seen in our case. Intracranial pressure-volume dynamics vary significantly among individuals due to factors like spinal anatomy and underlying pathologies, and is a relevant variable that should be considered in SCS procedures through CSF pressure monitoring (7).

Treatment of isolated CNVI palsy includes maximization of visual function, conservative adaptation therapy, and any measure to increase the patient's quality of life. Treatment modalities include alternate patching, prism glass therapy, botulinum toxin (Botox) injection, epidural blood patch, steroids, and strabismus surgery (4). Current literature on complications associated with SCS insertion remains almost nonexistent. This patient was treated with strabismus surgery in best interest after exhausting all conservative and supporting measures, which resulted in positive improvement.

CONCLUSIONS

We report bilateral CNVI palsy as a rare and debilitating complication of SCS surgery that significantly detriments patient independence and quality of life. This complication should be considered as neuromodulation continues to evolve in the world of pain medicine.

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