ORIGINAL ARTICLE

Long-Term Outcomes of Percutaneous Radiofrequency Thermocoagulation of Gasserian Ganglion for 2nd- and Multiple-Division Trigeminal Neuralgia

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■ **Abstract**

Objectives: The objective of this study was to examine the long-term outcome of percutaneous radiofrequency thermocoagulation (PRT) of the Gasserian ganglion for the 2nd division and multiple division trigeminal neuralgia (TN), compared to the isolated 3rd division TN.

Methods: One hundred and forty-eight procedures performed in 89 patients with typical TN between April 2004 and September 2011 in a single pain center were retrospectively analyzed. Baseline characteristics of these patients, immediate outcome, duration pain-free, and complications were obtained from their medical records and questionnaires sent in June 2012. Duration pain-free was assessed by Kaplan–Meier analysis.

Results: Of the 148 PRT of the Gasserian ganglion, 37 procedures were performed for isolated 2nd-division TN (V2 TN), 67 procedures were for both 2nd- and 3rd-division TN (V2 + V3 TN), and 38 procedures were for isolated 3rd-division TN (V3 TN). The remaining 6 procedures were performed for V1 + V2 TN and V1 + V2 + V3 TN. Immediate success rates of PRT for V2 TN, V2 + V3 TN, and V3 TN were 100%, 86.6%, and 100%, respectively, whereas the durations pain-free for V2 TN and V2 + V3 TN were significantly shorter than that for V3 TN (9, 12, and 36 months, respectively: $P = 0.012$).

Conclusion: For 2nd-division TN and multiple-division TN, less long-term pain relief after PRT of the Gasserian ganglion can be expected compared with that for isolated trigeminal 3rd-division neuralgia, even if immediate pain relief is achieved. ■

Key Words: trigeminal neuralgia, trigeminal neuralgia, idiopathic, radiofrequency ablation, Gasserian ganglion, outcomes

INTRODUCTION

Trigeminal neuralgia (TN) is a neuropathic disorder, characterized by paroxysmal electric shock-like pain confined to the distribution of one or more divisions of the trigeminal nerve. To patients refractory to medication therapy, surgical treatments such as microvascular decompression (MVD), Gamma knife radiosurgery, and percutaneous destructive procedures can be selected as therapeutic options. Among these

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procedures, percutaneous radiofrequency thermocoagulation (PRT), characterized by the lack of a need for endotracheal anesthesia and short hospitalization, remains the most common procedure.[1] Although the recurrence rate appears to be higher than for MVD,[1–3] this procedure can be selected for elderly patients who reject other invasive procedures or for patients who recur after MVD, Gamma knife radiosurgery or other percutaneous destructive procedures such as alcohol injection, glycerol rhizotomy, and balloon compression.

Although several studies have shown the efficacy of PRT of the Gasserian ganglion,[4–7] the long-term outcome has not been well evaluated according to each trigeminal branch other than the isolated 3rd division, which is easily accessible.[8] Since thermocoagulation for 2nd-division or multiple-division TN is technically more difficult than for isolated 3rd-division TN because of its anatomical distribution, the duration of pain relief appears to be shorter despite its excellent immediate outcome. Therefore, we investigated the long-term outcome of PRT of the Gasserian ganglion, targeted for 2nd-division or multiple-division TN compared with isolated 3rd-division TN.

METHODS

The institutional committee of Shiotani Pain Clinic approved this study protocol. Between April 2004 and September 2011, 89 patients with medically refractory idiopathic TN underwent PRT of the Gasserian ganglion. All procedures were performed under fluoroscopy. Patients were sedated by injection of 0.05 mg/kg midazolam during the procedures. A 22-gauge, straight radiofrequency lesioning electrode with a stylet (Sluyter-Mehta cannula) was inserted through the foramen ovale, and the tip of the electrode was positioned appropriately in the Gasserian ganglion. Final location of the electrode tip was adjusted by the patient's response to electrical stimulation of 0.1 to 0.3 V at 50 Hz. When the proper location of the electrode had been confirmed, 0.2 mL of 2% lidocaine was injected through the needle to produce anesthesia in the diseased division and radiofrequency themocoagulation was then performed at 90°C for 180 seconds. In principle, a single lesion was made per procedure.

The immediate success of the treatment was examined at 2 weeks after the procedures. Immediate success was defined as satisfactory pain relief in the involved divisions. Additional PRT of the Gasserian ganglion or a peripheral nerve branch was performed if satisfactory pain relief was not achieved in the diseased area at the first clinical visit after the procedure. These additional procedures were considered as the part of initial intervention. Once satisfactory pain relief was obtained, the patients were then followed up every 3 months. Patients were questioned about the degree of pain relief, sensory loss, and treatment complications such as dysesthesia, muscle weakness, and eye problems at each clinical visit. Complete recurrence is defined as constant lancinating paroxysmal pain recurring partially and fully in the same divisions and repeat treatment being required. The level of initial sensory loss was graded as anesthesia: complete loss of touch sensation, severe hypesthesia: loss of $\geq$ 50% of touch sensation, and mild hypesthesia: loss of $<$ 50% of touch sensation. Repeated PRT of the Gasserian ganglion or PRT or alcohol block of the peripheral nerve was performed when complete recurrence was found.

In June 2012, questionnaires were mailed to all patients to ask them about the present degree of pain relief. Data regarding the recurrence of pain was retrieved from the questionnaires and the medical records. Patients who neither visited periodically after the procedure nor returned questionnaires were considered to be lost to follow-up, and patients who did not return questionnaires were counted in the analysis alone up to their last contact.

The probability of remaining pain free was calculated by Kaplan–Meier analysis, and comparisons between the subgroups were performed using log-rank test. Statistical significance was assigned at P value of < 0.05.

RESULTS

Between April 2004 and September 2011, 148 PRT of the Gasserian ganglion were performed for 89 patients with typical TN. Patients with atypical facial pain and those with TN secondary to brain tumor or multiple sclerosis were excluded. The patient characteristics are described in Table 1. Most patients received oral medication such as carbamazepine or alternative anticonvulsant before visiting our clinic. Two patients did not take any medication owing to their side effects. Prior to visiting our clinic, 56 patients (62.9%) underwent one or more surgical treatments such as MVD, Gamma knife radiosurgery, PRT, or alcohol block. In most patients, the 2nd (V2), 3rd (V3), or both divisions were affected, whereas 6 patients had pain in the 1st (V1) division accompanied by V2 and/or V3.

Table 1. Baseline Characteristics of Patients

Age at the first procedure at our clinic, mean (range)	69.4 (38–88)
Sex, no. (%)	
Female	59 (66.3)
Male	30 (33.7)
Prior drug treatment, no. (%)	
Carbamazepine or other anticonvulsant	87 (97.8)
None	2 (2.2)
Prior procedure, no. (%)	
Microvascular decompression	5 (5.6)
Gamma-knife	18 (20.2)
Radiofrequency thermocoagulation or alcohol injection	39 (43.8)
None	27 (30.3)
Distribution of pain localization, no. (%)	
V2 only	19 (21.3)
V3 only	29 (32.6)
V1 and V2	3 (3.4)
V2 and V3	35 (39.3)
V1, V2, and V3	3 (3.4)

Of 148 PRT of the Gasserian ganglion, 37 procedures were performed for isolated 2nd-division TN (V2 TN), 67 procedures were for both 2nd- and 3rd-division TN (V2 + V3 TN), and 38 procedures were for isolated 3rd-division TN (V3 TN). The remaining 6 procedures were performed for V1 + V2 TN and V1 + V2 + V3 TN. Ten patients were lost to follow-up.

The immediate success rates of the procedures at 2 weeks after the procedure were 100% for isolated V3 TN, 100% for isolated V2 TN, and 86.6% for V2 + V3 TN. Nine procedures (13.4%) for V2 + V3 TN required an additional procedure at the first clinical visit after discharge, and all of those patients had complete pain relief after the additional procedure. Six patients who had pain in the V1 division required additional PRT or alcohol block of the supraorbital nerve, which is a peripheral branch of the ophthalmic nerve. The PRT for V3 TN showed better long-term outcome than those for V2 TN or V2 + V3 TN ($P = 0.0012$). The probabilities of pain relief of V3 TN being maintained were 80.2% at 12 months and 54.9% at 24 months, whereas those of V2 TN and V2 + V3 TN were 40.5% and 49.3% at 12 months, and 19.6% and 17.1% at 24 months, respectively. The median pain-free durations for patients with V2 TN, V2 + V3 TN, and V3 TN were 9, 12, and 36 months, respectively (Figure 1).

Of 104 procedures for V2 TN and V2 + V3 TN, 39 (37.5%) were associated with anesthesia, 30 (28.8%) with severe hypesthesia, and 10 (9.6%) with mild hypesthesia in the selective 2nd division at 2 weeks of the initial procedure. For the remaining 26 (24.8%) procedures, information on sensory loss was not available from the medical records. The median pain-free durations were 18 months in patients with anesthesia,

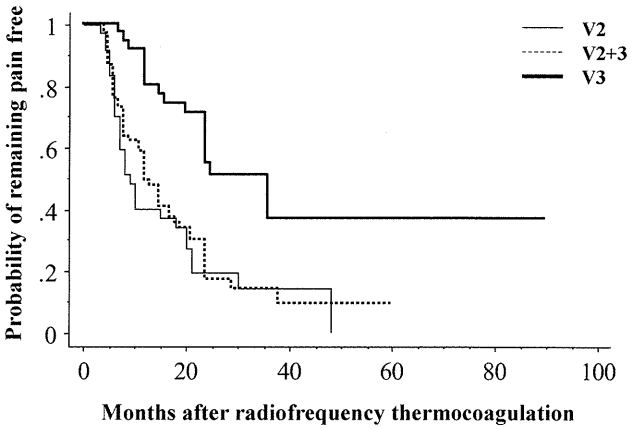

Figure 1. Kaplan–Meier analysis showing the probability of remaining pain-free after radiofrequency thermocoagulation according to the affected division. 37 procedures were for isolated V2 TN, 38 procedures for isolated V3 TN, and 67 procedures for V2 + V3 TN.

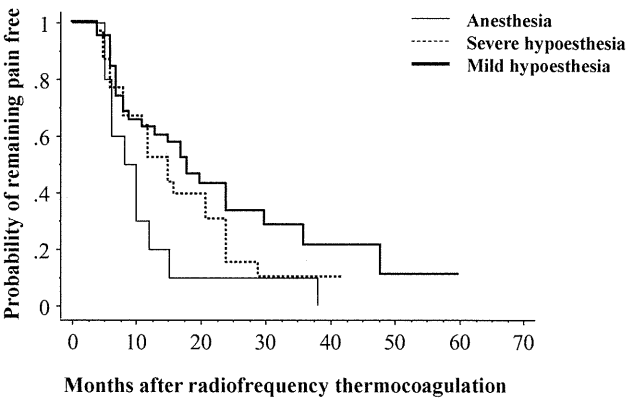

Figure 2. Kaplan-Meier analysis showing the probability of remaining pain-free after radiofrequency thermocoagulation for V2 and V2 + 3TN according to the severity of sensory loss of the V2 division.

15 months in patients with severe hypesthesia, and 9 months in patients with mild hypesthesia. The probability of remaining pain-free differed significantly between patients with anesthesia and those with mild hypesthesia ($P = 0.017$) (Figure 2).

Of 37 procedures for V2 TN, 28 (75.7%) patients required repeated PRT of the Gasserian ganglion or PRT of infraorbital nerve from 3 to 48 months after the initial procedure. Likewise, of 73 procedures for multiple-division TN, 57 (78.1%) patients required repeated PRT of the Gasserian ganglion or PRT of peripheral nerves from 4 to 38 months. Of these 57 patients, 2 (3.5%) patients were treated for recurrence in V1, 47 (82.5%) were for recurrence in V2, and 8 (14.0%) were for recurrence in V3 (Table 2). There was no mortality

Table 2. Treatments for Pain Recurrence

		Multiple-division TN (N = 57)		
		Recurred division		
	Isolated V2 TN (N = 28)	V1 (N = 2)	V2 (N = 47)	V3 (N = 8)
Repeat PRT of GG	16	0	33	7
PRT of infraorbital nerve	12	0	14	0
PRT of mandibular nerve	0	0	0	1
PRT or alcohol block of supraorbital nerve	0	2	0	0

GG, Gasserian ganglion; PRT, percutaneous radiofrequency thermocoagulation.

related to the procedures. Major complications included 10 cases of weakness of masticatory muscles (12.2%), 4 intolerable dysesthesia (4.9%), and 4 eye problems without keratitis (4.9%).

DISCUSSION

The present study examined the long-term outcomes of PRT of the Gasserian ganglion, targeted for 2nd-division or multiple-division TN. We showed that (1) the immediate success rate was high regardless of the affected division, except for V1 division; (2) the long-term outcomes of pain relief were better in the isolated V3 TN than in V2 TN or V2 + V3 TN; and (3) the duration pain-free for V2 TN and V2 + V3 TN depended on the degree of sensory loss in the V2 division.

Although the present study was unable to clarify the precise mechanism of differences in durability of response in patients between with V3 division and with multiple divisions TN, it could be the result of anatomical and/or technical difficulties of selective thermocoagulation to approach maxillary fibers. When treating V2 pain, adjusting the position of the electrode is technically tough because the electrode needs to be placed more medial and deeper to touch the maxillary fibers rather than the mandibular fibers. If advanced too deep, it could involve the ophthalmic fibers, which affect the corneal sensation, indicating the difficulty of selective thermocoagulation of the V2 division.[9] Nevertheless, for V2 TN and V2 + V3 TN, even if the electrode contacts only the inferior part of maxillary fibers, thermal effects of radiofrequency could spread to destroy the upper part of the maxillary fibers away from the electrode. In such cases however, the durability of nerve destruction by diffused heat may not last as long as that by direct effects. That could, in turn, account for our findings that, despite the high immediate success rate, the probability of being pain-free was considerably lower in V2 TN and V2 + V3 TN than in isolated V3 TN, for which direct lesion was easy to achieve. A curved tip electrode could be beneficial to achieve a more precise approach to affected nerve fibers, and concurrently to obviate undesirable side effect. However, there is no report to date regarding the rate of recurrence when used the curved tip electrode compared to smaller straight tip electrode.[10]

Once the appropriate location of the needle was determined, a single thermocoagulation was made after injecting a small dose of lidocaine into the Gasserian ganglion. This method is much simpler and less stressful for both physicians and patients to complete each procedure with immediate success and with no need for additional intravenous anesthesia for lesioning. Moreover, it is less likely to cause harm as long as the operator confirms that contrast dye stays within the trigeminal cistern without flowing into a blood vessel or the subarachnoid space. However, the efficacy of thermocoagulation could not be assessed intra-operatively, resulting in the variability of sensory loss and long-term efficacy. Such variability of treatment efficacy was more likely to be observed when treating for V2 and V2 + 3 TN than for V3 TN, in which the durability of pain relief was comparable with previous studies.[11–14] In particular, in the treatment of V2 + V3 TN, discrepancy in the severity of the lesion may occur between the V2 and V3 regions. In fact, we have often experienced situations in which the V3 division is well thermocoagulated while not achieving a sufficient lesion in the V2 division. Some may recommend several lesions be made to reduce the unevenness of lesioning by altering the location of the electrode based on patients' self-assessment.[11] However, it may be challenging to obtain reliable assessment for the degree and extent of lesioning obtained from patients under sedation. Additionally, since it often takes a few days to reach an ultimate outcome, we believe that several lesions per procedure could result in overtreatment.

Our experience showed that pain in the V2 division was more likely to recur than pain in the V3 division, and the degree of sensory loss in the V2 division may be a decisive factor for the durability of pain relief for V2 TN and V2 + V3 TN. With recurrence in the V2 division, satisfactory pain relief was obtained by either repeat PRT of the Gasserian ganglion or PRT of the infraorbital nerve. PRT of the infraorbital nerve is an even simpler thermoneurotomy than that of the Gasserian ganglion, and we selected this peripheral procedure

if the recurrent pain was limited to the infraorbital area, not including the superior alveolar area. In 6 patients who had V1 pain, pain relief was not accomplished only by PRT of the Gasserian ganglion because we intentionally tried to avoid lesioning ophthalmic fibers. However, it was complemented by additional percutaneous destructive procedures of the supraorbital nerve that did not affect corneal sensation. These peripheral procedures were also effective as a treatment when recurrence was limited to the V1 division. Some may argue that the recurrence rate was high especially as to V2 and multiple division TN. Since the recurred pain could be treated effectively by repeat procedure, we do not believe that they were serious events.

There are some reports recommending balloon compression or glycerol rhizotomy for TN confined to the V1 or V2 division, or TN affecting more than one division.[2,9] However, there is no prospective study to compare the outcome of PRT to those of balloon compression or glycerol rhizotomy. The median pain-free duration of these procedures has been reported to be from 6 to 42 months,[15–19] which may depend on previous procedures and medical history.[2] History of previous surgery, and frequent repeat balloon compression and glycerol rhizotomy have been reported to be associated with a higher risk of technical failure,[9,15–17] which may not be seen in frequent repeat PRT.[13] In our series, nearly half of the patients had one or more relevant factors in their surgical history prior to visiting our clinic, and we believe these recurrent cases could benefit from PRT rather than from other percutaneous procedures.

There are, however, some disadvantages reported in PRT, such as a higher rate of corneal sensation deficit compared with that in other percutaneous destructive procedures.[9,20] In our series, the incidences of eye problems, dysesthesia, and weakness of masticatory muscles after the procedure were similar to those in other studies on balloon compression[21–23] or glycerol rhizotomy.[12,24,25] Masticatory muscle weakness was likely to be seen early after the procedures. However, this symptom recovered gradually and did not seem to have a major detrimental effect on the patients' daily life.

There are several limitations affecting the interpretation of the data herein. *First*, owing to the constraints associated with retrospective analyses, the follow-up intervals among the subjects varied and 11.2% were lost to follow-up. An insufficiency of systematic recording of sensory loss might also preclude more accurate evaluation of the durability in the present study. *Second*, there are few reports addressing the therapeutic effects dependent on each trigeminal division and it may not be appropriate to simply compare our results with previous reports in which wide variations in technique and equipment existed. Some may argue that our treatment approach cannot be extrapolated to other institutions. A prospective study should be warranted to validate the results of present study.

CONCLUSIONS

Although the immediate success rate is high, the durability of pain relief of PRT for 2nd-division TN and multiple-division TN could not be expected to be as great as for isolated trigeminal 3rd-division neuralgia. However, the recurrence of pain can be treated safely and effectively by repeated PRT of the Gasserian ganglion or percutaneous destructive procedures of peripheral nerves.

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LETTERS TO THE EDITOR

A Rare Cause of Lumbar Radiculopathy: Perineural Cyst

Disclosure: All the authors disclose no financial support, including "ghost" writing; all authors mentioned on the title page substantially contributed to the writing, and there is no other sources of potential bias (e.g., expert testimony, device or process ownership, or financial interest, etc).

Dear Editor,

Lumbosacral perineural cysts are formed by the arachnoid membrane of the nerve root at the lumbosacral level. Sacral perineural cysts called Tarlov cysts were identified by Tarlov for the first time in 1938 [1]. Langdown et al. reported that Tarlov cysts, which are a relatively common finding on lumbosacral magnetic resonance imaging (MRI) scans, have a prevalence of 1–2%, and only 13% of these cysts are symptomatic [2]. Symptomatic perineural cysts, which are relatively less common when compared with Tarlov cysts, are found in the lumbar region where they cause nerve root compression, which then leads to radiculopathy mimicking disc herniation [3]. Herein, we report a case with lumbosacral radiculopathy due to a perineural cyst that responded well to a transforaminal epidural steroid injection.

A 19-year-old male patient was admitted to the Physical Medicine and Rehabilitation Clinic presenting with complaints of lower back and left leg pain ongoing for 6 weeks. He had no history of trauma, heavy lifting, morning stiffness, night pain, fever, nor weight loss, and his pain was relieved by rest. His physical examination showed bilateral paravertebral muscle spasm, limited and painful lower back flexion. Straight leg raise test was positive at 40 degrees on the left and negative on the right. Achilles and patellar deep tendon reflexes were normal bilaterally. Sensory and motor examination revealed normal results except his left extensor hallucis longus strength of 4/5. His lumbar MRI scan revealed a 7 × 4-mm cystic lesion with well-defined contours (perineural cyst) in close proximity with the left L5 root (Figure 1A and B). We thought that the symptoms were due to this compression and did a left L5 fluoroscopy-guided transforaminal epidural steroid injection. His pain level before the procedure was 5/10 in visual analogue scale (VAS) that regressed to 0/10 after the injection.

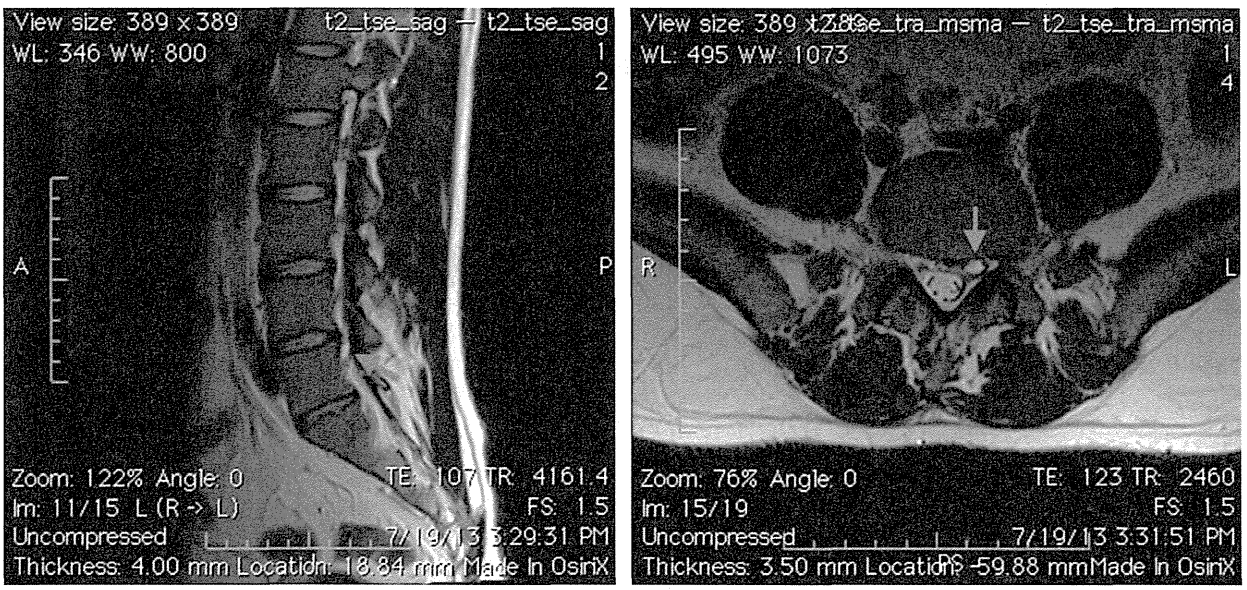

Figure 1 Lumbar spine T2-weighted sagittal (A) and axial (B) magnetic resonance imaging (MRI) scans showing a 7 × 4-mm cystic lesion (red arrows) with well-defined contours (perineural cyst) in close proximity with the left L5 root. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

We found three cases with lumbar perineural cysts mimicking lumbar disc herniation by causing nerve root compression in the literature search. Our case resembles the one published by Takatori et al., where the patient presented with pain at his lower back and left leg, and a perineural cyst compressing the nerve root at L5 on the left side was found during the MRI scan [3].

In our case, patient's complaints of left radicular pain and the fact that a perineural cyst was found at L5 level on the patient's left side during MRI scanning in accordance with his complaint suggest that presence of the cyst might be the source of his pain. However, in our case, the MRI scans revealed a bulging at L4–L5 level, but it was decided that this was not significant enough to cause the patient's symptoms.

Today, both surgical and conservative methods can be used for the treatment of lumbosacral perineural cysts; however, which method is more effective remains a matter of debate. There are studies which suggest that oral or epidural steroid treatments should be considered as the first choice of treatment in cases of perineural cysts presenting with complaints of lower back and radicular pain [4]. Supporting the findings of these studies, in our study, an hour after a left L5 transforaminal epidural steroid injection was administered to the patient, his pain level was decreased from 5 to 0 in VAS that remained for 6-month follow-up.

In conclusion, even though they are usually asymptomatic, it should be kept in mind that symptomatic lumbosacral perineural cysts that can mimic disk herniation should be taken into consideration when obtaining a differential diagnosis between the causes of lower back and radicular extremity pain and that transforaminal epidural steroid injection might be a good treatment option for these cysts.

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Chronic Neck Pain and Episodic Vertigo and Tinnitus

The patient was managed by B Peng, X Pang, and H Yang. The report was prepared by B Peng.

No conflict of interest and financial interest were declared.

Dear Editor,

The term "cervical vertigo" was coined by Ryan and Cope [1] in 1955, which involves vertigo, tinnitus, hearing loss, and neck pain. To date, however, the syndrome remains only a theoretical possibility awaiting a reliable clinical test to demonstrate its independent existence. We present a case with cervical vertigo syndrome that is diagnosed and managed successfully to support its existence and provide direct clinical evidence.

In July 2012, a 54-year-old female presented with 24 years of history of chronic neck pain and episodic vertigo and tinnitus irresponsive to extensive conservative therapies. The patient was free of any other neurological symptoms. Her general and otolaryngologic and neurological exams were completely normal. Cervical spine MRI scan indicated the cervical lordosis disappeared and cervical 5/6 disc protruded slightly (Figure 1). The computerized tomography angiography (CTA) scan of the cerebral vessels showed that the left vertebrobasilar artery was normal, whereas the right vertebrobasilar artery was absent (Figure 2).

Cervical discography was recommended to identify the pain-generating site [2,3]. The patient underwent provocative discography at C5/6 and C6/7 discs. The result of discography identified the C5/6 disc as the source of pain. Accordingly, C5/6 disc decompression was recommended using radiofrequency nucleoplasty [3,4]. Cervical disc nucleoplasty percutaneous disc decompression utilized patented Coblation technology for partial disc removal. The Coblation Mode was used at the tip of the Perc-DC Spine Wand (DC SpineWand, Artho-Care Spine, Stockholm, Sweden). The patient felt the

symptoms of neck pain and vertigo almost completely disappeared after treatment. In last follow-up in August 2013, her symptoms never relapsed. The patient was reexamined with CTA and color Doppler duplex scan of left vertebrobasilar artery the second day after treatment. The diameters of left vertebrobasilar artery were measured from CTA before and after treatment. The peak systolic maximal blood flow velocity (Vmax, cm/s) and the intervascular flow volume (mL/min) of left vertebrobasilar artery were calculated and compared according to the results of color Doppler ultrasound evaluation before and after treatment. The results showed that the diameter of left vertebral artery increased dramatically after treatment (starting segment: 4.3 vs 3.5 mm; atlas transverse process segment: 3.8 vs 3.3 mm). The Vmax also increased after treatment (57.2 vs 51.8 cm/s) and so did the flow volume (175.8 vs 117.4 mL/min).

Insufficient blood supply to posterior circulation is called vertebrobasilar insufficiency. The most common complaint in patients with vertebrobasilar insufficiency is vertigo. It has been showed that the patients with cervical spondylosis complaining of vertigo have significant lower blood flow parameters than nonvertigo patients with cervical spondylosis [5]. Clinical studies have indicated that anterior cervical discectomy and fusion can eliminate the accompanied vertigo syndrome in the patients with cervical radiculopathy or myelopathy [6]. A potential association between cervical spondylosis and vertebral artery occlusion resulting in vertigo due to vertebrobasilar insufficiency was suggested [7].

Because the patient did not respond to conservative therapies, the percutaneous radiofrequency nucleoplasty

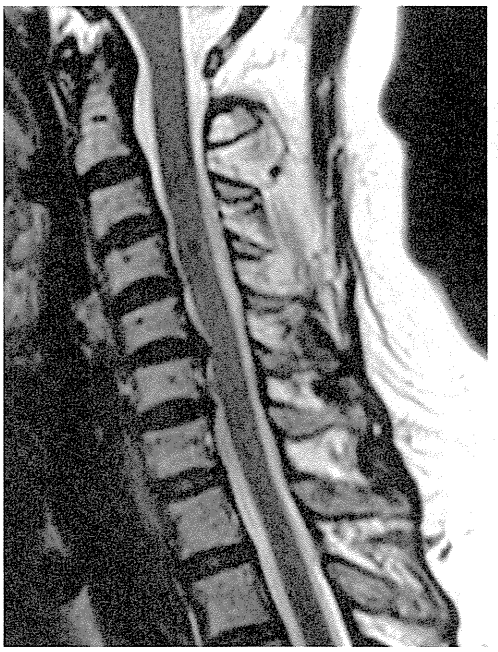

Figure 1 MRI showed C5/6 disc protrusion.

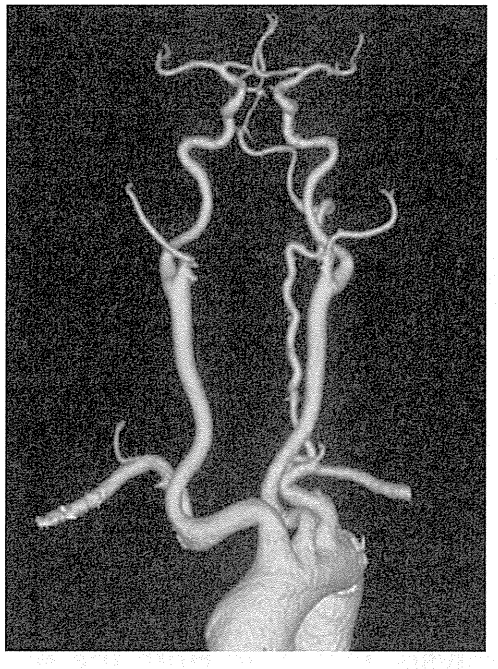

Figure 2 Computerized tomography angiography (CTA) showed the absence of right vertebrobasilar artery.

should be considered [3,4]. Open fusion surgery cannot guarantee relief especially when treatment is for the patient with chronic neck pain without radiculopathy or myelopathy. As the patient is congenitally defected with the absence of the right vertebrobasilar artery, the posterior circulation cannot be compensated by collateral circulation from the right vertebrobasilar artery. When left vertebrobasilar artery is occluded under stimulation, there will be insufficiency of blood supply. According to our current study, we think that there is a direct link between cervical disc pathology and vertebrobasilar insufficiency as mediated by sympathetic nerves. Degenerative painful disc may have a significant increase in inflammatory cytokines that could theoretically irritate the sympathetic nerves that innervate cervical disc and cause vertebral artery insufficiency [8,9], which subsequently induces ischemia of vestibulocochlear organ.

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Neurolysis Targeting Both the Aorticorenal Ganglia and Lumbar Sympathetic Plexus for Kidney Tumor–Related Pain

Dear Editor,

Neurolysis of the celiac plexus and/or the retrocrural splanchnic nerves is a valuable approach to treat upper abdominal organ-related pain, particularly pancreatic cancer pain [1]. Few reports, however, have demonstrated celiac plexus block for kidney-related pain. The kidney is governed by a diverse nerve supply, such as sympathetic, parasympathetic, and sensory afferent fibers [2], and its related pain radiates from the flank and back to the hypogastric area, rather than from the upper abdominal region. Although sensory and autonomic nerve supply is relayed *via* the celiac plexus, it is questionable whether patients with kidney-related pain can benefit from celiac plexus neurolysis. We report a case of neurolytic block targeting both the aorticorenal ganglia and the upper lumbar sympathetic plexus for metastatic kidney tumor-related pain.

A 41-year-old man, diagnosed with spindle cell sarcoma in the right lower leg 6 months previously, was admitted to our hospital because of uncontrolled right-side

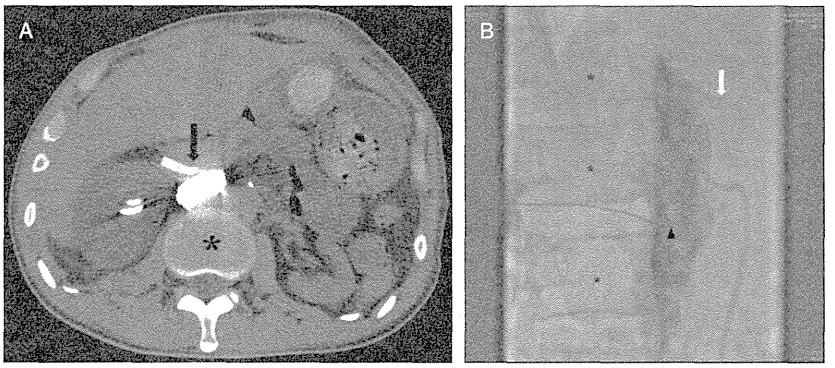

Figure 1 (A) Computed tomographic scan shows the contrast dye spread around the right renal artery (arrow) and right-laterally and posteriorly to the aorta at the level of the L1/L2 intervertebral disk (asterisk). (B) Fluoroscopy shows the contrast dye spread ventrally to the L1–L3 vertebrae (asterisks), including at the level of the right renal artery with an endovascular stent (arrow). The needle tip was located at the level of L2/L3 intervertebral disk (arrowhead). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

umbilical pain. For the 2 weeks prior to admission, the patient experienced abdominal discomfort that gradually worsened. Subsequently, a tumor in the lower part of the right renal medulla associated with lymph node swelling around the right renal and superior mesenteric artery was identified by computed tomography (CT) and magnetic resonance imaging. This was diagnosed as metastatic sarcoma. He complained of sharp intense pain in the right umbilical area and intolerable dull pain spreading down to the right hypogastric region, which required a 75 μg/hour transdermal fentanyl patch, accompanied by continuous intravenous infusion of fentanyl at a rate of 30 μg/hour and a bolus of 50 μg of intravenous fentanyl as a rescue using a patient-controlled analgesia (PCA) device. The average numerical rating scale (NRS) ranged between 4 and 6 out of 10, whereas intense pain over NRS 6 was felt when standing or walking for a long time.

As this pain was visceral rather than somatic in origin, a neurolytic block of the celiac plexus, especially targeting the ipsilateral aorticorenal ganglion, was performed. The procedure was performed using a posterior approach with the patient lying on his left side because the patient had difficulty maintaining in the prone position. Under CT guidance to identify the root of the right main renal artery clearly with an endovascular stent that had been placed previously for renal artery stenosis, a 14-cm 21-gauge needle was inserted at the level of the L2 vertebra and was advanced so that the needle tip was placed just right-laterally of the abdominal aorta and inferior to the root of the right renal artery, where upper lumbar sympathetic plexus, the right aorticorenal ganglion, and renal plexus should be located. After confirming that contrast dye did not flow into the bloodstream or an undesirable area, 15 mL of solution of regional anesthetic and contrast dye (0.2% ropivacaine, iohexol) was injected. The contrast spread around the right renal artery, along with the aorta, at the level of L1–L3 lumbar spine was obtained (Figure 1), whereas the solution did not spread to the root of the celiac artery at the level of Th12L1 intervertebral disk, where the celiac ganglia could be located. After confirming pain relief and no neurological problems, 15 mL of 99.5% ethyl alcohol was injected through the needle.

Following the procedure, pain at rest was alleviated to an average NRS of 1–2 out of 10, which was not exacerbated even when walking for a long time. Intravenous fentanyl as PCA was discontinued by tapering for a week, whereas the fentanyl patch was continued for the residual mild abdominal pain. Two weeks after the procedure, he was transferred to a regional hospital with improved pain control.

Noxious stimuli derived from the kidneys pass through the renal plexus, which travels through the celiac ganglia and aorticorenal ganglia [2]. In addition, some sensory fibers directly travel through the upper lumbar sympathetic and aortic plexus [3]. However, it remains unclear which ganglia or plexus is the most responsible for kidney-related pain.

In this patient, the contrast spread along the lateral wall of the aorta at the level of the upper lumbar spine, and extended around the right renal artery, whereas it did not spread to the celiac artery where celiac ganglia should be located. Furthermore, 15 mL of neurolytic agent, which was less than in previously reported studies in which more than 30 mL was used [1,4], was sufficient to alleviate the intractable pain, indicating that satisfactory pain relief was obtained by the blockade of the ipsilateral aorticorenal ganglion and the upper lumbar sympathetic plexus alone. On the other hand, when performing celiac plexus block for upper organ malignancy, celiac artery is considered as the most reliable landmark at the level of Th12 or L1 [4]. For kidney-related visceral pain, however, it may be optimal for the needle tip to be advanced in the caudal direction so that the aorticorenal ganglia and the lumbar sympathetic plexus can be blocked at the same time. This approach can be performed in the same way as the classic lumbar sympathetic plexus block targeting superior ganglion. As no clinical trial regarding the effectiveness of neurolysis for kidney-related visceral pain has been performed, further clinical reports are required to confirm our findings.

In conclusion, neurolysis, targeted to the aorticorenal ganglia and the upper lumbar sympathetic plexus, may provide a key to successful treatment for renal-related visceral pain.

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PLOS ONE

Validity and Reliability of the Japanese Version of the Newest Vital Sign: A Preliminary Study

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Abstract

Health literacy (HL) refers to the ability to obtain, process, and understand basic health information and services, and is thus needed to make appropriate health decisions. The Newest Vital Sign (NVS) is comprised of 6 questions about an ice cream nutrition label and assesses HL numeracy skills. We developed a Japanese version of the NVS (NVS-J) and evaluated the validity and reliability of the NVS-J in patients with chronic pain. The translation of the original NVS into Japanese was achieved as per the published guidelines. An observational study was subsequently performed to evaluate the validity and reliability of the NVS-J in 43 Japanese patients suffering from chronic pain. Factor analysis with promax rotation, using the Kaiser criterion (eigenvalues $\geq$1.0), and a scree plot revealed that the main component of the NVS-J consists of three determinative factors, and each factor consists of two NVS-J items. The criterion-related validity of the total NVS-J score was significantly correlated with the total score of Ishikawa et al.'s self-rated HL Questionnaire, the clinical global assessment of comprehensive HL level, cognitive function, and the Brinkman index. In addition, Cronbach's coefficient for the total score of the NVS-J was adequate (alpha = 0.72). This study demonstrated that the NVS-J has good validity and reliability. Further, the NVS-J consists of three determinative factors: "basic numeracy ability," "complex numeracy ability," and "serious-minded ability." These three HL abilities comprise a 3-step hierarchical structure. Adequate HL should be promoted in chronic pain patients to enable coping, improve functioning, and increase activities of daily living (ADLs) and quality of life (QOL).

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Introduction

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Pain is the most common patient-reported complaint in clinical practice, and is strongly associated with quality of life (QOL). Therefore, pain has been suggested as an important QOL indicator for patients with chronic illness (e.g., cancer) [2]. In clinical practice, patients' pain recognition and persistency are profoundly influenced by the strength of noxious stimuli and affective status, as well as various other factors [e.g., medical knowledge, social skills, activities of daily living (ADLs), economic status, interpersonal relationships]. The biopsychosocial model proposes that clinical pain management must incorporate psychological and social factors, along with biological variables [3]. In this model, pain is considered an interactive and psychophysiological pattern of behaviors that cannot be separated into distinct, independent psychosocial and physical components. Numerous studies support the usefulness of cognitive behavioral therapy and other psychological approaches to chronic pain management, in addition to those that support a pharmacotherapeutic approach [4,5]. These psychological approaches yield similar outcomes, and commonly focus on educating patients with chronic pain to build coping skills and improve functioning. Successful treatment with pharmacotherapies requires the education of chronic pain patients regarding proper drug administration, side effects, and communicating with their physicians about unrelieved pain and prescription changes [6]. Thus, it is important to educate patients on the management of chronic pain. For example, opioids are prescribed to alleviate patients' chronic pain and improve their overall functioning. However, concerns regarding opioid abuse, addiction, adverse outcomes (e.g., respiratory depression and/or deep sedation from overdosing, and withdrawal symptoms from unintended discontinuation), and tolerance have been increasing. To address such concerns, chronic pain patients need to have adequate numeracy

skills to ensure that they consume the right amounts of opioids. In other words, it is highly important that their physicians teach them how to count and take the correct number of pills dutifully.

Health literacy (HL) refers to the capacity to obtain, process, and understand basic health information and services, and is necessary to make appropriate health decisions. In other words, HL is a social skill that embodies the ability to access necessary information in order to maintain and promote better health [7]. More specifically, it refers to the ability to read, understand, and use health care information to make decisions and follow treatment instructions. From the viewpoint of health care professionals, patients need to possess a particularly sophisticated level of understanding to receive the care they need, and lower HL is commonly found among older adults and patients with chronic illnesses [8]. Lower HL has been associated with lengthier hospitalizations, greater use of emergency care, a lower rate of screening examinations, poorer medication compliance, and a lower ability to interpret labels and health messages, as well as lower overall health status and higher mortality among older adults [9]. Several HL assessment tools have already been developed. One such assessment is the Newest Vital Sign (NVS), which is comprised of 6 questions about an ice cream nutrition label and assesses HL numeracy skills [10]. HL numeracy skills facilitate adherence to medication regimens [11]. This is particularly important for opioid medications, where adequate adherence to dosing schedules is necessary to avoid unfavorable consequences (e.g., respiratory depression, addiction, and withdrawal symptoms upon abrupt discontinuation). Assessment of HL numeracy skills is consequently of great importance in clinical practices for treating chronic pain [12]. English, Turkish, Dutch, and Spanish versions of the NVS have already been validated in primary care patients; however, a highly necessary Japanese version has yet to be validated. In the present study, we developed and validated a Japanese version of the NVS (NVS-J) in patients with chronic pain. While the original NVS assessments were conducted via face-to-face interviews, the NVS-J was designed as a questionnaire available for routine use in a variety of situations.

Materials and Methods

Participants

This study was approved by the Institutional Ethics Committee, Faculty of Medicine, The University of Tokyo (#3678), and consistent with the Declaration of Helsinki. A unique aspect of the NVS is that it can potentially be used to screen for limited numeracy skills. The original NVS was validated in primary care patients. However, as we mentioned earlier, numeracy skills are vital to patients with chronic pain who are using opioid analgesics. Therefore, we focused on chronic pain patients in our research.

A subset of patients who had been seen more than three times in our outpatient clinic, the Department of Anesthesiology and Pain Relief Center, The University of Tokyo Hospital, were enrolled in the study. During the study period of January–February 2012, the participants eligible for recruitment were randomly selected from the appointment logs of the attending physicians. All of the participants reported pain of an intensity of 3 or higher out of 10 on an 11-point numerical rating scale (NRS: 0 = no pain, 10 = worst pain imaginable), and the attending physicians evaluated their pain as necessitating continuous treatment. Participants with cultural or language barriers, or poor mental health statuses, that prevented them from understanding or responding to the questionnaires were excluded from this study. Among 44 identified eligible patients, 43 provided oral informed consent to participate in the study, and completed the questionnaires. Demographic data were obtained on each participant through the self-report questionnaire [i.e., age, sex, height, body weight, occupation, intensity of pain (NRS), smoking history (Brinkman index = daily number of cigarettes * year), and education level].

Measures

All patients were asked to complete the following 4 questionnaires: 1) the NVS-J; 2) a simple dementia screening test that assessed cognitive functioning (a total score of 12 or less out of 15 indicated possible dementia) [13]; 3) the Brief Pain Inventory (BPI) (Japanese version) for assessing ADLs [14]; and 4) a self-rated HL Questionnaire (HLQ) by Ishikawa et al., in which functional, communicative, and critical HL were assessed separately, with the total score of all three HL perspectives indicating an individual's comprehensive HL level [15]. Further, the attending physicians of each participant completed a clinical global impression scale of participants' comprehensive HL levels (CGI-HL) that consisted of a 5-point Likert-type scale (1 = "very poor," 2 = "poor," 3 = "fair," 4 = "moderate," 5 = "good"), on the basis of the following appraisals: 1) the participant always keeps his/her consultation appointments, 2) the participant understands the

Table 1. Participant demographics.

	Mean	SD
Age (yrs)	64.5	14.4
Male/Female	25/18	
Height		
Male (cm)	167.2	6.5
Female (cm)	151.1	6.9
Weight		
Male (kg)	64.4	10.6
Female (kg)	47.8	8.4
BMI		
Male	23.0	3.4
Femle	20.9	3.3
Brink Mann Index	247.3	480.1

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Table 2. Distribution of total NVS-J scores.

NVS-J score	0	1	2	3	4	5	6
Number (n = 43)[%]	13 [30.2]	7 [16.3]	4 [9.3]	8 [18.6]	4 [9.3]	6 [14.0]	1 [2.3]

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psycho-education concept about chronic pain management presented by the attending physician, 3) the participant can adequately adhere to medication regimens, 4) the participant can answer open questions, and 5) the participant can communicate coherently with the attending physician.

Development of a Japanese version of the NVS

Translation and cross-cultural adaptation of the NVS-J was performed in accordance with the established guidelines [16,17]. First, a forward translation of the original NVS into Japanese involving independent translations by a professional native Japanese translator and bilingual Japanese physician was obtained. Then, an expert committee including specialists in pain management, public health, and methodology, synthesized the two translations. Finally, two native English translators, who were uninformed about the nature of the study, completed back-translations of the translated NVS; thereafter, the back-translations were sent to an expert committee to detect cultural bias. When the NVS-J was deemed free of cultural bias, it was considered complete and suitable for administration to participants.

Data analysis

A score of two or less on the CGI-HL was considered in this study as indicative of low HL. Sensitivity and specificity ratios, as well as the stratum-specific likelihood ratio (SSLR) were then calculated for the NVS-J score of each participant. The cut-off point for the NVS-J was set for screening purposes on the basis of these parameters and the area under the receiver operating characteristic (ROC) curve.

Feasibility. The feasibility of the NVS-J was determined by analyzing the number of unanswered questions.

Validity. Construct validity was established through an exploratory factor analysis with principal components extraction. The Kaiser criterion (eigenvalues >1.0) and scree plot were used to determine the number of factors. Criterion-related validity was assessed through the calculation of a Pearson correlation coefficient between the dementia screening score, BPI, NRS, NVS-J, HLQ, and physicians' impressions. The following are generally accepted rankings for coefficients: 1.0–0.81 (excellent), 0.80–0.61 (very good), 0.60–0.41 (good), 0.40–0.21 (fair), and 0.20–0 (poor) [18].

Reliability. Internal consistency was measured with Cronbach's alpha. Alpha coefficients of a magnitude ≥0.70 were considered evident of adequate scale reliability at the level of group comparisons [19]. Repeatability was assessed by a test-retest method. Intra-class correlation coefficients (ICCs) between test and retest scores were calculated based on data from participants who reported no symptom changes between the times of the two surveys. Coefficients >0.80 were considered indicative of excellent reliability [20].

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 11.0) software.

Table 3. Percentage of correct answers for each NVS-J question.

	Kcal	Cup	Gram	%	Allergy	Reason
Correct (%)	37.2	18.6	51.2	25.6	41.9	37.2

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Results

Participant characteristics

The sociodemographic and clinical characteristics of the participants are displayed in Table 1. The total score distribution of the NVS-J is presented in Table 2. The percentage of participants who answered correctly is shown for each NVS-J question in Table 3.

Validity

Factor analysis with promax rotation, using the Kaiser criterion (eigenvalues ≥1.0), and a scree plot revealed that the main component of the NVS-J consists of three determinative factors that constitute 100% of the variance (Table 4). The first of these determinative factors consisted of the first and second questions, and was termed "basic numeracy ability," which referred to the capacity of participants to perform a simple calculation. The second factor consisted of the third and fourth questions, and was termed "complex numeracy ability," which referred to the ability of participants to extract necessary information from a nutrition label and perform complex calculations. Finally, the third factor consisted of the fifth and sixth questions, and was termed "serious-minded ability," which referred to the ability of participants to make reasonable health-related decisions. This factor was assessed by instructing participants to imagine they had been diagnosed with an allergic condition and asking whether they would consider avoiding allergenic foods.

In the analysis of criterion-related validity, the total NVS-J score was significantly correlated with the total HLQ score ($p = 0.004$, $R = 0.43$), functional HL score in the HLQ ($p = 0.009$, $R = 0.39$), and profoundly with the CGI ($p < 0.0001$, $R = 0.72$). Furthermore, we observed that the NVS-J was significantly correlated with cognitive function ($p = 0.016$, $R = 0.37$) and the Brinkman index of smoking history ($p < 0.05$, $R = -0.30$). These results also indicated the criterion-related validity of the NVS-J. Conversely, the total score of the NVS-J did not demonstrate any correlation with communicative and critical HL scores in the HLQ ($p = 0.064$, $R = 0.39$; $p = 0.11$, $R = 0.25$; respectively), body mass index ($p = 0.79$, $R = -0.042$), or pain intensity ($p = 0.98$, $R = -0.004$).

Reliability

Cronbach's coefficient for the total NVS-J score was adequate (alpha = 0.72). We were able to recruit 18 participants for a test-retest study, all of whom reported no changes in their symptoms. The data for each participant were evaluated. The average period between the two surveys was 12.2 weeks [standard deviation (SD): 1.7]. A significant correlation between the two surveys was

Table 4. Factor analysis of the NVS-J.

Factor analysis	Factor1	Factor2	Factor3
Kcal	0.831	−0.179	−0.031
Gram	0.709	0.210	0.046
%	−0.182	0.828	−0.029
Cup	0.238	0.640	0.017
Allergy	0.000	−0.040	0.855
Reason	−0.012	0.043	0.834

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demonstrated by a Pearson's correlation analysis ($p<0.001$, $R = 0.82$), which suggests good reproducibility. The applicable rate is shown in Table 5. There were no unanswered questions on any surveys administered during either time point in the data that were analyzed.

Cut-off point for low HL

The area under the ROC curve for the CGI-HL was 0.87. The theoretical maximum of this value is 1.00, which indicates perfect discrimination. A score of 2 on the NVS-J showed very high sensitivity (94.7%) but moderate specificity (75.0%); a score of 1 showed high sensitivity (84.2%) and relatively high specificity (83.3%). Further, the SSLR score of 1 was the maximum (5.05) among all the scores (Table 6). Therefore, a score of 1 on the NVS-J would be the suitable clinical cut-off point for screening purposes of low HL. This is compatible with the original cut-off point.

Discussion

This study demonstrated that the NVS-J has good validity and reliability. The results obtained in this study were comparable to those in previous studies [10,21]. With regard to criterion-related validity, significant correlations between the NVS-J, HLQ, and the CGI-HL by the physicians were observed. Furthermore, the NVS-J score was significantly correlated with cognitive function and smoking history, suggesting that the NVS-J would reflect overall numeracy ability and health practices. With regard to construct validity, we conducted a factor analysis and found that the six items of the NVS-J consist of three determinative factors, which can be defined as "basic numeracy ability," "complex numeracy ability," and "serious-minded ability." A factor analysis of this nature has not yet been attempted with regard to the NVS. One was not performed in the original NVS study conducted by Barry et al. (2005) in the US, or in the validation study of the screen by Rowlands et al. (2013) in the UK [10,21]. The factor analysis was fundamental in revealing covert psychometric properties of the NVS-J and the relationships between them. Here, we compared the present factor structure of the NVS-J to the HLQ. The HLQ assesses three components of HL: functional, communicative, and critical HL [15]. Functional HL refers to the ability to read and comprehend basic medical information. Communicative HL denotes the ability to extract important information and independently apply that information to personal health maintenance. Communicative HL is thus more advanced than functional HL, but still relatively basic. Critical HL refers to the extent to which individuals can thoroughly examine the necessity and suitability of medical information, and use that information to make decisions about personal health maintenance. These three HL abilities comprise a 3-step hierarchical structure. The present three extracted factors of the NVS-J are likely consistent with these core HL abilities in the HLQ [15].

In fact, our research revealed correlations between patients' NVS-J scores and total scores on the HLQ. NVS-J scores were also associated with functional HL, which is the fundamental subscale of the HLQ. These results indicate that the NVS-J has good criterion-related validity in evaluating overall HL and fundamental HL. On the other hand, NVS-J scores were not correlated with scores on the communicative and critical subscales of the HLQ. Its potential use for detecting limited numeracy skills makes the NVS one of a kind, as the HLQ cannot currently be used to ascertain such skills in individuals. Therefore, the NVS-J can be used independently or on its own to evaluate HL, especially numeracy skills.

Further, the distribution of scores attained by participants on the NVS-J, detailed in Table 2, varied from the one observed on the original NVS. However, our analysis utilizing ROC Curves clearly demonstrated that a score <2 on the NVS-J had moderately high sensitivity (84.2%) and specificity (83.3%) for predicting limited literacy, consistent with assessments by patients' attending physicians. This cut-off point was similar to that used in the original NVS study, in which the researchers also observed that scoring <4 could predict adequate literacy based on the stratum-specific likelihood ratios they obtained. However, our ratios (see Table 6) did not enable us to clearly categorize individuals in terms of whether they had adequate or robust health literacy. Therefore, differing from the original NVS, the present NVS-J could predict limited literacy when scores were <2 with a moderately high degree of specificity, but could not separate patients with adequate health literacy from those who had high health literacy.

Individuals with limited health literacy are less knowledgeable about their health problems [22–27], endure lengthier hospital-

Table 5. Applicable rate of the respective questions.

	Kcal	Cup	Gram	%	Allergy	Reason
Applicable rate (%)	90.1	86.0	79.1	74.4	81.4	79.1

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Table 6. Stratum-specific likelihood ratios for NVS-J cut-off scores by the CGI-HL.

Score of the NVS-J	Sensitivity	Specificity	Stratum-specific likelihood ratio (SSLR)
0	47.4	87.5	3.79
1	84.2	83.3	5.05
2	94.7	75.0	3.79
3	94.7	41.7	1.62
4	100	29.2	1.41
5	100	4.17	1.04
6	100	0.00	1.00

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izations [28,29], pay higher health care costs [30,31], and are less healthy [32–36] than those with adequate or high health literacy. Health information can be tailored for delivery to patients in an understandable format, provided patients have adequate health literacy. Additionally, patients with low health literacy have poor knowledge of pain medications, including their proper use and intake. Opioid analgesics are potent and thus commonly prescribed for chronic pain treatment; however, these drugs carry significant dependence and abuse risk for a portion of patients. Health care professionals should consequently be trained to recognize patterns of opioid abuse and misuse, and educate chronic pain patients on proper opioid administration. Training and ongoing education should be provided for chronic pain patients on effective dosing schedules and risks of pain medications, particularly opioids, that have a high potential for misuse, abuse, dependence, and life-threatening withdrawal symptoms. Patients should be required to demonstrate adequate numeracy ability prior to receiving an opioid prescription intended for self-administration. Furthermore, chronic pain patients should be capable of understanding the specifics of non-pharmacological coping strategies that may improve functioning, ADLs, and QOL. Given that HL encompasses these basic cognitive abilities, HL assessment is essential for chronic pain patients, as well as patients suffering from other chronic illnesses (e.g., congestive heart failure, diabetes mellitus, and asthma).

Limitations

The sample size of this study was small. In the original Newest Vital Sign (NVS) study by Barry et al. (2005) that enrolled 250 participants [10], the validity of the NVS was not directly associated with patients' health literacy (HL) levels as evaluated by health care professionals. Instead, by including the Test of Functional Health Literacy in Adults (TOFHLA), which can be used to assess medical linguistic problems [37], the original NVS demonstrated sensitivity and specificity for detecting low levels of HL. However, we felt that a conventional test/assessment utilizing medical words might be insufficient for detecting low HL levels in our study population (chronic pain patients). We thus decided to evaluate HL by also asking patients' attending physicians to complete a clinical global impression scale of patients' comprehensive HL levels, as they had expertise in educating patients on health and helping them understand health related information in their clinical practice. Because of this, the number of participants was fairly limited, but we were able to more precisely screen for limited HL with a higher degree of sensitivity and specificity. While the results of our preliminary study demonstrated the validity of the NVS-J in screening for limited HL, further research is required. From our pilot data, we could calculate the ideal sample size for more confirmatory investigations of its validity.

Author Contributions

Conceived and designed the experiments: TK M. Sumitani KK. Performed the experiments: M. Sumitani TO. Analyzed the data: M. Suka HI MK MO HS KK. Contributed reagents/materials/analysis tools: AI. Wrote the paper: TK M. Suka HI HS.

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《腰痛治療最前線》

2 慢性腰痛に対する薬物療法はどのように行うか

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ポイント

- わが国には慢性運動器疼痛患者が人口あたり15.4%いる.
- 慢性運動器疼痛患者の60%以上が腰背部痛を訴えている.
- 慢性腰痛の約30%が,神経障害性疼痛を病態に持つ.
- 神経障害性疼痛の第1選択薬はプレガバリンと三環系抗うつ薬である.
- 慢性腰痛症ではQOLの改善を意識した治療が重要である.

キーワード 侵害受容性疼痛,神経障害性疼痛,薬物療法,痛みの悪循環

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慢性的に運動器の痛みを抱える患者は人口の15.4%にもおよび,そのうちの60%以上が腰背部の痛みを挙げておりもっとも多い[1].これまで慢性腰痛の病態は,骨関節の変性などによる機械的刺激や炎症による侵害受容性疼痛が考えられていたが,痛みの性質から病態を推察する質問表PainDETECT[2,3]を用いて評価すると,慢性腰痛患者の約30%が神経障害性疼痛の病態を持ち,腰痛が重症なほど神経障害性疼痛となることが示されている[4].また,わが国の脊椎脊髄病学会主導研究でも脊椎関連の疼痛の80%以上が神経障害性疼痛の要素を含むことが示されている.神経障害性疼痛は,侵害受容性/炎症性疼痛に対して用いられる消炎鎮痛薬(ステロイドやNSAIDs)が基本的に無効であることが多く,神経障害性疼痛に特化した鎮痛薬を選択しなければならない.この薬剤の選択については,国際疼痛学会をはじめとして欧米諸国では神経障害性疼痛の薬物療法治療指針や推奨が提案されている.わが国では2011年に日本ペインクリニック学会からEBM情報にわが国の臨床環境を加味した神経障害性疼痛薬物療法ガイドライン(図1)が発行されており,その内容について概説する[5].

◉神経障害性疼痛の薬物療法

神経障害性疼痛に対する第1選択薬として,三環系抗うつ薬とCaチャネル$\alpha 2\delta$リガンドであるプレガバリンとガバペンチンが推奨されている.これらの薬剤は複数の神経障害性疼痛疾患に対する鎮痛効果が無作為化プラセボ対照試験(RCT)で示されており,有効性が実際に示されていない神経障害性疼痛疾患に対しても有効性が期待できることから第1選択薬として推奨されている.また,重篤な副作用や長期連用に伴う副作用が少なく忍容性が高いことも特徴である.RCTのほと

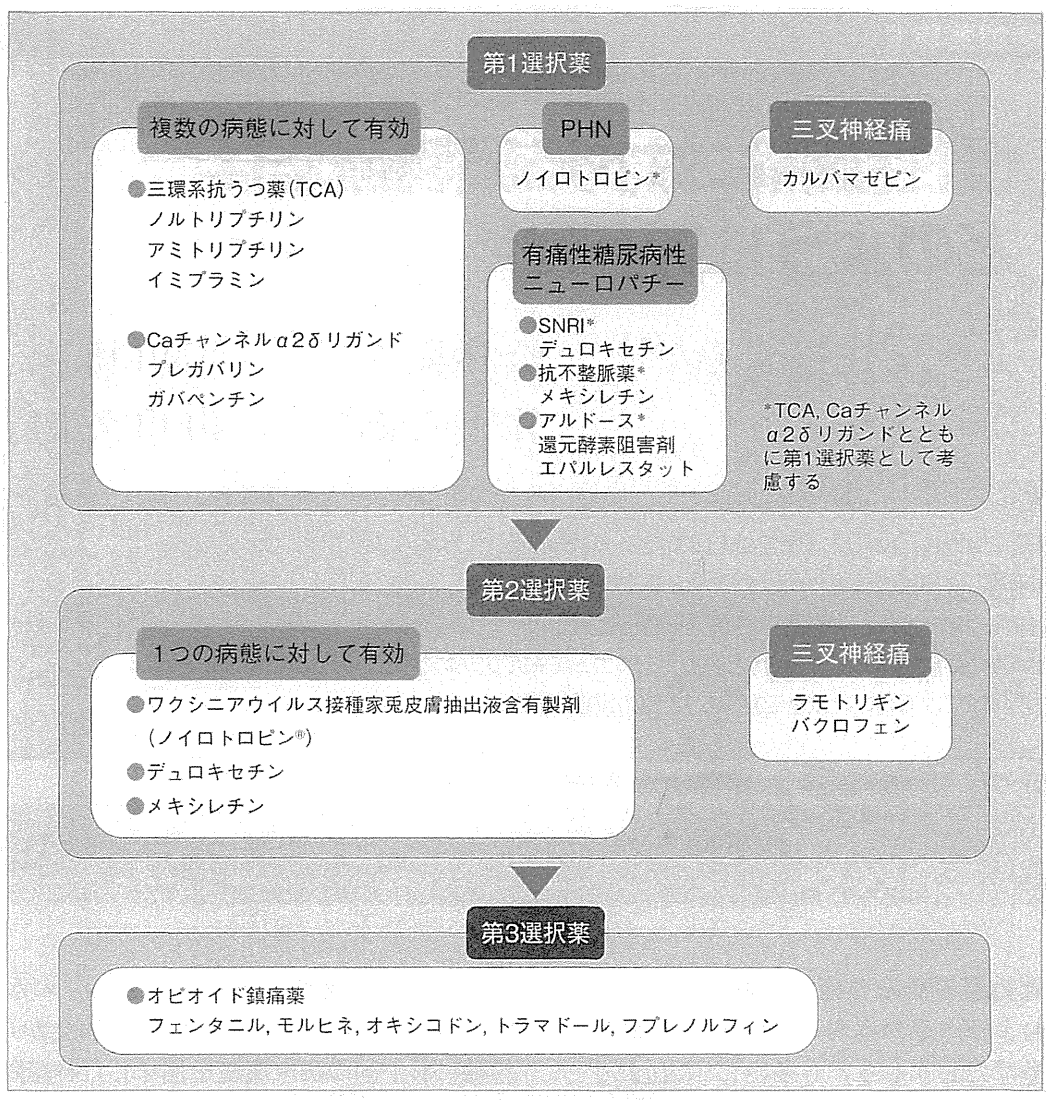

図 1　神経障害性疼痛薬物療法の推奨アルゴリズム

末梢性神経障害性疼痛全般に対する薬物療法の第 1 選択薬から第 3 選択薬までを示す．帯状疱疹後神経痛（PHN）と糖尿病性ニューロパチーでは，選択順位や薬剤が異なる．三叉神経痛だけは他の神経障害性疼痛疾患とはまったく異なる薬物療法が推奨される．

（日本ペインクリニック学会神経障害性疼痛薬物療法ガイドライン作成ワーキンググループ 編：神経障害性疼痛薬物療法ガイドライン．真興交易医書出版部，東京，pp 1-102，2011[5] より引用して改変）

んどは帯状疱疹後神経痛（PHN）と糖尿病性ニューロパチーを対象に実施されているが，プレガバリンは最近，脊髄損傷後疼痛に対して国際共同試験で有用性が示され[6]，保険適応病名が「神経障害性疼痛」となり末梢性/中枢性の区別なく処方できるようになった．三環系抗うつ薬は末梢性神経障害性疼痛疾患と中枢性神経障害性疼痛疾患とで至適使用量がほぼ同用量（60～80 mg/日）であるが，プレガバリンは末梢性神経障害性疼痛に対しては平均 357 mg/日であったのに対して中枢性神経障害性疼痛には平均 410 mg/日と異なっていることは臨床上重要で，病態に応じた至適用量まで漸増することが必要である．

第 2 選択薬には，1 種類の神経障害性疼痛疾患に鎮痛効果が示された薬剤が挙げられている．糖尿病性ニューロパチーに対して有効性が認められる選択的セロトニン・ノルアドレナリン再取り込み阻害薬のデュロキセチン，PHN に対して有効

表 薬物療法の不適切使用のチェックリスト

1．Over-sedationを目的としている
2．情動面の落ち着きがなくなっている
3．酩酊しているように見える
4．不潔感が増し，健康状態が悪化してきている
5．交通事故その他の事故に関わっている
6．薬物の効果を十分に確認する前から薬物の変更を要求する
7．医療者の許可なく薬物の使用量を増やす
8．薬物あるいは処方箋を紛失した，盗まれたと訴える
9．他の医療機関で処方箋，薬物をもらおうとする
10．投与経路を勝手に変更する
11．心理的ストレスに対する治療として，鎮痛薬を使用する
12．特定の薬物の名前を挙げて，その処方を要求する
13．違法薬物を使用できる環境にある
14．アルコールや違法薬物の乱用がある
15．薬物を貯め込んでいる
16．逮捕歴がある
17．虐待を受けたことがある

（Passik SD, et al.：Clin Ther 26：552-561，2004[7]より引用して改変）

性が認められるノイロトロピン®，糖尿病性ニューロパチーに対して有効性が認められるメキシレチンが挙げられている．腰痛症に対してはノイロトロピン®はすでに保険適応を持ち，その有用性が示されている．デュロキセチンも腰痛症に対して有効性が示されており，抗うつ作用と併せた鎮痛効果が期待される．メキシレチンは第2選択薬として挙げられているが腰痛症に対して用いるエビデンスはない．

第3選択薬にはオピオイド鎮痛薬が挙げられている．オピオイド鎮痛薬にはわが国では，非がん性慢性疼痛に対して適応を持つ薬剤としてトラマドール（単剤あるいはアセトアミノフェンの合剤）とフェンタニル貼付剤，ブプレノルフィン貼付剤がある．また，わが国ではがん性疼痛に対してのみ適応を持つオキシコドン，ほかがある．これらオピオイド鎮痛薬のうち神経障害性疼痛に対してもっとも豊富なエビデンスを持つ薬剤はトラマドール，オキシコドン，モルヒネである．オピオイド鎮痛薬には吐き気，便秘，眠気などの使用開始初期から現れる副作用に加えて，長期的には依存性の発現の懸念がある．このことから，オピオイド鎮痛薬は複数の神経障害性疼痛疾患に対する鎮痛効果が示されているが，第1選択薬としては推奨されていない．また，オピオイド鎮痛薬は腰痛症に対しても豊富なエビデンスを示しているが，いずれも比較的短期間の観察期間であり，中長期的な副作用（依存性）まで評価できていないことが理解されなければならない．このことを鑑みて日本ペインクリニック学会は神経障害性疼痛薬物療法治療指針に続いて，非がん性慢性疼痛に対するオピオイド鎮痛薬使用治療指針を発行し，オピオイド鎮痛薬の適切な使用を推奨している．具体的には，がん性疼痛に対する用法用量と異なり，オピオイド鎮痛薬は他の鎮痛薬が無効な場合に限って適応を検討し，その用量の上限を経口モルヒネ換算120 mg/日に設定し，疼痛増強時の頓用は原則として推奨されない．オピオイド鎮痛薬に対する依存性の発現は，高用量のオピオイド鎮痛薬，頓用によるオピオイド鎮痛薬の血中濃度の乱高下，非器質的疼痛に対するオピオイド鎮痛薬の使用，精神疾患（うつ病など）の合併などが危険因子として考えられており，患者を中長期的副作用（依存性）から保護するためにはオピオイド鎮痛薬の使用上の注意点が厳守されなければならない．また，うつ病患者の約60%は腰痛を訴え，腰痛患者の30%前後が抑うつ症状を示すので，オピオイド鎮痛薬の適応を検討する場合には精神