3 小児における精神・社会的問題による痛み

強い右前腕痛を訴え書字困難であったが，家族への介入が功を奏した症例

症例 9歳，女児.

主　訴：手が痛い．字が書けない.

現病歴：10カ月前，体育の授業中に右前腕を強く打撲し，それをきっかけにして徐々に右前腕に痛みを訴えるようになった．近医の整形外科を受診，検査を受け単純X線像では骨折などの異常はみられず，NSAIDsが処方された．しかし，内服によっても全く痛みは軽減しなかった．3カ月前からは痛みがひどく，字が書けないことが苦痛で，学校にも行けなくなった．家では携帯ゲームなど左手を使ってすることはできるが，急に痛がって大声で泣き出すこともあった．また，両親が確認したところ夜間には痛みで眠ることができない様子であった．何カ所かの病院を受診したが原因は明らかとならず，当院を受診した.

既往歴：特記すべきことはなし.

患者背景：小学4年生．成績は上位で，勉強に対しては積極的であった．両親はともに薬剤師で教育熱心であった.

現　症：受診時，保護のためタオルで右前腕を巻いており，右前腕の浮腫，角化は著しかった．検査のため手に触れようとすると，大声で「痛い，痛い」と叫ぶ．痛みの部位の周辺から触覚を調べると，前腕内側から上腕内側まで広範囲にアロディニアを認めた．また，肘関節を屈曲させることはできなかった．受診時の問診票ではNRS 8/10，PDAS 56/60，破局化スケール29/52であった．また，母親も一緒に受診したが，表情や患児に対する態度はやや固く，家族関係について尋ねても口を濁して語らなかったため日を改めて面接を行うこととした.

治療経過：まず治療チームで話し合いを行った．現在の右前腕の痛みは不動化による痛覚過敏が主体であり，運動療法を中心に整形外科医，理学療法士が担当することになった．また，家族背景が症状に影響している可能性があったため，精神科医が患児と両親の面接にあたることにした．薬物療法としては，痛みによる不安が強くまた睡眠障害も伴っていたが，年齢を考慮し，ベンゾジアゼピン系の抗不安薬，睡眠導入薬の使用は避けることとし，神経障害性疼痛に対してプレガバリン25 mg/日を使用開始した．母親は夜間の睡眠量は増加したとの評価をしたが，日中の眠気があり，活動性が低下したため数週間で中止とした.

また，母親の面接では，夫婦お互いが薬剤師であり仕事の余裕がなくコミュニケーションが難しいとの状況が語られ，1年前からは離婚についても話し合いが行われていることもわかった．患児とは，両親に伝えてほしくないことは伝えないという約束のうえ，別に面接を開始した．そのなかで，消しゴムを並べてしまう，プリントの枚数を何度も確認してしまうとの強迫症状が明らかになる一方，両親の離婚問題は知っており，怖くて仕方がないと少しずつ話をす

西原真理

こんな時、もしかしたら

- 器質変化に見合わない痛みの訴え
- 複雑な家族背景をもつ場合
- 学校，友達関係などに問題を抱える場合

この症例への対応は

- 最小限の薬物療法
- 家族も含めた幅広い情報収集
- 精神療法の構造化

表1　精神療法での注意点(家族も含めて)

1. 言語的な表出が困難な場合があり，詳細な行動観察も重要になる．
2. ユーモアや遊びの要素も取り入れる．
3. 日常生活の具体的な話題を中心にして，抽象的な話は避ける．
4. ケースによっては，患児と両親を別に面接するが(できれば異なる治療者が好ましい)，前提として患児が自由に話しができるような設定を行う．
5. 両親の面接では，『「症状を抱える子どもを見守る」ことの不安』へのアプローチを中心にする．
6. 可能な限り身体治療を行う者と精神療法を行う者を別に設定する(管理者と治療者)．
7. 家族を批判したりすることなく，「困っている症状⇔みんな」という構図を作る．

るようになった．3カ月の面接で徐々に不安が軽減し，両親の離婚がないと患児が確信するようになってからは，手の激しい痛みを訴えることはなくなり，強迫症状も消失した．また，治療期間中，装具などを利用しながら関節を動かすトレーニングを継続したところ，前腕部の動きはほぼ罹患前の状態に戻り，通学も可能となった．

考察　本症例は，診断学的にはCRPSとして取り扱うことが可能であるが，心理的な問題が解決することで症状の消失を認めた症例である．臨床経過からは家族内力動が患児の臨床症状を直接的に支配していると考えられた．このような症例に限らず，小児における痛みの治療では難渋することが多い．発達の側面からみると，学童期は課題に挑戦し，それを達成していく自己効力感を獲得する時期であり，また，社会的には対人認知において他者がどう思うかという理解が進んでくる時期でもある．しかし，些細なことや，大人の理解し難いことでも不安が増強する点には注意が必要である[1]．また，抽象的な概念を成立させることもできないため，内的世界について言語的な表出が未発達な状態であることも重要な視点となる．特にこの言語的表出の不十分さは，心理的葛藤を身体症状として生み出しやすい背景を形作っている．治療では，もちろん薬物療法を最小限にとどめることも重要であるが，心理的な問題が身体に器質的変化を及ぼすこともあり，精神療法的アプローチが不可欠なケースも存在することを常に意識しておきたい(表1)[2]．

References

1) 本田秀夫：精神科治療 26：383-386，2011
2) 宮川香織：臨精医 41：307-312，2012

関連事項

小児に多い慢性疼痛 ▶▶ 136頁
小児の複合性局所疼痛症候群(CRPS) ▶▶ 138頁
疼痛性障害 ▶▶ 146頁
うつ病 ▶▶ 150頁

1 心気症

肺がんを疑ってさまざまな病院を受診し続ける患者に対して漢方治療と精神療法が有効であった症例

症例 62歳，男性．

主　訴：以前工場で吸ったガスが原因で胸が痛い．肺がんだと思うがどこで検査をしてもらっても異常ないといわれる．何とか証明して欲しい．

現病歴：60歳で退職してから，軽い咳や喉の痛みに気づくようになった．徐々に胸部に痛みを感じるようになり，2年前，近医を受診した．胸部単純X線像には異常陰影は認められず，血液・生化学検査も正常であった．その頃から「工場で吸ってきたガスが原因で肺がんになっている」と考えるようになり，2つの大学病院を含めて10カ所以上の病院を受診した．MRIなどの精査も5回以上受けたが，異常は指摘されなかった．また1年前より，陰茎部の痛みも感じるようになり，これもがんによるものではないかと複数の泌尿器科を受診したが，これらの診療機関における検査でも特記すべき異常は認められなかった．受診した診療科の医師からは心療内科や精神科における診察も勧められたが拒否していた．痛みの原因ががんであることを示して欲しい，手術をして欲しいという目的で当院を受診した．

既往歴：小児期より難聴がある．

患者背景：高校を卒業後から，工場勤務を40年以上続けてきた．仕事に対しては勤勉であるが，職人気質で他人の指示にはあまり従わず，黙々と進めるタイプであったという．

現　症：やや多弁気味に一日中胸の痛みで苦しく，もともと好きであったジムに行くこともできなくなっていると話す．血液・生化学検査，胸部単純X線像，心電図，頭部MRIなどに異常所見は得られなかった．受診時の問診票ではNRS 7/10，PDAS 13/60，破局化スケール39/52であった．これまでの受診経緯，検査結果など，ところどころ赤で強調しながら写真も含め，20ページ以上ワープロでまとめていた．難聴があり，コミュニケーションにやや難しさはあるものの，会話のなかで理解力には問題なかった．表情は険しく怒りながら，とにかくがんであることを証明して欲しいと繰り返した．

治療経過と考察 がんを示唆するような臨床所見は得られないにもかかわらず，がんであるとの考えが頭から離れない状態であった．時間をかけて検査結果などについて説明し，がんの所見はないことを伝えると，いったんその場では納得する様子であるが，次回の受診時には同じ状態であった．社会機能も障害されており，また，そのほかの精神障害は否定的であったため，心気症として治療を開始した．精神療法としては診察時間を設定し，現時点ではがんを示唆するものはないが，感じている「苦痛」を少しでも軽くすること，ジムに通えるようになることなどを目標に設定し，理解を得られるよう説明を繰り返した．薬物療法としては，

西原真理

こんな時、もしかしたら

- 初診時から特定の病名を挙げ，固執する
- これまでの検査結果について詳細にまとめている
- 病気が認められないことに怒りを感じている

この症例への対応は

- まず必要な検査は十分に行い，経過を傾聴する
- 病気の否定を中心に置かず，苦しみに目を向けるように試みる
- 抗うつ薬や漢方薬などの薬物療法も検討する

表1 DSM-IV-TR：心気症

1．身体症状に対する患者の誤った解釈に基づき，自分が重篤な病気にかかる恐怖，または病気にかかっているという観念へのとらわれ
2．そのとらわれは，適切な医学的評価または保証にもかかわらず持続する
3．基準1の確信は(妄想性障害，身体型のような)妄想的強固さがなく，(身体醜形障害のような)外見についての限られた心配に限定されていない
4．そのとらわれは，臨床的に著しい苦痛または，社会的・職業的，またはほかの重要な領域における機能の障害を引き起こしている
5．障害の持続期間は，少なくとも6カ月である
6．そのとらわれは，全般性不安障害，強迫性障害，パニック障害，大うつ病エピソード，分離不安，またはほかの身体表現性障害ではうまく説明されない

「恐ろしさ」を減らすことを目的に抑肝散(よくかんさん)中心に漢方薬を使用した．それでも，身体的に気になることがあると，がんに対する検査を度々要求するため検査そのものも制限するように試みた．そのうち，面接のなかでは父親が肺がんで死去し，その終末期の看病で父親が苦しむ姿を見ることが辛かったと語るようになった．いろいろな不安が病気と結びつくことについて話し合うなかで，病気への固執は続くものの徐々に検査の要求などはしなくなった．またジムに行けるようになるなど，行動面の改善も自覚するようになった．

心気症は表1に示したような基準により診断される．疼痛性障害などと比較すると，症状に対する固執ではなく病気そのものに対する執着が主体であり，医療者としてはより厄介なイメージをもちやすい．薬物療法についてのエビデンスは確立していないが，疾患に対する強迫性という捉え方をすれば，SSRIであるフルボキサミン，パロキセチンなどの使用が有効な場合もある．また，病態レベルによっては妄想に近づく場合もあり，この際には抗精神病薬の少量投与も検討すべきである．しかし，患者自身はあくまでも向精神薬による治療は拒絶することが多く，漢方薬などによる治療から導入することも考慮したい．精神療法としては病気を完全に否定することから始めるのではなく，患者が感じている苦悩に焦点をあてて治療同盟を形成することが肝要である．治療が進めば，保障しながらも検査の制限などの行動療法的なアプローチも可能になってくる．しかし，心気症状そのものは治療反応性が低いため，治療者はまず患者のドクターショッピングを止めることのみを目標に設定することが望ましいと思われる．

Recommended Readings

- 西原真理：身体化障害．疼痛性障害．心気症．今日の治療指針(山口 徹ほか 編)．医学書院，東京，2013，pp.887-888
- 賀古勇輝ほか：臨精医 40：232-234，2011

関連事項

疼痛性障害 ▶▶ 146頁
うつ病 ▶▶ 150頁

Randomized Trial

Combinations of Low-Dose Antidepressants and Low-Dose Pregabalin as Useful Adjuvants to Opioids for Intractable, Painful Bone Metastases

Makoto Nishihara, MD[1], Young-Chang P Arai, MD[1], Yoshihiro Yamamoto, PhD[1], Kikuyo Nishida, PhD[1], Maki Arawawa, MD, Takahiro Ushida, MD[1], and Masahiko Ikeuchi, PhD[2]

From: [1]Multidisciplinary Pain Centre, Aichi Medical School, Karimata, Nagakute-cho, Aichi-gun, Aichi 480-1195, Japan; [2]Department of Orthopaedic Surgery, Kochi Medical School, Kochi University, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan

Address Correspondence: Masahiko Ikeuchi, MD Dept. of Orthopaedic Surgery, Kochi Medical School, Kochi University, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan E-mail: ikeuchim@kochi-u.ac.jp

Disclaimer: There was no external funding in the preparation of this manuscript. Each author certifies that he or she, or a member of his or her immediate family, has no commercial association, (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might post a conflict of interest in connection with the submitted manuscript.

Manuscript received: 06-25-2013
Revised manuscript received: 05-06-2103
Accepted for publication: 05-17-2013

Free full manuscript: www.painphysicianjournal.com

Background: Systemic analgesics would not provide good enough pain relief for some kinds of cancer pain. Metastatic bone pain is characteristic of one of the refractory cancer pains, since the pain is not only nociceptive but also neuropathic. A low-dose antiepileptic-antidepressant combination with opioids is effective in the management of neuropathic cancer pain.

Objective: The aim was to see whether a low-dose antiepileptic-antidepressant combination is effective in the treatment of bone metastases.

Study Design: Randomized, controlled trial

Setting: Pain Clinic in Japan.

Methods: Thirty-seven cancer patients, confirmed to have bone metastases, were allocated into 3 groups: P group took pregabalin 50 mg every 8 hours orally; P-I group took pregabalin 25 mg every 8 hours orally and imipramine 5 mg every 12 hours orally; P-M group took pregabalin 25 mg every 8 hours orally and mirtazapine 7.5 mg every 12 hours orally. Pain assessments were performed for 2 weeks.

Results: The total pain score significantly decreased in all 3 groups even one day after the start of the medication. The decreases in the P-I and P-M groups were significantly greater than those in the P group from Day 2. Also, the daily paroxysmal pain episodes significantly decreased in all 3 groups at Day 1. The decreases in the P-M groups were significantly greater than those in the P group from Day 1. The decreases in the P-I group were significantly greater than those in the P group from Day 3.

Conclusion: Low-dose pregabalin-antidepressant combinations with opioids were effective in the management of painful bone metastases.

Key words: Cancer pain, painful bone metastases, antidepressant and anticonvulsants, pregabalin, mirtazapin

Pain Physician 2013; 16:E547-E552

In the treatment of cancer pain, adequate pain relief has been obtained in a lot of cases by the recommended approach using systemic medications according to the World Health Organization analgesic ladder (1). However, systemic analgesics would not provide good enough pain relief for some kind of cancer pains. Metastatic bone pain is characteristic of cancer pain and one of the refractory cancer pains (2,3). Although the complete mechanism is not yet fully characterized, metastatic bone pain exhibits components of both inflammatory and neuropathic pain (4-6). Standard treatment includes radiotherapy

and a pharmacologic approach using nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and bisphosphonates. However, the current standard treatment is inadequate for a sizeable number of patients (7).

Neuropathic pain results from a dysfunction of peripheral and central nerves (8,9). Neuropathic cancer pain often shows little response to non-opioid and opioid analgesics, but may be relieved by adjuvants such as antidepressants and antiepileptics (10,11). Also, we previously reported that a low-dose gabapentin-imipramine combination with opioids was effective in the management of neuropathic cancer pain (12). Since mirtazapine is one of the noradrenergic and specific serotonergic antidepressants, it is believed to have potential as an adjuvant analgesic (13,14). However, mirtazapine alone does not provide an improvement in cancer pain. For this reason, we hypothesized that mirtazapine would lead to an improvement in pain when combined with antiepileptics. We thus performed an evaluation of the analgesic effect of a low-dose antiepileptic-antidepressant combination on metastatic bone pain.

Methods

Patients with intractable pain due to bone metastases were enrolled in this study from January 2010 to September 2011. Cancer metastases in bones were confirmed by bone scintigraphy and computed tomography (CT) in all patients. Approval from the local ethics committee and oral informed consent from the patients was obtained, and if the pain was not adequately relieved by opioids and NSAIDs, or the opioid dose was restricted by side effects, pregabalin and imipramine or mirtazapine were started after the first referral visit to our clinic.

In this randomized, controlled trial, the cancer patients were randomized to one of 3 groups using computer-generated random numbers:

1. P group: pregabalin 50 mg every 8 hours orally.
2. P-I group: pregabalin 25 mg every 8 hours orally and imipramine 5 mg every 12 hours orally.
3. P-M group: pregabalin 25 mg every 8 hours orally and mirtazapine 7.5 mg every 12 hours orally.

Previous 24-hour average intensity of total pain was assessed on 0 – 10 numerical scales and previous 24-hour paroxysmal pain (shooting or lancinating pain) episodes were recorded (12,15). Pain assessments were performed at the first visit (Day 0) and one to 7 days and 10 and 14 days after the start of the medication. Opioid "rescue" doses were available as needed. NSAIDs that were already administered were kept unchanged. No new drug was started during this period. An electrocardiogram (ECG) was performed before and at the end of the study and estimated glomerular filtration rate (eGFR) was measured before the study in all patients.

Our previous study showed the mean (SD) of the total pain score at 7 days after the start of the combination medication to be 2.3 (1.5). Thus, the sample size of 12 was needed to show intergroup differences of 2.0 (1.5) with a significant level of 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$). Data are presented as the median (range), number or the median with the twenty-fifth and seventy-fifth percentiles. Since the Kolmogorov-Smirnov test failed, the patients' characteristics, daily opioid dose (oral morphine equivalent (16), pain score, and paroxysmal pain episodes were analyzed using the Kruskal-Wallis test for intergroup comparison or the Friedman test for intragroup comparison followed by Dunn's method for multiple comparisons. Gender was analyzed by the chi-squared test. A P-value less than 0.05 was regarded as significant.

Results

There were no significant differences in patient characteristics and daily opioid dose (oral morphine equivalents) among the 3 groups (Table 1). Loxoprofen sodium (180mg/day) and bisphosphonates were used in all patients. Acetaminophen up to 2400 mg was used in 2 patients in the P group, 3 in the P-I, and 3 in the P-M. There were no patients with advanced chronic kidney disease who required a dose reduction of drugs.

The 3 groups were comparable with respect to the total pain score and daily paroxysmal pain episodes at base (Figs. 1 and 2). The total pain score significantly decreased in all 3 groups even one day after the start of the medication (Fig. 1). The decreases in the P-I and P-M groups were significantly greater than those in the P group from Day 2. Also, the daily paroxysmal pain episodes significantly decreased in all 3 groups even one day after the start of the medication (Fig. 2). The decreases in the P-M groups were significantly greater than those in the P group from Day one. The decreases in the P-I group were significantly greater than those in the P group from Day 3. Since pain control was not sufficient in the P group, mirtazapine was prescribed at Day 7 and the patients were withdrawn from the present study. Then, the P-I and P-M groups were followed.

Table 1. *Demographics and baseline characteristics of patients. Values are median (range) or number.*

	P (n = 12)	P-I (n = 12)	P-M (n = 13)	*P*
Age (year)	64 (47-71)	54 (40-77)	64 (37-72)	0.4709
Sex (M/F)	8/4	8/4	8/5	0.9538
Weight (kg)	54 (40-64)	53.5 (36-70)	50 (43-68)	0.7877
Daily opioid dose[a] (mg/day)	60 (20-180)	55 (20-200)	60 (20-120)	0.9342
Oxycodone SR	6	7	7	
Fentanyl Patch	6	5	6	

[a]Oral morphine equivalent.

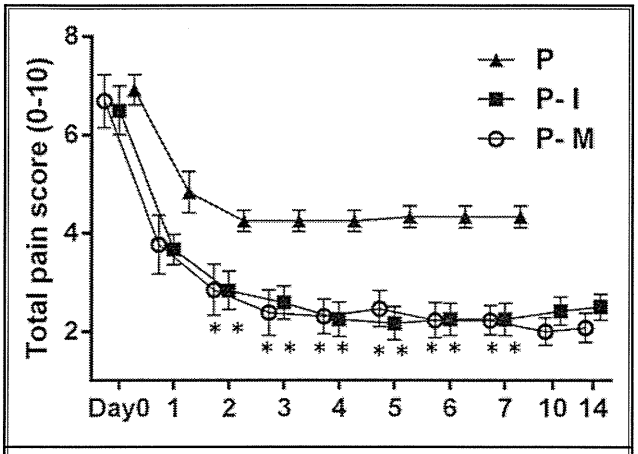

Fig. 1. *Changes of the total pain score. P, pregabalin. P-I, pregabalin- imipramine. P-M, pregabalin- mirtazapine. Error bar represents standard error of the mean (SEM). * P < 0.05 vs pregablin.*

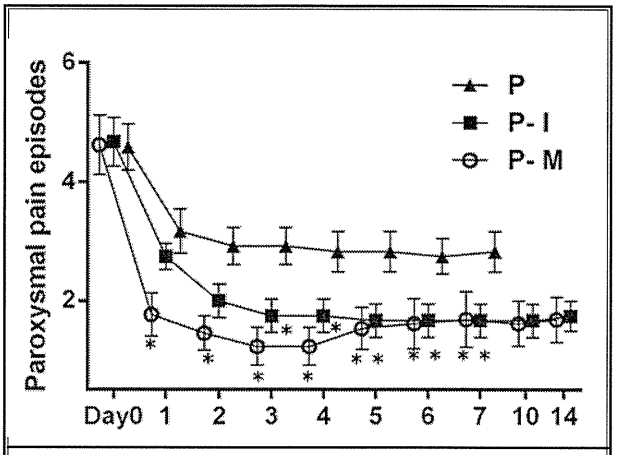

Fig. 2. *Changes of the daily paroxysmal pain episodes. P, pregabalin. P-I, pregabalin- imipramine. P-M, pregabalin-mirtazapine. Error bar represents standard error of the mean (SEM). * P < 0.05 vs pregablin.*

The pain relieving effects in the P-I and P-M groups were maintained for one more week (Figs. 1 and 2). A few patients developed adverse symptoms such as mild dizziness and mild drowsiness in the 3 groups. Significant ECG abnormalities including QT interval prolongation did not develop during the study in any of the patients.

Discussion

Some cancer pain syndromes are intractable even with the use of opioid analgesics. There are multiple mechanisms in the pathophysiology. Metastatic bone pain includes neuropathic as well as nociceptive factors (4-6). A neuropathic pathophysiology leads to a refractory outcome to opioid use. This fact indicates the need for the use of non-opioid analgesics in combination with opioids. Antiepileptics and antidepressants are the most commonly used adjuvant analgesics in pain syndromes of cancer patients when a neuropathic factor is implied from clinical observations (10,11). Thus, we intended to prescribe pregabalin, imipramine, and mirtazapine instead of increasing the opioid dose at the first visit in the present study.

Presently, antiepileptics, such as gabapentin and pregabalin, are widely used to relieve pain. They bind to the $\alpha 2\delta$ calcium channel subunits which are expressed in the central terminals of peripheral sensory nerves in the dorsal horn and inhibit the influx of calcium (17). Consequently, they inhibit signal transduction of pain by reducing the release of neurotransmitters (18). Several studies have confirmed that they are effective in the treatment of neuropathic pain caused by not only non-malignant but also malignant aetiology (19-25). Also, antiepileptics in combination with morphine or antidepressants provide better analgesia at lower doses of each drug than each drug alone (12,15,26-30). Morphine acts on opioid receptors located on neuronal

cell membranes and inhibits neurotransmitter release, which is considered to be the major mechanism of action responsible for its analgesic effects (31). The main proposed mechanism of action of antidepressants is reuptake inhibition of both serotonin and norepinephrine in the central nervous system, which increases the activity of these neurotransmitters and subsequently reduces the perception of pain by modulating the pain signals (19). Although these drugs are used in treating neuropathic pain (19), as monotherapy they are associated with limited efficacy and dose-related side effects. The combination of mechanically distinct analgesic agents is expected to result in additivity or synergism at lower doses and with fewer side effects than with the use of one drug alone.

Mirtazapine, which is a potent antagonist at central presynaptic α2-autoreceptors, postsynaptic 5HT2 and 5HT3 receptors, and H1 receptor, is an effective antidepressant drug (32,33). It differs in structure and mechanism action from other compounds of its class (32,33). Although mirtazapine alone is not used as an analgesic drug, its analgesic effects through opioid receptors and both serotonergic and noradrenergic receptors have been reported (34,35). Based on our results, low-dose pregabalin and mirtazapine were effective in the management of painful bone metastasis compared with twofold pregabalin. We thus believe that the present results showed the additive/synergistic effects of antiepileptic -antidepressant combination pharmacotherapy in the treatment of cancer-related neuropathic pain. Furthermore, mirtazapine has antiemetic effects as a 5HT antagonist (13,14), and as an H1 antagonist, it could stimulate appetite and increase body weight as well as regulate sleep disturbances (36). Although these beneficial secondary effects of mirtazapine were not evaluated in this study, the combination pharmacotherapy including mirtazapine might be an appropriate choice to treat cancer-induced bone pain in patients with many distressing somatic symptoms.

It is widely believed that the onset of beneficial antidepressant effects in depression is delayed for 2 or 3 weeks and maximal antidepressant-induced improvement of depression takes several weeks to occur (37). Also, the pain-relieving effects of antidepressants are generally believed to occur about 2 weeks after the initiation of treatment (38). Referring to our previous results (12), however, the pain-reducing effects of antidepressants combined with antiepileptics occur in a week. Moreover, an interesting finding in the present study was that the pain-relieving effects of antidepressants in combination with antiepileptics appeared within a few days after the initiation of the treatment and remained for 2 weeks, compared with those of 2 antiepileptics. We thus postulate that the pain-reducing effects of antidepressants could appear faster under combination pharmacotherapy.

Although the combination pharmacotherapy is promising in treating cancer-induced bone pain, drug-drug interactions should be taken into consideration. Many drug-drug interactions are the result of an alteration of cytochrome P450 (CYP450) metabolism (39,40). Physicians should be cautious when prescribing a drug known to be metabolized by CYP450. The target drug may need to be substituted or the dose adjusted to account for a potential decrease or increase in metabolism. Among drugs used in this study, oxycodone, imipramine, and mirtazapine are predominantly metabolized by CYP2D6 (41). We think that the absence of significant drug-drug interactions in this study was possibly due to the low dose of each drug. Compared with tricyclic antidepressants including imipramine, mirtazapine as a newer antidepressant rarely inhibits CYP isoforms and is not expected to affect the disposition of concomitantly administered drugs (41). Therefore, in terms of the drug-drug interaction, the combination of mirtazapine and pregabalin in addition to opioids would be theoretically more favorable than the combination of imipramine and pregabalin. Further clinical studies are needed to prove this.

Conclusion

In conclusion, low-dose pregabalin-antidepressant combinations with opioids were effective in the management of painful bone metastases without severe adverse effects.

References

1. World Health Organization. Cancer Pain Relief. WHO, Geneva, Switzerland, 1996.
2. Delaney A, Fleetwood-Walker SM, Colvin LA, Fallon M. Translational medicine: Cancer pain mechanisms and management. *Br J Anaesth* 2008; 101:87-94.
3. Smith HS. Painful osseous metastases. *Pain Physician* 2011; 14:E373-E403.
4. Honore P, Rogers SD, Schwei MJ, Salak-Johnson JL, Luger NM, Sabino MC, Clohisy DR, Mantyh PW. Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. *Neuroscience* 2000; 98:585-598.
5. Selvaggi K, Abrahm J. Metastatic spinal cord compression: The hidden danger. *Nat Clin Pract Oncol* 2006; 3:458-461.
6. Urch C. The pathophysiology of cancer-induced bone pain: Current understanding. *Palliat Med* 2004; 18:267-274.
7.. Laird BJ, Walley J, Murray GD, Clausen E, Colvin LA, Fallon MT. Characterization of cancer-induced bone pain: an exploratory study. *Support Care Cancer* 2011; 19:1393-1401.
8. Ross JR, Goller K, Hardy J, Riley J, Broadley K, A'hern R, Williams J. Gabapentin is effective in the treatment of cancer-related neuropathic pain: A prospective, open-label study. *J Palliat Med* 2005; 8:1118-1126.
9. Cavenagh J, Good P, Ravenscroft P. Neuropathic pain: Are we out of the woods yet? *Intern Med J* 2006; 36:251-255.
10. Berger A, Dukes E, Mercadante S, Oster G. Use of antiepileptics and tricyclic antidepressants in cancer patients with neuropathic pain. *Eur J Cancer Care* 2006; 15:138-145.
11. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007; 132:237-251.
12. Arai YC, Matsubara T, Shimo K, Suetomi K, Nishihara M, Ushida T, Kobayashi K, Suzuki C, Kinoshita A, Kondo M, Matsubara S, Hayashi R, Tohyama Y, Nishida K, Arakawa M. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. *J Anesth* 2010; 24:407-410.
13. Cankurtaran ES, Ozalp E, Soygur H, Akbiyik DI, Turhan L, Alkis N. Mirtazapine improves sleep and lowers anxiety and depression in cancer patients: Superiority over imipramine. *Support Care Cancer* 2008; 16:1291-1298.
14. Theobald DE, Kirsh KL, Holtsclaw E, Donaghy K, Passik SD. An open-label, crossover trial of mirtazapine (15 and 30 mg) in cancer patients with pain and other distressing symptoms. *J Pain Symptom Manage* 2002; 23:442-447.
15. Caraceni A, Zecca E, Bonezzi C, Arcuri E, Yaya Tur R, Maltoni M, Visentin M, Gorni G, Martini C, Tirelli W, Barbieri M, De Conno F. Gabapentin for neuropathic cancer pain: A randomized controlled trial from the Gabapentin Cancer Pain Study Group. *J Clin Oncol* 2004; 22:2909-2917.
16. Hall S, Gallagher RM, Gracely E, Knowlton C, Wescules D. The terminal cancer patient: effects of age, gender, and primary tumor site on opioid dose. *Pain Med* 2003; 4:125-134.
17. McClelland D, Evans RM, Barkworth L, Martin DJ, Scott RH. A study comparing the actions of gabapentin and pregabalin on the electrophysiological properties of cultured DRG neurones from neonatal rats. *BMC Pharmacol* 2004; 4:14.
18. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. *Epilepsy Res* 2007; 73:137-150.
19. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010; 150:573-581.
20. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005 Mar 31; 352:1324-1334.
21. Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: A randomized open trial. *J Pain Symptom Manage* 2007; 34:183-189.
22. Gilron I, Max MB. Combination pharmacotherapy for neuropathic pain: Current evidence and future directions. *Expert Rev Neurother* 2005; 5:823-830.
23. Caraceni A, Zecca E, Martini C, De Conno F. Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain. *J Pain Symptom Manage* 1999; 17:441-445.
24. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: A randomized controlled trial. *JAMA* 1998; 280:1831-1836.
25. Mueller ME, Gruenthal M, Olson WL, Olson WH. Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. *Arch Phys Med Rehabil* 1997; 78:521-524.
26. Hayashida K, Eisenach JC. Multiplicative interactions to enhance gabapentin to treat neuropathic pain. *Eur J Pharmacol* 2008; 598:21-26.
27. Garassino MC, Piva S, La Verde N, Spagnoletti I, Carbone C, Febbaro A, Bianchi A, Bramati A, Moretti A, Ganzinelli M, Marabese M, Gentilli M, Torri V, Farina G. Randomised phase II trial (NCT00637975) evaluating activity and toxicity of two different escalating strategies for pregabalin and oxycodone combination therapy for neuropathic pain in cancer patients. *PLos One* 2013; 8:e59981.
28. Gatti A, Longo G, Sabato E, Sabato AF. Long-term controlled-release oxycodone and pregabalin in the treatment of non-cancer pain: An observational study. *Eur Neurol* 2011; 65:317-322.
29. Tanenberg RJ, Irving GA, Risse RC, Ahl J, Robinson MJ, Skliarevski V, Malcolm SK. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: An open-label, randomized, noninferiority comparison. *Mayo Clin Proc* 2011; 86:615-626.
30. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. *Lancet* 2009; 374:1252-1261.
31. Pasternak GW. The pharmacology of mu analgesics: From patients to genes. *Neuroscientist* 2001; 7:220-231.
32. Fawcett J, Barkin RL. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. *J Affect Disord* 1998; 51:267-285.
33. Szegedi A, Schwertfeger N. Mirtazapine: A review of its clinical efficacy and tolerability. *Expert Opin Pharmacother* 2005; 6:631-641.

34. Sikka P, Kaushik S, Kumar G, Kapoor S, Bindra VK, Saxena KK. Study of antinociceptive activity of SSRI (fluoxetine and escitalopram) and atypical antidepressants (venlafaxine and mirtazepine) and their interaction with morphine and naloxone in mice. *J Pharm Bioallied Sci* 2011; 3:412-416.
35. Schreiber S, Rigai T, Katz Y, Pick CG. The antinociceptive effect of mirtazapine in mice is mediated through serotonergic, noradrenergic and opioid mechanisms. *Brain Res Bull* 2002: 58:601-605.
36. Enomoto T, Yamashita A, Torigoe K, Horiuchi H, Hirayama S, Nakahara K, Yanase M, Sakai H, Ikegami D, Nagase H, Suzuki T, Iseki M, Inada E, Narita M. Effects of mirtazapine on sleep disturbance under neuropathic pain-like state. *Synapse* 2012; 66:483-488.
37. Frazer A, Benmansour S. Delayed pharmacological effects of antidepressants. *Mol Psychiatry* 2002; 7:S23-S28.
38. Chan HN, Fam J, Ng BY. Use of antidepressants in the treatment of chronic pain. *Ann Acad Med Singapore* 2009; 38:974-979.
39. Michalets EL. Update: Clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* 1998; 18:84-112.
40. Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 Testing in the Clinical Setting. *Mol Diag Ther* 2013 Apr 16 [Epub ahead of print].
41. Spina E, Trifiro G, Caraci F. Clinically significant drug interactions with newer antidepressants. *CNS Drugs* 2012; 26:39-67.

J Orthop Sci
DOI 10.1007/s00776-013-0515-x

ORIGINAL ARTICLE

Usefulness of QuickDASH in patients with cervical laminoplasty

Hideki Nakamoto · Yasushi Oshima · Katsushi Takeshita · Hirotaka Chikuda · Takashi Ono · Yuki Taniguchi · Sakae Tanaka

Received: 27 June 2013 / Accepted: 27 November 2013

Abstract
Purpose Clumsiness and numbness of the upper extremity is one of the most common complaints of patients with cervical myelopathy. However, most previous evaluations after cervical laminoplasty have only been based on physicians' points of view. We used Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) self-report questionnaire, which was designed to measure physical function and symptoms in people with upper-limb disorders to evaluate functional outcomes after laminoplasty.
Methods Ninety-four patients who underwent laminoplasty for cervical myelopathy and replied to the questionnaire were included in this study. The average age was 62 years, and mean follow-up period was 61 months. The Japanese Orthopedic Association (JOA) score, Neck Disability Index (NDI), Short-Form Health Questionnaire of 36 questions (physical component score, PCS), upper-extremity pain (Numerical Rating Scale), and QuickDASH (0–100, 0 being least severe) were used to evaluate surgical outcomes. Satisfaction with treatment was also investigated, and internal consistency and criterion-related validity were evaluated. The QuickDASH cutoff value for patient satisfaction was determined by receiver operating characteristic curve (ROC) analysis.
Results The mean total JOA scores were 10 before and 13 after surgery, and average postoperative QuickDASH score was 30. Cronbach α of the QuickDASH was 0.94. QuickDASH was significantly correlated with JOA score for upper-extremity motor and sensation, NDI, PCS, and pain. Cutoff value of the QuickDASH was 34.0 by ROC analysis. Significantly better QuickDASH scores were found for patients who were satisfied with treatment than for those who were not, whereas JOA score for upper-extremity motor function did not show a significant difference.
Discussion QuickDASH had significant correlations with disease-specific JOA scores and other generic outcome measures. Moreover, QuickDASH significantly reflected patients' satisfaction with treatment, whereas the JOA score for upper-extremity motor function did not.
Conclusion QuickDASH was useful in evaluating upper-extremity functional outcomes after cervical laminoplasty.

H. Nakamoto · Y. Oshima (✉) · K. Takeshita · H. Chikuda · T. Ono · Y. Taniguchi · S. Tanaka
Department of Orthopedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: yoo-tky@umin.ac.jp

Introduction

Patients with cervical compressive myelopathy usually have loss of dexterity and nonspecific weakness, numbness, and paresthesia of the upper extremities, as well as gait disturbances and urinary dysfunction [1]. These symptoms have an insidious course and gradually deteriorate. In cases of severe compression or progressive course, operative decompression is the accepted treatment for cervical myelopathy [2]. Cervical laminoplasty is a well-established procedure for the disease, and several studies on cervical laminoplasty report favorable results even after 10 years or more [3, 4]. However, most previous evaluations were determined from assessment methods based on physicians' points of view, such as the Japanese Orthopedic Association (JOA) score.

Dysfunction in the upper extremity is one of the main disabilities that could affect patients' activity of daily

Published online: 06 January 2014

living. There are numerous, well-known conditions that can influence upper-extremity function, such as postoperative C5 palsy [5, 6] and late neurological deterioration [4]. Because upper-extremity function is more subtle and complicated than that of the lower extremity, a more detailed measure is essential for evaluation. However, there are few quantitative measures for total evaluation; the JOA score and its subscores are expressed as discrete variables, and the visual analog scale (VAS) can evaluate sensory function only.

The Disability of the Arm, Shoulder, and Hand (DASH) questionnaire was devised as a region-specific, patient-reported outcome measure to evaluate symptoms and functional status of the upper extremity, and the QuickDASH was developed as a shortened version [7, 8]. Many authors reported positive results of validity and responsiveness of DASH in patients with upper-extremity disorder [8, 9]. DASH and QuickDASH are appropriate for assessing disorders affecting upper-extremity functions, and symptoms can be assessed in a single, combined scale.

Although there are a few reports on the relationship between neck pain and DASH [10, 11], no report has documented the usefulness of DASH or QuickDASH for evaluating cervical myelopathy. We determined the efficacy of the QuickDASH questionnaire for evaluating functional outcomes of the upper extremity after cervical laminoplasty and compared the results with those of other commonly used assessment measures. To our knowledge, this is the first report on the usefulness of QuickDASH for cervical myelopathy.

Materials and methods

Study approval was given by the institutional review board of the Clinical Research Support Center of the University of Tokyo Hospital. Records of patients who underwent double-door laminoplasty for treatment of cervical laminoplasty between 1985 and 2008 and whose cases were followed at our department were retrospectively investigated. We mailed the questionnaires to the patients, and 608 patients who replied the questionnaires were included in the study. There were 351 patients who responded to all items. In addition, 139 were excluded by the following criteria; previous cervical spine surgery or other concomitant disease influencing symptoms and functional status of the upper extremity, including cerebral palsy, diabetic neuropathy, rheumatoid arthritis, or others. Of the 212 patients remaining, patients who had outpatient at the time of survey were included in this study.

Finally, 94 patients (59 men, 35 women) were enrolled. Average age at surgery was 62 (range 30–82) years, and mean follow-up was 61 (range 12–274) months. Diagnoses were cervical spondylosis in 57 patients, ossification of the posterior longitudinal ligament in 33, cervical disc herniation in nine, and ossification of yellow ligament in two.

The questionnaires included the QuickDASH Japanese version, Short-Form Health Survey of 36 questions (SF-36) [12, 13], Neck Disability Index (NDI) [14], and upper-extremity pain scale (Numerical Rating Scale 0–10). Patient satisfaction was also assessed by choosing either "satisfied,", "dissatisfied," or "neither."

QuickDASH consists of 11 items derived from DASH (Table 1). Each item has five response options ranging from "no difficulty or no symptom" to "unable to perform activity or very severe symptom," each scored on a scale of 1–5. These 11 items provide the QuickDASH score, which ranges from 0 (no disability) to 100 (the most severe disability) after summation of scores from all items and transformation [8].

The JOA score was used to evaluate preoperative and postoperative neurological functions at the time of survey (Table 2). The Hirabayashi method [15] was used to calculate the recovery rate of the JOA score according to the following formula: recovery rate (%) = (postoperative JOA score − preoperative JOA score) × 100/(17 − preoperative JOA score). A recovery rate >50 % was defined as an effective clinical result in JOA score [16, 17].

Table 1 Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) questionnaire

Question no.	Item
qDASH-1	Open a tight or new jar
qDASH-2	Do heavy household chores (e.g., wash walls, wash floors)
qDASH-3	Carry a shopping bag or briefcase
qDASH-4	Wash your back
qDASH-5	Use a knife to cut food
qDASH-6	Recreational activities that require little effort (e.g., card playing, knitting, etc.)
qDASH-7	During the past week, to what extent has your arm, shoulder, or hand problem interfered with your normal social activities with family, friends, neighbors, or groups?
qDASH-8	During the past week, were you limited in your work or other daily activities as a result of your arm, shoulder, or hand problem?
qDASH-9	Arm, shoulder, or hand pain
qDASH-10	Tingling (pins and needles) in your arm, shoulder, or hand
qDASH-11	During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder, or hand?

Table 2 Scoring system for cervical myelopathy proposed by the Japanese Orthopaedic Association (JOA score)

Motor dysfunction of the upper extremity
Score
0. Cannot eat with spoon
1. Can eat with a spoon, but not with chopsticks
2. Can eat with chopsticks, to a limited degree
3. Can eat with chopsticks, but awkward
4. No disability
Motor dysfunction of the lower extremity
Score
0. Cannot walk
1. Needs cane or aid on flat ground
2. Needs cane or aid only on stairs
3. Can walk without cane or aid, but slowly
4. No disability
Sensory deficit
A. Upper extremities
Score
0. Severe sensory loss or pain
1. Mild sensory loss
2. None
B. Lower extremities same as A
C. Trunk same as A
Sphincter dysfunction
Score
0. Unable to void
1. Marked difficulty in micturition (retention, strangury)
2. Difficulty in micturition (pollakiuria, hesitation)
3. None

Statistical analysis

SPSS version 17 software (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Internal consistency was evaluated by Cronbach α. The criterion-related validity was evaluated by calculating correlation coefficients (Spearman's ρ) between QuickDASH and other outcome measures; Student's t test, Mann–Whitney U test, Pearson's correlation coefficient, and chi-square test were used to evaluate the association between groups. Differences were considered significant at $P < 0.05$.

We also plotted the receiver operating characteristic (ROC) curves to investigate the QuickDASH cutoff value for patient satisfaction with cervical laminoplasty.

Results

The mean JOA score w as 10.1 (range 3–15) points before surgery and 13.3 (range 3–17) points after surgery. Mean JOA recovery rate was 46.2 % (range 0–100 %). Preoperative and postoperative average JOA scores were 2.4 ± 0.8 and 3.3 ± 0.8, respectively, for upper-extremity motor function and 0.8 ± 0.4 and 1.1 ± 0.5, respectively, for upper-extremity sensory function. Total JOA score and subscore for the upper extremities improved significantly after surgery ($P < 0.05$). The average postoperative QuickDASH score was 30.0 (range 0–100) points. Cronbach α of QuickDASH was 0.94, which is generally regarded as an excellent score. Table 3 shows correlations between QuickDASH and outcomes; QuickDASH showed significant correlation with outcomes from all the other assessment scales, particularly with NDI and SF-36 ($r > 0.75$).

We then determined the QuickDASH cutoff value for patient satisfaction as an endpoint. According to ROC curve analysis, a cutoff value of 34.0 gave the maximum power of QuickDASH for assessing patient satisfaction based on clinical results with cervical laminoplasty [area under the curve (AUC) 0.730] (Fig. 1).

We classified the patients into two groups according to treatment satisfaction. Patients who chose "neither" were classified into the not satisfied group. The satisfied group comprised 57 patients, and the not satisfied group comprised 37. QuickDASH score, JOA score for upper-extremity sensory function, and recovery rate were significantly better in the satisfied group than in the not satisfied group. However, there was no significant difference in JOA score for upper-extremity motor function between groups (Table 4).

Discussion

This study was conducted to evaluate the validity of QuickDASH as a measure of functional status of the upper extremity for patients after cervical laminoplasty. Results show that QuickDASH had significant correlations not only with disease-specific JOA scores but also with other generic patient-reported outcome measures. In addition, QuickDASH had an excellent correlative coefficient and significantly reflected patient satisfaction with treatment, whereas the JOA score for the upper-extremity motor function did not.

Upper-extremity function is affected by many factors, such as dexterity, weakness, numbness, and paresthesia. It is difficult to strictly divide the upper extremities into distinct parts, such as arm, shoulder, hand, neck, and scapular. Our results show that the QuickDASH was suitable for comprehensively evaluating symptoms and functional status of the upper extremities. In contrast, the JOA score is an ordinal variable, not a continuous variable, and the subscore is expressed as only 5 (motor) or 3 (sensory)

Table 3 Correlation between Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) self-report questionnaire and other test outcomes

	Correlation coefficient	*P* value
JOA score		
Motor (U/E)	−0.495	<0.01
Sensory (U/E)	−0.324	<0.01
Recovery rate	−0.509	<0.01
SF-36(PCS)	−0.753	<0.01
NRS (pain in U/E)	0.693	<0.01
NDI	0.834	<0.01

JOA Japan Orthopedic Association, *U/E* upper extremities, *PCS* physical component score, *NRS* Numeric Rating Scale, *NDI* Neck Disability Index

Table 4 Comparison between groups

	Satisfied	Not satisfied	*P* value
QuickDASH	23.2	40.5	<0.01
JOA score			
Motor (U/E)	3.4	3.2	N.S.
Sensory (U/E)	1.2	1	0.03
SF-36 (PCS)	36.3	27.6	0.02
NRS (pain in U/E)	2.2	4.6	<0.01
NDI	21.8	37.3	<0.01

QuickDASH Quick Disabilities of the Arm, Shoulder, and Hand, *U/E* upper extremity, *SF-36* Short-Form Health Questionnaire of 36 questions, *PCS* physical component score, *NRS* Numeric Rating Scale, *NDI* Neck Disability Index

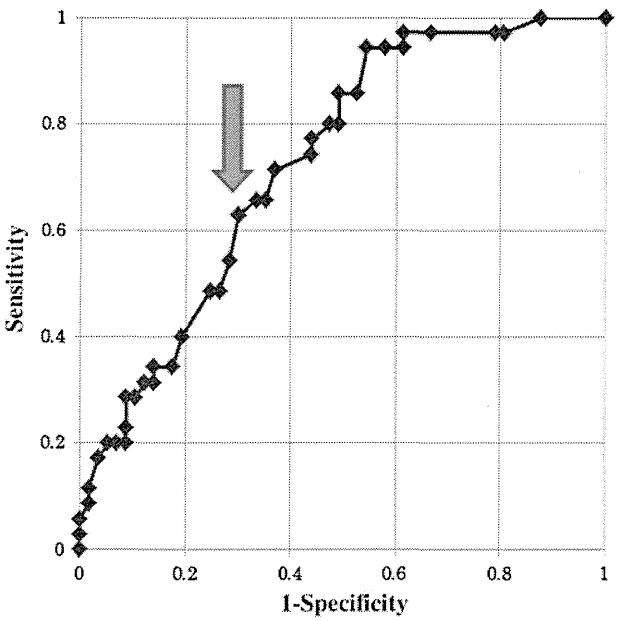

Fig. 1 Receiver Operating Characteristics (ROC) curve for determining the cutoff value for patient satisfaction following cervical laminoplasty. The *arrow* indicates the plotted point that determines the cutoff value

discrete variables [18]. This may be why the JOA score for the upper-extremity motor function did not affect postoperative satisfaction.

Several performance tests have been developed for objectively assessing the severity of hand myelopathy. For example, Kimura et al. [19] proposed the tally counter test, and Hosono et al. [20] proposed the 15-s grip–release test in addition to the conventional 10-s test. These tests are simple, reliable, and capable of detecting small functional changes. However, they do not evaluate sensory function or provide patient-reported outcomes. On the other hand, the QuickDASH is a patient-reported outcome, and we must evaluate the correlation between the QuickDASH and the other objective evaluations, such as these performance tests.

We determined the QuickDASH cutoff value to be 34.0. Although we had no preoperative QuickDASH data, the value obtained is considered to be reasonable because the mean QuickDASH scores were reported to be approximately 30 in the studies that evaluated patients with upper-extremity disorders [8]. We used patient satisfaction as an endpoint in order to determine the QuickDASH cutoff value.

However, it must also be affected by the function of the lower extremities or the degree of recovery. Preoperative QuickDASH scores are also required.

There were some limitations in this study. First, it was a retrospective design, and the relatively low follow-up rate indicates the possibility of patient selection bias. Second, there were no preoperative outcomes except for JOA score. To precisely investigate the reliability and responsiveness of the QuickDASH questionnaire to assess cervical surgery outcomes, we need to evaluate both pre- and postoperative outcomes. Finally, there are variations in the follow-up period (range 12–274 months). Late neurologic deterioration after laminoplasty is well known [4]. In order to avoid the effects of aging, outcome evaluation should take place in all patients at the same time period after operation. Also, for the same reason, comparison between QuickDASH assessment of cervical myelopathy patients and that of an age-matched control is required. However, there are no significant correlations ($r = 0.2$) between QuickDASH and the follow-up periods in this study. Imaeda et al. reported the low correlation between QuickDASH and age in their study group, so the aging effect on function may be negligible in our study. Some changes may also occur in the procedure or postoperative therapy during the long follow-up period. Our procedure was basically C3-7 laminoplasty with the hydroxyapatite (HA) spacer, and we think that

such changes across time did not affect postoperative function of the upper extremities.

Nevertheless, we regard QuickDASH as a reliable tool for obtaining patient-reported outcomes in evaluations of cervical interventions, not only because the QuickDASH scores had significant correlations with other disease-specific and general outcomes commonly used for assessing cervical diseases but also because Cronbach α for QuickDASH was excellent and reliable.

One possible problem in using QuickDASH is the influence of lower-limb function. Dowrick et al. [21] reported that the DASH score also measured disability in patients with injuries to the lower limb, and care must be taken when attributing disability measured by the DASH score to injuries of the upper limb if problems are also present in the lower limb. In fact, the QuickDASH questionnaire includes some items that must be influenced by lower-extremity function. For example, question no. 3, "Carry the shopping bag or briefcase," includes two actions: holding the bag and walking at the same time. Taking these factors into consideration, the significant correlation between QuickDASH and the other assessment outcomes may have been affected by lower-extremity function.

Finally, this study provides evidence to support the use of QuickDASH to measure upper-extremity symptoms and disability in patients with cervical surgery. The use of this questionnaire to obtain patient-reported outcomes allows subtle but significant changes in the upper extremity to be detected, which can truly reflect patient satisfaction with treatment.

Acknowledgments The authors thank patients and and their families for allowing us to present the clinical data reported here.

Conflict of interest No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. Bernhardt M, Hynes RA, Blume HW, White AA. Cervical spondylotic myelopathy. J Bone Joint Surg Am. 1993;75:119–28.
2. Yonenobu K, Fuji T, Ono K, Okada K, Yamamoto T, Harada N. Choice of surgical treatment for multisegmental cervical spondylotic myelopathy. Spine (Phila Pa 1976). 1985;10:710–6.
3. Chiba K, Ogawa Y, Ishii K, Takaishi H, Nakamura M, Maruiwa H, Matsumoto M, Toyama Y. Long-term results of expansive open-door laminoplasty for cervical myelopathy–average 14-year follow-up study. Spine (Phila Pa 1976). 2006;31:2998–3005.
4. Seichi A, Takeshita K, Ohishi I, Kawaguchi H, Akune T, Anamizu Y, Kitagawa T, Nakamura K. Long-term results of double-door laminoplasty for cervical stenotic myelopathy. Spine (Phila Pa 1976). 2001;26:479–87.
5. Chiba K, Toyama Y, Matsumoto M, Maruiwa H, Watanabe M, Hirabayashi K. Segmental motor paralysis after expansive open-door laminoplasty. Spine (Phila Pa 1976). 2002;27:2108–15.
6. Sakaura H, Hosono N, Mukai Y, Ishii T, Yoshikawa H. C5 palsy after decompression surgery for cervical myelopathy: review of the literature. Spine (Phila Pa 1976). 2003;28:2447–51.
7. Beaton DE, Wright JG, Katz JN, Group UEC. Development of the QuickDASH: comparison of three item-reduction approaches. J Bone Joint Surg Am. 2005;87:1038–46.
8. Imaeda T, Toh S, Wada T, Uchiyama S, Okinaga S, Kusunose K, Sawaizumi T. Impairment Evaluation Committee JpSfSotH. Validation of the Japanese Society for Surgery of the Hand Version of the Quick Disability of the Arm, Shoulder, and Hand (QuickDASH-JSSH) Questionnaire. J Orthop Sci. 2006;11:248–53.
9. Gummesson C, Atroshi I, Ekdahl C. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskelet Disord. 2003;4:11.
10. Huisstede BM, Feleus A, Bierma-Zeinstra SM, Verhaar JA, Koes BW. Is the disability of arm, shoulder, and hand questionnaire (DASH) also valid and responsive in patients with neck complaints. Spine (Phila Pa 1976). 2009;34:E130–8.
11. Mehta S, Macdermid JC, Carlesso LC, McPhee C. Concurrent validation of the DASH and the QuickDASH in comparison to neck-specific scales in patients with neck pain. Spine (Phila Pa 1976). 2010;35:2150–6.
12. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 health survey for use in Japan. J Clin Epidemiol. 1998;51:1037–44.
13. Fukuhara S, Ware JE, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 health survey. J Clin Epidemiol. 1998;51:1045–53.
14. Vernon H, Mior S. The neck disability index: a study of reliability and validity. J Manip Physiol Ther. 1991;14:409–15.
15. Hirabayashi K, Miyakawa J, Satomi K, Maruyama T, Wakano K. Operative results and postoperative progression of ossification among patients with ossification of cervical posterior longitudinal ligament. Spine (Phila Pa 1976). 1981;1981(6):354–64.
16. Satomi K, Nishu Y, Kohno T, Hirabayashi K. Long-term follow-up studies of open-door expansive laminoplasty for cervical stenotic myelopathy. Spine (Phila Pa 1976). 1994;19:507–10.
17. Kohno K, Kumon Y, Oka Y, Matsui S, Ohue S, Sakaki S. Evaluation of prognostic factors following expansive laminoplasty for cervical spinal stenotic myelopathy. Surg Neurol. 1997;48:237–45.
18. Suzuki A, Misawa H, Simogata M, Tsutsumimoto T, Takaoka K, Nakamura H. Recovery process following cervical laminoplasty in patients with cervical compression myelopathy: prospective cohort study. Spine (Phila Pa 1976). 2009;34:2874–9.
19. Kimura A, Seichi A, Endo T, Norimatsu Y, Inoue H, Higashi T, Hoshino Y. Tally counter test as a simple and objective assessment of cervical myelopathy. Eur Spine J. 2013;22:183–8.
20. Hosono N, Takenaka S, Mukai Y, Makino T, Sakaura H, Miwa T, Kaito T. Postoperative 24-hour result of 15-second grip-and-release test correlates with surgical outcome of cervical compression myelopathy. Spine (Phila Pa 1976). 2012;37:1283–7.
21. Dowrick AS, Gabbe BJ, Williamson OD, Cameron PA. Does the disabilities of the arm, shoulder and hand (DASH) scoring system only measure disability due to injuries to the upper limb? J Bone Joint Surg Br. 2006;88:524–7.

Spine

SPINE Volume 38, Number 26, pp E1691-E1700

EPIDEMIOLOGY

Identification of Risk Factors for New-Onset Sciatica in Japanese Workers

Findings From the Japan Epidemiological Research of Occupation-Related Back Pain Study

Ko Matsudaira, MD, PhD,* Mika Kawaguchi, MSc,† Tatsuya Isomura, MSc,†‡ Mayumi Arisaka,* Tomoko Fujii, MD, MDH,* Katsushi Takeshita, MD, PhD,§ Tomoaki Kitagawa, MD, PhD,¶ Kota Miyoshi, MD, PhD,¶ and Hiroaki Konishi, MD, PhD‖

Study Design. Two-year, prospective cohort data collected for the Japan epidemiological research of Occupation-related Back pain study were used for the analysis.

Objective. To identify potential risk factors for the development of new-onset sciatica in initially symptom-free Japanese workers with no history of sciatica.

Summary of Background Data. Although the associations between individual and occupational factors and cases of new-onset sciatica are established, the effect of psychosocial factors on the development of sciatica has still not been adequately clarified.

Methods. In total, 5310 participants responded to a self-administered baseline questionnaire (response rate: 86.5%). Furthermore, 3194 (60.2%) completed both 1- and 2-year follow-up questionnaires. The baseline questionnaire assessed individual characteristics, ergonomic work demands, and work-related psychosocial factors. The outcome of interest was new-onset sciatica with or without low back pain during the 2-year follow-up period. Incidence was calculated for participants who reported no low back pain in the preceding year and no history of lumbar radicular pain (sciatica) at baseline. Logistical regression assessed risk factors associated with new-onset sciatica.

Results. Of 765 eligible participants, 141 (18.4%) reported a new episode of sciatica during the 2-year follow-up. In crude analysis, significant associations were found between new-onset sciatica and age and obesity. In adjusted analysis, significant associations were found for obesity and mental workload in a qualitative aspect after controlling for age and sex. Consequently, in multivariate analysis with all the potential risk factors, age and obesity remained statistically significant (odds ratios: 1.59, 95% confidence interval: 1.01–2.52; odds ratios: 1.77, 95% confidence interval: 1.17–2.68, respectively).

Conclusion. In previously asymptomatic Japanese workers, the risk of developing new-onset sciatica is mediated by individual factors. Our findings suggest that the management of obesity may prevent new-onset sciatica.

Key words: sciatica, new-onset, prospective study, obesity, industrial health, risk factors, Japanese workers, asymptomatic, low back pain, psychosocial factors.

Level of Evidence: 3

Spine 2013;38:E1691–E1700

Sciatica is a symptom, rather than specific diagnosis,[1] characterized by low back pain (LBP) radiating below the knee.[2,3] The condition is also known as lumbosacral radicular syndrome, radiculopathy, nerve root pain, and nerve root entrapment or irritation. A variety of pathologies lead to sciatica: although lumbar disc herniation with nerve root compression is the main cause, lumbar spinal stenoses and tumors have also been reported.[2] The lifetime prevalence of sciatica ranges from 12.2% to 43% and can be influenced by varying definitions of sciatica and/or methods of assessing the condition.[1] Sciatica is usually more persistent and severe than nonspecific LBP, which is not attributable to any identifiable pathology in the spine. Although the symptoms usually improve within several weeks of onset, 40% still experience restriction in work 3 months after new-onset sciatica, and more than 30% continue to experience restriction in work 1 year after new-onset cases.[4] Sciatica often leads to deterioration in individual well-being, prolonged absence from work, and a significant health care burden.[4–8]

From the *Clinical Research Center for Occupational Musculoskeletal Disorders, Kanto Rosai Hospital, Kanagawa, Japan; †Clinical Study Support, Inc., Chikusa-ku, Nagoya Japan; ‡Division of Clinical Research Consultation, Institute of Medical Science, Tokyo Medical University, Japan; §Department of Orthopaedic Surgery, the University of Tokyo, Tokyo, Japan; ¶Department of Orthopaedic Surgery, Yokohama Rosai Hospital, Yokohama, Japan; and ‖Department of Orthopaedic Surgery, Nagasaki Rosai Hospital, Nagasaki, Japan.

Acknowledgment date: October 30, 2013. First revision date: July 12, 2013. Second revision date: August 23, 2013. Acceptance date: August 24, 2013.

The manuscript submitted does not contain information about medical device(s)/drug(s).

Dissemination project on the 13 fields of occupational injuries and illness of the Japan Labor Health and Welfare Organization grant funds were received to support this work.

Relevant financial activities outside the submitted work: grant.

Address correspondence and reprint requests to Ko Matsudaira, MD, PhD, Clinical Research Center for Occupational Musculoskeletal Disorders, Kanto Rosai Hospital, 1-1 Kizukisumiyoshicho, Nakahara-ku, Kawasaki 211-8510, Japan; E-mail: kohart801@gmail.com

DOI: 10.1097/BRS.0000000000000003

Prior research has identified individual and occupational factors that act as risk factors for the development of sciatica. For example, strong associations were found with age,[9] height,[10] obesity,[11] smoking, driving,[10] leisure-time physical activity,[9,11] occupation,[11] and twisting of the trunk at work.[8] Unlike individual and occupational factors, the association between psychosocial factors and the development of new-onset sciatica is still ambiguous due to both a lack of research in the area and inconsistencies in results.[9,10,12,13]

Serious cases of sciatica impact both individuals and society in the context of the workplace and health care burden inflicted. Therefore, identification of risk factors is highly important. However, research is limited, particularly on the effect of psychosocial factors on the development of sciatica. Therefore, this study aimed to examine the associations between new-onset sciatica and individual factors, ergonomic work demands, and work-related psychosocial factors in initially symptom-free Japanese workers.

MATERIALS AND METHODS

Data Source

The study analyzed a 2-year prospective cohort of the Japan epidemiological research of Occupation-related Back pain study. Ethical approval was granted by the review board of the Minister of Labour, Health and Welfare (MLHW) of Japan. Participants for the Japan epidemiological research of Occupation-related Back pain study were recruited at 16 local offices of participating organizations in or near Tokyo. The occupations of the participating employees were diverse (*e.g.*, office workers, nurses, sales/marketing personnel, and manufacturing engineers). Self-administered baseline questionnaires were dispersed among the employees by the board of each participating organization. Participants provided written informed consent for participation and returned completed questionnaires, along with their name and address for the purpose of follow-up, directly to the study administration office.

Baseline questionnaires on a prior diagnosis of lumbar radicular pain (sciatica) by an orthopedician, experience of pain and/or numbness radiating below the knee with or without LBP, episodes and severity of LBP, individual characteristics (*e.g.*, age, sex, obesity, height, smoking habits, education), ergonomic work demands (*e.g.*, manual handling at work, frequency of bending, twisting, hours of driving per day), and work-related psychosocial factors (*e.g.*, interpersonal stress at work, job control, reward to work, somatization, depression). To evaluate psychosocial factors, the Brief Job Stress Questionnaire (BJSQ) developed by the MLHW of Japan[14,15] was used. This questionnaire contains 57 questions and assesses 19 work-related factors: mental workload (quantitative aspect), mental workload (qualitative aspect), physical workload, interpersonal stress at work, work environmental stress, job control, utilization of skills and expertise, job fitness, job satisfaction, vigor, anger, fatigue, anxiety, depressed mood, somatic symptoms, support by supervisors, support by coworkers, support by family or friends, and daily-life satisfaction. Work-related stress factors were rated on a 5-point Likert scale ranging from the lowest score of 1 to the highest score of 5.

The BJSQ incorporates questions from various standard questionnaires such as the JCQ (Job Content Questionnaire),[16] the NIOSH (National Institute for Occupational Safety and Health),[17] the POMS (Profile of Mood States),[18] the CES-D (Center for Epidemiologic Studies Depression Scale),[19] the STAI (State-Trait Anxiety Inventory),[20] the SSD (Screener for Somatoform Disorders),[21] and the SUBI (Subjective Well-Being Inventory).[22] Standardized scores were developed for the 19 individual factors based on a sample of approximately 10,000 Japanese workers. The BJSQ has been shown to have internal consistency, reliability, and criterion validity with respect to the Job Content Questionnaire and NIOSH.[23]

The follow-up questionnaire was distributed 1 and 2 years after the baseline assessment. The follow-up questionnaires included questions on the experience of pain and/or numbness radiating below the knee with or without LBP (sciatica) in the past year, episodes of LBP, and severity of LBP.

Data Analysis

The outcome of our interest was the development of new-onset sciatica during the 2-year follow-up period. In this study, new-onset sciatica was defined if a participant reported no LBP in the preceding year as well as no history of lumbar radicular pain (sciatica) diagnosed by an orthopedician at the time of completion of the baseline questionnaire, but subsequently reported new-onset sciatica with or without LBP in the year before either the 1-year or 2-year follow-up survey. Workers were excluded from the analysis if they had lower extremity trauma, osteoarthritis, or peripheral arterial disease during the follow-up period.

For data analysis, the following factors were initially included: (1) individual characteristics, (2) ergonomic work demands, and (3) work-related psychosocial factors. Individual characteristics included age, sex, obesity (body mass index (BMI) $\geq$ 25 kg/m^2), smoking habits (Brinkmann Index $\geq$ 400), education, hours of sleep, exercise habits, flexibility, experience at current job, working hours per week ($\geq$60 hr per wk of uncontrolled overtime), work shift, employment status, and family history of LBP with disability. Ergonomic work demands included manual handling at work; bending, twisting, lifting, pushing ($\geq$½ of the day as frequent), hours of driving per day, hours of desk work ($\geq$6 hr was determined as static posture), and monotonous work (the presence of feelings of monotony or boredom at work). Psychosocial factors were assessed with the BJSQ. The 5-point Likert scale was reclassified into 2 categories: the "not feeling stressed" category, where low, slightly low, and moderate were combined, and the "feeling stressed" category, where slightly high and high were combined.

The MLHW of Japan defines obesity as a BMI of 25 kg/m^2 or higher[24] whereas the World Health Organization definition of obesity is BMI of 30 kg/m^2 or higher.[25] The Japan Society for the Study of Obesity recommends the lower cutoff point for BMI because it is more appropriate for Japanese

due to low prevalence and mild degree of obesity.[26] For the same reasons, the World Health Organization reported that in some Asian countries including Japan lower cutoff points for BMI may be more appropriate.[27] To assess smoking habits, the Brinkmann Index[28] was calculated on the basis of the total number of cigarettes smoked per day multiplied by duration of smoking in years. A Brinkmann Index value of 400 or higher indicated that a participant was a heavy smoker, whereas a value of less than 400 indicated that a participant was a nonheavy smoker. Participants were defined as flexible if their wrists could reach beyond the knees but the fingertips could not reach the ankles, and not flexible if their wrists could not reach beyond the knees.[29]

In addition to descriptive statistics, the baseline characteristics of the participants who followed-up (the follow-up group) and those who did not follow-up (the non–follow-up group) were compared using the χ^2 test. Next, logistic regression was run to examine the associations between risk factors and new-onset sciatica. Crude and adjusted odds ratios (ORs) and the respective 95% confidence intervals were calculated to assess potential risk factors. Age and sex were included in the model because both are well-established potential confounders. Subsequently, multivariate logistical regression analysis was run and included both the potential confounders and all potential risk factors for sciatica, which were reported at a significant level of $P < 0.1$ according to the initial crude and adjusted ORs. All the factors selected in the final model were statistically significant with a P value of less than 0.05. All tests were 2-tailed. The software package STATA 9.0 (StataCorp LP, College Station, TX) was used for all statistical analyses.

RESULTS

Baseline Characteristics of the Follow-up Group and the Non–Follow-up Group

The baseline questionnaire was distributed to 6140 workers and a response rate of 86.5% was achieved (5310 workers). Of these participants, 3194 workers successfully completed and returned both 1-year and 2-year follow-up questionnaires (a follow-up rate of 60.2%) (Figure 1).

The characteristics of the follow-up group and non–follow-up group at baseline were summarized. With regards to age, 37.7%, 31.1%, and 31.2% of the follow-up groups were aged less than 40; between 40 and 49; and 50 or more, respectively, with respective proportions of 58.5%, 23.7%, and 17.9% for the non–follow-up group. Males accounted for the vast majority of individuals in both the follow-up and non–follow-up groups (80.7% *vs.* 82.4%, respectively). The majority of the follow-up group and the non–follow-up group were not obese (76.4% *vs.* 73.7%, respectively). In respect to the distribution of manual handling at work, 72.6% of the follow-up group did not engage in manual handling at work, 9.9% engaged in manual handling of objects less than 20 kg, 17.6% engaged in manual handling of objects 20 kg or more or worked as a caregiver. The respective values for the non–follow-up group were 65.3%, 13.9%, and 20.7%. The majority of the follow-up group and the non–follow-up group undertook desk work without manual handling. However, in the category of manual handling of objects less than 20 kg, the majority of the follow-up group and non–follow-up group worked in manufacturing/engineering, whereas those who fell into the category of manual handling of objects 20 kg or more were predominantly involved in nursing or worked as caregivers. There were statistically significant differences between the follow-up and non–follow-up groups in age ($P < 0.001$), obesity ($P = 0.013$), and manual handling at work ($P < 0.001$), whereas no significant difference was found in sex (Table 1).

Baseline Characteristics of the Participants for This Study

Of the 3194 participants, 765 who reported no LBP during the preceding year and had no history of sciatica at the time of completing the baseline questionnaire were included in the analyses (Figure 1). In the distribution of age groups, 37.6% were less than 40; 29.6% were between 40 and 49; and 32.8% were 50 or more. The majority were males (n = 661; 88.5%). The number of obese participants was 164 (22.1%). The jobs of 569 participants (78.4%) did not involve manual handling. However, 77 (10.6%) participants manually handled objects

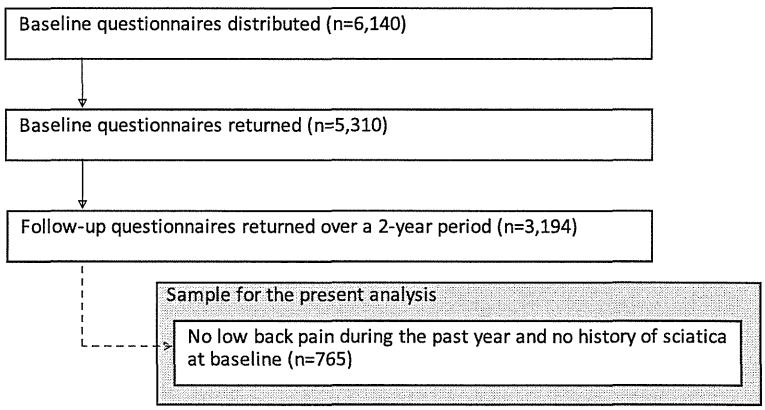

Figure 1. Flow chart of the sample selection for this analysis.

TABLE 1. Comparison of Baseline Characteristics of Follow-up Group and Non–Follow-up Group

Factors	Non–Follow-up (%)	Follow-up (%)	P*
Age (yr)			
<40	1631 (58.5)	1205 (37.7)	<0.001
40–49	660 (23.7)	993 (31.1)	
≥50	499 (17.9)	996 (31.2)	
Sex			
Male	2417 (82.4)	2577 (80.7)	0.092
Female	517 (17.6)	616 (19.3)	
Obesity			
<BMI 25 kg/m²	2117 (73.7)	2422 (76.4)	0.013
≥BMI 25 kg/m² (obese)	757 (26.3)	747 (23.6)	
Manual handling at work			
No manual handling	1823 (65.3)	2231 (72.6)	<0.001
Manual handling of <20 kg	389 (13.9)	303 (9.9)	
Manual handling of ≥20 kg	578 (20.7)	541 (17.6)	

Totals may not sum to 100% because of rounding.
**Pearson χ^2.*
BMI indicates body mass index.

less than 20 kg, 80 (11.0%) manually handled objects 20 kg or more, or worked as a caregiver.

Incidence of New-Onset Sciatica

Of a total of 765 eligible participants, 141 (18.4%) reported a new episode of sciatica during the 2-year follow-up period (18 missing cases).

Association Between New-Onset Sciatica and Potential Risk Factors

Crude and adjusted ORs for new-onset sciatica and their 95% confidence intervals are shown in Table 2. In crude analyses, age and obesity were significantly associated with new-onset sciatica (ORs of 1.50–1.84) ($P < 0.1$). Similarly, in adjusted analyses, obesity and mental workload in a qualitative aspect were significantly associated with new-onset sciatica after adjusting for age and sex (ORs of 1.39–1.80) ($P < 0.1$). Finally, all of these factors were simultaneously included in the same model to control for the other factors, as well as age and sex. As shown in Table 3, age (≥50 *vs.* <40) and obesity remained statistically significant in the multivariate analysis ($P < 0.05$). The ORs for age and obesity remained similar in both the multivariate analysis and the crude and/or adjusted analyses. A univariate logistic regression analysis was also performed in each age and sex strata to examine whether their effects on obesity and mental workload in a qualitative aspect in relation to new-onset sciatica ($P < 0.05$). As shown in Table 4, obesity in age (≥50) and male sex, and mental workload in age (<40) were statistically significant.

DISCUSSION

It is established that individual and work-related factors predispose the development of new-onset sciatica. However, information on the influence of psychosocial factors is conflicting. In our earlier study using data from the Japan epidemiological research of Occupation-related Back pain study, ergonomic factors (*i.e.*, frequent lifting) and work-related psychosocial factors (*i.e.*, interpersonal stress at workplace, monotonous tasks) were identified as potential risk factors for new-onset of nonspecific LBP with disability in workers who had no LBP during the year before the baseline survey.[30] Conversely, in this study, individual factors were the only identified potential risk factors in workers who reported no history of sciatica as well as no LBP in the year before baseline. Both studies were conducted among asymptomatic workers at baseline, yet the results varied depending upon the presence of pathology.

In this study, age was associated with the risk of developing new-onset sciatica, which is consistent with earlier research.[9] Although age is often used as a control variable in exploratory studies, not as an independent variable, it is appropriate to include age as an independent risk factor when exploring new-onset sciatica. The risk of sciatic pain seems to increase with age as the intervertebral discs and the spinal canal can often degenerate because of morphologic and functional alternations.[9] As a result, posterior disc bulges cause sciatic pain.[31]

Obesity was also found to be a risk factor for new-onset sciatica, which is again consistent with the findings of a previous report.[7] Obesity may increase the mechanical load on the intervertebral discs, but recent research has revealed that obesity may also be associated with neuropathic disorders. It has been found that obesity alters production of adipokines, including leptin and resistin, and locally produced proinflammatory cytokines such as TNF-α and IL-6 induced by obesity leads to a subclinical inflammatory condition of the white adipose tissue (WAT).[32,33] Similarly, animal work has shown that the adipokine, produced mainly by adipocytes, plays an important role not only in metabolic regulation and obesity, but also in the development of neuropathic disorder.[34–36] In addition, Miscio *et al*[37] suggested that peripheral nerve conduction abnormalities, in the lower extremities of nondiabetic obese patients with subclinical peripheral nerve impairment, increased risk for peripheral neuropathy. Thus, it seems reasonable that metabolic dysfunction may hypothetically mediate neuropathic pain including sciatica in humans. Given these earlier findings, obesity may create an environment that could easily trigger new-onset sciatica.

Results of this study implicate that reduction or prevention of obesity may offer important protection against the development of sciatica. The management of overweight and obesity by exercising, weight control, and improving dietary

TABLE 2. Crude and Adjusted Odds Ratios of Baseline Factors for Cases of New-Onset Sciatica

Factors	%	Crude OR	95% CI	*P*	Adjusted OR	95% CI	*P*
Age (yr)							
<40	37.6	1.00					
40–49	29.6	1.50	0.94–2.37	0.087			
≥50	32.8	1.57	1.00–2.46	0.048			
Sex							
Male	88.5	1.00					
Female	11.5	0.90	0.50–1.62	0.718			
Obesity							
<BMI 25 kg/m^2	77.9	1.00			1.00		
≥BMI 25 kg/m^2 (obese)	22.1	1.84	1.23–2.78	0.003	1.80	1.19–2.72	0.005
Height							
<167 cm (female)/<180 cm (male)	94.0	1.00			1.00		
≥167 cm (female)/≥180 cm (male)	6.1	0.78	0.34–1.79	0.564	0.87	0.37–2.00	0.736
Smoking habits							
Nonheavy smoker	71.5	1.00			1.00		
Heavy smoker	28.5	1.35	0.89–2.03	0.157	1.20	0.76–1.88	0.432
Education							
College/university	71.8	1.00			1.00		
High school/junior high school	28.2	0.94	0.62–1.42	0.765	0.85	0.56–1.31	0.468
Hours of sleep							
< 5 hr	3.9	1.00			1.00		
≥ 5 hr	96.1	1.67	0.72–3.85	0.229	1.93	0.82–4.51	0.131
Exercise habits							
≥Once per week	36.6	1.00			1.00		
<Once per week	63.4	0.97	0.66–1.42	0.866	1.03	0.69–1.52	0.899
Flexibility							
Flexible	76.6	1.00			1.00		
Not flexible	23.4	1.05	0.67–1.64	0.846	1.00	0.64–1.58	0.986
Experience in current job							
<5 yr	31.4	1.00			1.00		
≥5 yr	68.6	0.74	0.50–1.08	0.121	0.72	0.49–1.07	0.102
Working hours per week							
<60 hr	85.9	1.00			1.00		
≥60 hr	14.1	0.87	0.51–1.50	0.620	0.94	0.54–1.64	0.829
Work shift							
Regular shift	86.4	1.00			1.00		
Irregular shift	13.6	1.22	0.73–2.04	0.449	1.30	0.77–2.19	0.328

(*Continued*)