表 1 EFNS 神経障害性疼痛 薬物療法ガイドライン，各疾患別エビデンスレベルおよび推奨される治療薬

		有痛性多発性神経障害	帯状疱疹後神経痛	中枢性疼痛	三叉神経痛
エビデンスレベル	レベル A	三環系抗うつ薬 ガバペンチン プレガバリン SNRI トラマドール オピオイド	三環系抗うつ薬 ガバペンチン プレガバリン オピオイド	プレガバリン カンナビノイド	カルバマゼピン
	レベル B	ラモトリジン	トラマドール リドカイン カプサイシン (バルプロ酸)	プレガバリン 三環系抗うつ薬 ラモトリジン ガバペンチン	オクスカルバゼピン
推奨される薬剤	第一選択	ガバペンチン プレガバリン 三環系抗うつ薬	ガバペンチン プレガバリン 三環系抗うつ薬 リドカイン	プレガバリン 三環系抗うつ薬 ガバペンチン	オクスカルバゼピン カルバマゼピン
	第二選択	SNRI ラモトリジン トラマドール オピオイド	カプサイシン トラマドール オピオイド	カンナビノイド ラモトリジン オピオイド	手術

(Jensen T S：Pain 2008 An Update Review：287-295, 2008 より引用)

るべき手段は，

・オピオイドを増量する

・オピオイド増量で効果がなく，「しびれる」「びりびりする」など神経障害性疼痛に特有の症状があれば鎮痛補助薬への変更または併用を試みる．

・神経ブロック療法，脊髄鎮痛法などを考慮する．

◉鎮痛補助薬の選択

神経障害性疼痛が疑われ，それでオピオイドが効かないと判断されたときは鎮痛補助薬の使用を検討する．鎮痛補助薬には抗けいれん薬，三環系抗うつ薬，セロトニン・ノルアドレナリン再取り込み阻害薬（SNRI）などがよく使用される．その使用に当たっては，副作用の少ない継続投与が可能な薬剤から選択したほうがよい．ここでは，非がん性神経障害性疼痛に使用されている薬剤から紹介する．

表 1 に欧州神経学会（European Federation of Neurological Society：EFNS）が推奨する神経障害性疼痛治療薬を示す．有通性多発神経障害，帯状疱疹後神経痛，中枢性疼痛のいずれもガバペンチン，プレガバリン，アミトリプチリンが第一選択薬となっている．第二選択としてトラマドールや SNRI などが含まれている[1]（**表 1**）

鎮痛補助薬としてどのような病態にどの薬剤を使用すべきかについては決まった指針は示されていないが，**表 1** から理解できるのは，一般的な神経障害性疼痛にはガバペンチン，プレガバリン，アミトリプチリン（三環系抗うつ薬）を使用し，カルバマゼピンは三叉神経痛に限って使用すべきであるという点である．がん性疼痛で鎮痛補助薬としてカルバマゼピンを安易に使用するのは副作用の観点からも厳に慎むべきである．

筆者は以下の優先順位で使用している．

1．プレガバリン

プレガバリン（商品名リリカ®）は副作用に眠気，ふらつき，下肢浮腫があるが他の鎮痛補助薬に比べると副作用が軽度である点から第一選択薬として使用する．EFNS ガイドラインでも第一選

択薬に名を連ねている．また，化学療法後の末梢神経障害性疼痛に対する効果も認められている[2]．

その使用量は，150 mg/day（分2）となっているが，ふらつき・転倒などの事故を防ぐ意味で，50 mg/day（分2）から始めて増量していったほうがよい．

2．アミトリプチリン

プレガバリン，ガバペンチンが発売されるまでは帯状疱疹後神経痛など神経障害性疼痛治療薬の代表であった．口渇，ふらつき，尿閉などの副作用によって継続投与や増量が困難なことが少なくない．

使用量は，10 mg/day（分1眠前投与）で開始し，徐々に増量する．海外では150 mg/dayまで増量するとされているが，わが国では副作用で継続できなくなることが多く50 mg/日を超えることは少ない．

3．トラマドール

トラマドールは，オピオイド受容体に作用する鎮痛薬であるが，μ受容体に対しては中等度の親和性を持つ一方で，下行抑制系に対してはセロトニン・ノルアドレナリンの再取り込みを阻害することで下行抑制系を賦活化し鎮痛効果を発揮する“atypical”なオピオイドである[3]．副作用はオピオイドとほぼ同じで吐き気，便秘，眠気などであるが，便秘に関してはオピオイドよりも軽い．

使用量は，100 mg/日（分4：6時間毎投与）で開始して，症状に応じて400 mg/日まで増量する．先行するオピオイドがある場合には副作用はあまり出現しないことが多い．オピオイドとの併用に関しては併用注意とされているが，臨床上は併用しても特に問題となることはない．

4．ガバペンチン

プレガバリンと作用機序は似ており，下行性抑制系にも作用する点が異なるが臨床上の作用に差は認められない[4]．プレガバリンが末梢神経障害性疼痛，帯状疱疹後神経痛に適応が認められている一方で，ガバペンチンの適応症はてんかんの二次性全般化発作，部分発作であるので保険適応上からわが国ではプレガバリンを使用すべきである．

カルバマゼピンは，三叉神経痛に使用されるに限定されるべきであり，オピオイドが効かないときの鎮痛補助薬としては推奨できない．

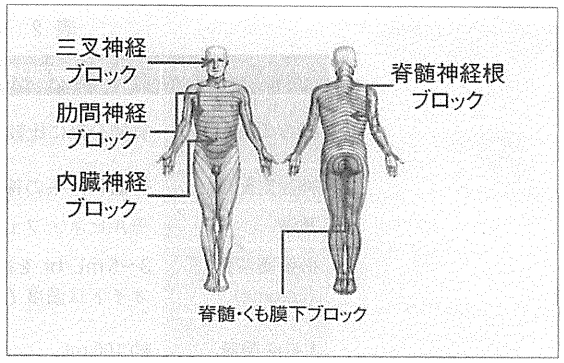

図2　がんの痛みに行う神経ブロック

上記薬剤を順に投与し，効果が見られれば増量し，効果がなければ投与を中止する．効果を認めて増量したのち残存する神経障害性疼痛がある場合には他剤を併用していくこともある．いずれにしても，症状の改善度，副作用の発現を観察しながら患者ひとりひとりに合わせてTry and errorで使用することが重要である．決してオピオイドで取れない痛みを改善してくれる救世主のような見方をせずに，あくまで「補助」薬として併用するのが望ましい．

◉神経ブロック療法の選択

わが国では非がん性慢性疼痛患者に初期からオピオイドが使用されることは少なく，多くはオピオイドが使用される前に末梢神経ブロック，神経根ブロック，交感神経ブロックなどの神経ブロック療法が実施されている．痛みの治療経過でオピオイド使用後に神経ブロックが選択されるのはがん性疼痛である．がん性疼痛に使用される神経ブロック療法はエタノールやフェノールを使用した神経破壊が主である．がん性疼痛でよく選択される神経ブロックを**図2**に示す．

顔面にできた上顎腫瘍や下顎腫瘍では顔面の痛みが強くなることがある．三叉神経ブロックが有効であるが，痛みが出現したときには腫瘍が大きくなっているために実施不可能であることが多い．

表 2　脊髄鎮痛法の適応

	硬膜外腔鎮痛法	脊髄くも膜下腔鎮痛法
痛みのある部位	脊髄分節に比較的限局しているとき	下半身・上半身などや広範囲の痛みに可
神経支配領域	脊髄神経系の神経支配領域の痛み	胸部脊髄神経以下の痛み
薬液	モルヒネ・フェンタニル	モルヒネ・フェンタニル
必要薬液量(volume)	3〜5 mL/hr を維持しながらオピオイドは濃度で調整する	0.1〜1.0 mL/hr でオピオイドは濃度調整する
1 日必要量	約 100 mL	ポンプの種類によるが，3 mL〜20 mL

また，頭蓋底への浸潤では効果が乏しい．

肋骨転移，胸膜浸潤などで胸壁の一部に痛みが限局している場合は，肋間神経ブロック（局所麻酔）で鎮痛効果を確認した後，胸部脊髄神経根ブロックあるいは脊髄くも膜下脊髄神経ブロックで神経破壊を行うとよい．

膵臓癌，胆管癌など上腹部の内蔵痛には腹腔神経叢ブロックを，腹部・下腹部の痛みには上腸間膜動脈神経叢ブロック，下腸間膜動脈神経叢ブロックを，骨盤内腔の痛みには上下腹神経叢ブロックがよい適応となる．

肛門部，会陰部の痛みには脊髄くも膜下フェノールサドルブロックが適応となる．

いずれのブロックも神経破壊による合併症の危険性についてはよく説明しておかなくてはならない．特に，腹腔神経叢ブロックによる起立性低血圧，フェノールサドルブロックによる排尿排便障害，下肢運動麻痺に注意が必要である．

神経破壊によってすべてのオピオイドを中止できるようになることはまれであるが，除痛できずに増やしてきたオピオイドを減量することが可能となることが多い．注意点として，神経ブロックが奏効すると劇的に痛みが軽減することがあり，それまでに使用してきたオピオイドが相対的に過量となり傾眠，呼吸抑制などが起こることがある．その場合，速やかにそれまで使用していたオピオイドを減量する．減量の方法は，オピオイドの種類に関わらず痛みが再出現するまで半分量/日のペースで減量する．

脊髄刺激，硬膜外刺激電極埋め込みについては，ペインクリニック医師，脳神経外科，整形外科に相談し，慎重にその適応を判断してもらったほうがよいと思われる．オピオイドが効かないときにすぐに代替治療法として適用できる治療法ではない．

◉脊髄鎮痛法の選択

脊髄鎮痛法は，痛みが比較的限局し，オピオイドの全身投与では鎮痛効果が不十分で，その副作用が患者さんの QOL をいちじるしく妨げているときに考慮する．オピオイドに局所麻酔薬を合わせた鎮痛法ではあるが，脊髄近傍に投与することで必要オピオイド量を減量することができ，神経障害性疼痛にも効果を示す．硬膜外腔鎮痛法，脊髄くも膜下腔鎮痛法のいずれを選択するかの参考基準を**表 2** に示す[5]．

痛みの範囲が脊髄神経支配領域の一部に限局している場合は硬膜外腔鎮痛法を，広範囲または複数部位に点在する場合は脊髄くも膜下腔鎮痛法を選択する．硬膜外腔鎮痛法は持続投与量を 3〜5 mL/hr で維持するため，必要な薬液量が 100 mL/日となり 2〜3 日に 1 回の薬液充填となるため在宅での管理には向かない．脊髄くも膜下腔鎮痛法では，薬液が脳脊髄液のなかを拡散するため高濃度のオピオイドを少量投与すればよく，薬液充填が 1 週間に 1 回（約 100 mL 充填で 0.5 mL/hr のとき）となり在宅疼痛管理に適している．

絶対的禁忌は，出血傾向がある場合，全身感染がある場合，免疫抑制が強い場合，穿刺部位・ポート設置部位の皮膚感染がある場合，感染性髄

膜炎がある場合，本人・家族が治療を望まない場合などが挙げられる．相対的禁忌として，患者の予後が週単位の場合や，退院後に疼痛管理をしてくれる社会的資源がない場合などである．硬膜外腔や脊髄くも膜下腔へのカテーテル留置に際しては，その手技に熟練している麻酔科医，ペインクリニック医師，経験者に依頼することが望ましい．

脊髄鎮痛法に使用するオピオイドにはモルヒネとフェンタニルとがある．フェンタニルは脂溶性が高く，経皮投与も脊髄近傍投与も同じ量が必要になるため，水溶性のモルヒネが選択される．モルヒネを投与経路で見た場合の鎮痛に対する効力比を**表 3** に示す[6]．内服オピオイドから変更する場合，効力比を参考に投与量を変更するが，計算上の等鎮痛用量の 50～75%から開始してタイトレーションするほうが安全である．

当院で使用しているモルヒネおよびフェンタニルの初期投与量について**表 4** に示す．局所麻酔薬にはモルヒネと併用すると双方の必要量を減らす（opioid sparing effect）ことができるブピバカインを使用する．あくまでモルヒネ主体の鎮痛であり，局所麻酔薬は低濃度で使用する．これは，交感神経の抑制や運動麻痺を避けるためである．

脊髄鎮痛法は中・長期的に使用することが多いため，カテーテルの抜去，破損などのリスクがある．持続投与を行う場合は，皮下ポートなどと接続してこのようなリスクを回避する必要がある（**図 3**）．海外では皮下埋め込み型ポンプがあるが，わが国では脊髄疾患のバクロフェン投与用にしか使用できない．今後の適応拡大に期待したい．

表 3　モルヒネの投与経路と効力比

投与経路	効力比
内服	1
皮下投与	2
静脈内投与	3
硬膜外腔投与	20
脊髄くも膜下腔	300

ま と め

オピオイドは鎮痛薬のなかでは臓器障害を起こすことなく痛みを軽減することが可能な薬剤である．しかしながら万能の鎮痛薬ではなく，どのような「痛み」でも取り除けるわけではない．オピオイドで痛みが取り除けないときは，その原因，病態を再確認したうえで他の治療法がないかを探

表 4　脊髄鎮痛法におけるモルヒネ濃度の初期設定

	モルヒネ濃度	局所麻酔薬	持続投与量
硬膜外腔	0.1 mg/mL	0.05%レボブピバカイン	3～5 mL/hr
	調整例：機械式 PCA ポンプ　4 mL/hr 総充填量が 300 mL の場合， ・モルヒネ注射薬　30 mg（3 mL） ・0.5%レボブピバカイン　30 mL ・生理食塩水　267 mL		
脊髄くも膜下腔	モルヒネ濃度	局所麻酔薬	持続投与量
	0.1 mg/mL	0.05～0.10%ブピバカイン	0.1～1.0 mL/hr
	調整例：機械式 PCA ポンプ　0.5 mL/hr 総充填量が 100 mL の場合， ・モルヒネ注射薬　10 mg　(1 mL) ・脊麻用 0.5%等比重ブピバカイン　10 mL ・生理食塩水　89 mL ※シリンジタイプやディスポーザブルタイプでは 60 mL 以下の規格が多いが，わかりやすくするために 100 mL 充填での調整例を示した．		

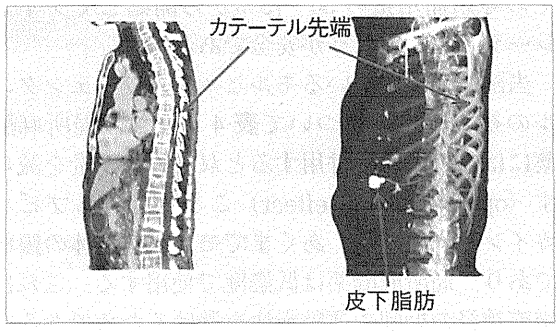

図 3　硬膜外・脊髄くも膜下カテーテル留置および皮下アクセスポート設置

すべきである．病態治療，鎮痛補助薬の使用，神経ブロックの適用など，痛みに対して多面的かつ柔軟に対応することが寛容である．

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Prevalence of Malignant Hyperthermia and Relationship with Anesthetics in Japan

Data from the Diagnosis Procedure Combination Database

Masahiko Sumitani, M.D., Ph.D.,* Kanji Uchida, M.D., Ph.D.,* Hideo Yasunaga, M.D., Ph.D.,† Hiromasa Horiguchi, Ph.D.,‡ Yoshiomi Kusakabe, M.D.,§ Shinya Matsuda, M.D., Ph.D.,‖ Yoshitsugu Yamada, M.D., Ph.D.#

ABSTRACT

Background: Malignant hyperthermia (MH) is a rare but life-threatening disease that occurs during general anesthesia. The actual prevalence of MH remains unclear, and the association between MH and various anesthetic drugs remains controversial because of a lack of universal reporting.

Methods: Using the Japanese Diagnosis Procedure Combination database, we collected data of inpatients who had general anesthesia between July and December 2006–2008. Patients' age, gender, diagnoses, procedures, and the use of drugs during anesthesia, including volatile agents, muscle relaxants, and propofol, were investigated. Univariate comparisons were made to examine the relationship of each anesthetic drug or demographic factor with the occurrence of MH.

Results: Of 1,238,171 surgical patients undergoing general anesthesia, we identified 17 MH patients (odds ratio: 13.7, 95% CI 7.2–20.3 per million). Only one in-hospital death was identified. Men were significantly more likely to contract MH (odds ratio: 3.49; 95% CI 1.14–10.7; $P = 0.029$). No MH patient was found among 19,871 suxamethonium users. The prevalence of MH was relatively high in users of sevoflurane (odds ratio: 15.0; 95% CI 7.1–22.9 per million) and rocuronium (odds ratio: 24.3; 95% CI 4.9–43.8 per million) compared with nonusers but was not statistically significant.

Conclusions: No single drug was significantly associated with the occurrence of MH. Data should be continuously compiled, and further analyses with larger numbers of cases are necessary to identify possible causative agents.

What We Already Know about This Topic

- In Japan, the prevalence of malignant hyperthermia was estimated to be 1:60,000

What This Article Tells Us That Is New

- Using a national database of more than 1.2 million inpatients, maligant hyperthermia was diagnosed in 17 (rate, 1:73,000), and males were three times more likely to be diagnosed

MALIGNANT hyperthermia (MH) is a potentially life-threatening pharmacogenetic disease associated with abnormal intracellular calcium regulation that occurs during general anesthesia.[1] The essential biochemical abnormality of MH is characterized by an increase in the release of calcium ions in skeletal muscle cells caused by genetic mutations mainly in two genes: ryanodine receptor type 1 (RYR1) and CACNA1S.[2] In addition to these genes, more than one MH-susceptible allele has been identified.[3]

In previous Western studies, the estimated prevalence of MH ranged widely from 1:10,000 to 1:220,000.[4,5] In Japan, the prevalence of MH was presumed to be approximately 1:60,000.[6] In New York State, the prevalence of MH was confirmed to be 9.6 per million surgical discharges using a macroscale database.[7] However, these figures were based on rough estimates or data from limited geographical areas. A national prevalence of MH remains unclear because of a paucity of universal reporting in any country.

Investigations on the drugs that might trigger MH have still not reached any conclusions. A well-known potential risk factor for MH is the use of depolarizing muscle relaxants (suxamethonium) or volatile anesthetic agents (sevoflurane, isoflurane, halothane, and enflurane).[1,8–10] However, the association between other anesthetic agents and MH occur-

* Assistant Professor, Department of Anesthesiology and Pain Relief Center, University of Tokyo Hospital, Tokyo, Japan, † Associate Professor, ‡ Assistant Professor, Department of Health Management and Policy, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, § Clinical Fellow, Department of Anesthesiology and Pain Relief Center, University of Tokyo Hospital, ‖ Professor, Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Fukuoka, Japan, # Professor, Department of Anesthesiology and Pain Relief Center, University of Tokyo Hospital.

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Address correspondence to Dr. Sumitani: 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan. sumitanim-ane@h.u-tokyo.ac.jp. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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rence remains unclear. Nondepolarizing muscle relaxants (vecuronium, pancuronium, and rocuronium) are considered to be safer than suxamethonium, but this still has not been fully evaluated. It is controversial whether propofol can induce MH.[11–13]

In this report, we verified the prevalence of MH in Japan and analyzed the relationship between the use of several drugs administered during general anesthesia and the occurrence of MH, using a nationally representative inpatient database, the Japanese Diagnosis Procedure Combination (DPC) database.

Materials and Methods

DPC Database

The DPC is a case-mix system, which is similar to the diagnosis-related groups in Medicare in the United States. This patient classification system was launched in 2002 by the Ministry of Health, Labor, and Welfare of Japan and linked with a lump-sum payment system. Key objectives of the DPC system are to implement a standardized electronic claims system and to provide transparency of hospital performance.[14] All 82 university teaching hospitals are obliged to adopt the DPC system, but adoption by community hospitals is voluntary. The survey of the DPC hospitals is conducted between July 1 and December 31 each year by the DPC Research Group, in collaboration with the Ministry of Health, Labor, and Welfare.[15–17] Not only administrative claims data, but also detailed patient data, are collected for all inpatients discharged from the participating hospitals between July 1 and December 31. Data are used mainly for profiling practice patterns, refinement of case-mix classification, and health policy planning, such as resource allocation. The survey started in 2003 with 82 teaching hospitals, and the number of participating hospitals steadily has increased: 262 in 2006, 926 in 2007, and 855 in 2008. Today, DPC hospitals are distributed throughout Japan. Data on all the acute-care patient admissions in the participating hospitals were compiled, and the capture rate of patient admissions was 100%. The numbers of patients included were 1.08, 2.99, and 2.86 million in 2006, 2007, and 2008, respectively. The number in 2008 (2.86 million) represented approximately 40% of all inpatient admissions to acute-care hospitals in Japan. All of the data for each patient were recorded at discharge. Hospitals sent all of the anonymous data for each month between July and December to the research group, and data were compiled in the database server in the Department of Health Management and Policy at the University of Tokyo.

The database includes the following data: location of hospitals; patients' age and gender; diagnoses and comorbidities at admission and complications after admission recorded with text data in the Japanese language and the International Classification of Diseases, 10th Revision codes; procedures coded with Japanese original codes; drugs and devices used; lengths of stay; and discharge status.

The DPC database partially corresponds to the Nationwide Inpatient Sample in the United States[18] but has several unique advantages. In the DPC database, complications that occurred after admission are clearly differentiated from comorbidities that were already present at admission. To optimize the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts. At discharge, the diagnoses and comorbidities were registered to the DPC database once per admission. Medical clerks and licensed medical information managers accurately record the dates of all major and minor procedures and of drug administration and device use. Physicians and hospitals have a strong incentive for data compliance because it is mandatory to obtain the DPC-based reimbursement of medical fees.

Data Extraction

From the DPC database, we identified records of all patients who underwent surgical procedures with general anesthesia in 2006–2008. We extracted information on patients' age and gender and the use of several potentially causative drugs, including volatile anesthetic agents (sevoflurane, isoflurane, enflurane, and halothane), muscle relaxants (suxamethonium, vecuronium, pancuronium, and rocuronium), and propofol.

For the identification of MH patients from the database, we performed a free text search with the term *malignant hyperthermia* (*akusei-konetsu* in Japanese), using Microsoft SQL Server 2008 software (Microsoft Corp., Redmond, WA). With regard to identification of MH patients, a simple search using the specific International Classification of Diseases code for MH (T883) was considered unreliable. Because T883 was rarely used and physicians and medical information managers in Japan were unfamiliar with the choice of T883 code, miscoding, such as a coding of R509 (fever, unspecified), could occur. For this reason, we performed a text-based search to accurately capture all of the patients with a diagnosis of MH. To ensure the reliability of the search results, two authors (Yasunaga and Horiguchi) independently performed these procedures.

Detailed profiles of the MH patients were collected, including age, gender, comorbid diagnoses, surgical procedures, use of causative agents, and use of dantrolene.

This study was based on a secondary analysis of the administrative claims data. Given the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from the Institutional Review Board in University of Occupational and Environmental Health (Kitakyushu, Fukuoka, Japan).

Statistics

Univariate logistic regression analyses were performed to examine the relationship of each anesthetic drug or demographic factor with the occurrence of MH. The threshold for

Table 1. Patients' Backgrounds and Use of Potentially Problematic Anesthetic Agents (N = 1,238,171)

Patient Characteristics and Anesthetic Agents	N	%
Patient gender		
Male	597,148	48.2%
Female	641,023	51.8%
Patient age (yrs)		
0–29	222,104	18.0%
30–69	650,571	52.6%
≥70	365,496	29.4%
Volatile anesthetic agents		
Sevoflurane	932,771	75.3%
Isoflurane	33,231	2.7%
Halothane	682	0.1%
Enflurane	35	0.0%
Muscle relaxants		
Suxamethonium	19,871	1.6%
Vecuronium	782,899	63.2%
Pancuronium	11,286	0.9%
Rocuronium	246,572	19.9%
Propofol	949,694	76.7%

significance was set at $P < 0.05$. All statistical analyses were conducted using the software Statistical Package for Social Sciences version 17.0 (Statistical Package for Social Sciences Inc., Chicago, IL).

Results

Of 6.9 million inpatients in the DPC database, a total of 1,238,171 surgical patients, who underwent general anesthesia, were identified during the survey period, including 344,224 (27.8%) in teaching hospitals and 893,947 (72.2%) in community hospitals. Table 1 shows the surgical patients' backgrounds and the use of potentially causative anesthetic agents. Overall, 48% of patients were men, and 18% were at least 29 yr of age. Sevoflurane was applied in approximately 75% of patients, whereas isoflurane, halothane, and enflurane were rarely used. Suxamethonium was infused in only 1.6% (19,871) of patients. Approximately 63% were given vecuronium, 20% were given rocuronium, and pancuronium was rarely used. Propofol was administered to 77% of patients.

We identified 17 patients with a diagnosis of MH during the study period. The two authors who independently per-

Table 2. Details of Cases with Malignant Hyperthermia

No.	Gender	Age	Diagnosis	Surgery	Dead or Alive	Sev	Iso, Hal, Enf	Sux	Vec	Pan	Roc	Pro	Dan
1	M	49	Acute epidural hematoma	Open craniotomy	Dead	+	−	−	+	−	−	−	+
2	M	12	Acute appendicitis	Appendectomy	Alive	+	−	−	+	−	−	+	+
3	M	28	Acute appendicitis	Appendectomy	Alive	+	−	−	+	−	−	+	+
4	M	59	Rectal carcinoma	Low anterior resection	Alive	+	−	−	+	−	−	+	+
5	M	60	Lung carcinoma	Thoracoscopic lobectomy	Alive	+	−	−	+	−	−	+	+
6	M	64	Metastatic chest wall tumor	Tumor resection	Alive	+	−	−	+	−	−	+	+
7	M	71	Volvulus of sigmoid colon	Hemicolectomy	Alive	+	−	−	+	−	−	+	−
8	M	77	Rectal carcinoma	Low anterior resection	Alive	+	−	−	+	−	−	+	+
9	F	61	Pancreatic head carcinoma	Pancreaticoduodenectomy	Alive	+	−	−	+	−	−	+	+
10	F	80	Thoracic aortic aneurysm	Aortic arch replacement	Alive	+	−	−	+	−	−	+	+
11	M	1	Undescended testicle, bilateral	Orchiopexy	Alive	+	−	−	−	−	−	−	−
12	M	30	Repeated shoulder abarticulation	Shoulder synovectomy	Alive	+	−	−	−	−	+	−	+
13	M	69	Lung carcinoma	Thoracoscopic lobectomy	Alive	+	−	−	−	−	+	+	+
14	F	62	Descending colon carcinoma	Colectomy	Alive	+	−	−	−	−	+	−	−
15	M	19	Auditory ossicle malformation	Tympanoplasty	Alive	−	−	−	−	−	+	+	−
16	M	41	Distal clavicle fracture	Open reduction and internal fixation	Alive	−	−	−	−	−	+	+	−
17	F	2	Severe respiratory depression	Tracheostomy	Alive	−	−	−	−	−	−	+	−

Dan = dantrolene; Enf = enflurane; Hal = halothane; Iso = isoflurane; Pan = pancuronium; Pro = propofol; Roc = rocuronium; Sev = sevoflurane; Sux = suxamethonium; Vec = vecuronium.

Table 3. Incidence of Malignant Hyperthermia and the Odds Ratio in Each Subgroup

Characteristics and Anesthetic Agents	Gender and Age	*N*	MH	Incidence [95% CI] (per 1 Million)	Odds Ratio [95% CI]	*P* Value
Gender	Females	641,023	4	6.2 [0.12–12.4]	Reference	
	Males	597,148	13	21.8 [9.9–33.6]	3.49 [1.14–10.7]	0.029
Age	≥ 30 yr	1,016,067	12	11.8 [5.1–18.5]	Reference	
	0–29 yr	222,104	5	22.5 [2.8–42.2]	1.91 [0.67–5.41]	0.226
Sevoflurane		932,771	14	15.0 [7.1–22.9]	1.53 [0.44–5.32]	0.505
Vecuronium		782,899	10	12.8 [4.9–20.7]	0.83 [0.32–2.18]	0.831
Rocuronium		246,572	6	24.3 [4.9–43.8]	2.19 [0.81–5.93]	0.122
Propofol		949,694	12	12.6 [5.9–19.9]	0.73 [0.26–2.07]	0.729

CI = confidence interval; MH = malignant hyperthermia.

formed the text-based search obtained the same results. The prevalence was calculated to be approximately 13.7 per million patients (or 1:73,000), and the 95% CI was 7.2–20.3 per million. None of the 1,238,171 patients had a preoperative diagnosis of MH. None of the 17 MH patients had a comorbid disease that was likely to constitute a risk factor for MH (*e.g.*, Duchenne muscular dystrophy).

Table 2 shows the details of the 17 patients with MH. Only one in-hospital death was identified (patient no.1), a 49-yr-old man, who underwent open craniotomy for acute epidural hematoma, and was given sevoflurane and vecuronium. Of the 17 MH patients, 14 were given sevoflurane, 10 vecuronium, 6 rocuronium, and 12 propofol, whereas no MH patient was found in patients who received isoflurane, halothane, enflurane, suxamethonium, or pancuronium. All 10 patients who were given vecuronium also received sevoflurane. Of the three patients without sevoflurane (patients no. 15, 16, and 17), all received rocuronium and two received propofol. Dantrolene was administered to 11 of 17 MH patients.

Table 3 shows the prevalence of MH in each subcategory, and the results of the univariate logistic regression analyses. Men were approximately 3.5 times more likely to have MH (odds ratio: 3.49; 95% CI 1.14–10.7; $P = 0.029$). The prevalence of MH in patients at least 29 yr of age was relatively high compared with those older than 30 yr (22.5; 95% CI 2.8–42.2 *vs.* 11.8; 95% CI 5.1–18.5 per million), but the difference was not significant. The rate of MH was relatively high in sevoflurane users (15.0; 95% CI 7.1–22.9 per million) or rocuronium users (24.3; 95% CI 4.9–43.8 per million), but no statistical significance was found for any drug.

Discussion

Diagnosis of MH

There are no validated gold-standard MH diagnostic criteria globally. The diagnosis of MH is based on clinical presentation with or without laboratory testing (*e.g.*, caffeine halothane contracture test). In the Clinical Grading Scale developed by Larach *et al.*,[19] differential weighting is given to each of the manifestations of MH, but not all the tests can be performed in an individual MH episode. In Japan, the original MH criteria established by the Japan Society of Anesthesiologists are widely used and consist of two elements: body temperature increase (more than 40°C or more than 38°C with a markedly increasing rate [*i.e.*, > 0.5°C per 15 min]) and other clinical presentations of MH (*e.g.*, tachycardia, arrhythmia, metabolic acidosis, muscle rigidity, and myoglobinuria).

Our study identified 17 patients diagnosed as MH during the study period in Japan, based on the designation as MH by the physicians in charge. The anesthesiologists in charge were responsible for diagnosing MH. However, we could not confirm whether the patients definitely fulfilled the MH criteria because we could not obtain information on the detailed clinical features or laboratory data through the DPC database.

Prevalence and Patient Fatality Rate in MH

A marked advantage of the DPC database is its population representativeness. According to the Survey of Medical Institutions 2008 in Japan,** the number of surgeries under general anesthesia performed throughout Japan was 187,097 per month. Our survey included 1,238,171 patients during a total of 18 months, which represented approximately 36.8% (1,238,171/18/187,097) of all surgeries under general anesthesia in Japan. Our results showed the actual prevalence of MH (13.7 per 1 million) in the Japanese population between 2006 and 2008, which was similar to the roughly estimated figure (16.7 per 1 million) presented in a previous Japanese report.[6] Our study was the first to confirm the actual nationwide prevalence of MH, based on large-scale cross-sectional data.

According to the reported evidence, the genetic background related to MH seems to be different between Japanese and Western patients. For example, recent progress in screening for causative MH mutations of the RYR1 gene has shown a genetic diagnosis in 30–50% of Swiss MH families, whereas only one Japanese family was reported to have the MH mutation.[20,21] The detection rate of RYR1 mutations in Japanese MH patients was lower than that in North Ameri-

** Survey of Medical Institutions 2008. Vital and Health Statistics Division, Ministry of Health, Labour and Welfare, Japan. http://www.mhlw.go.jp/toukei/saikin/hw/iryosd/08/index.html. Accessed August 13, 2010.

can MH patients.[22] Nevertheless, the prevalence of MH in the Japanese population (13.7 per million) was comparable with that in New York State (9.6 per million).[7] Although several genes related to MH have been identified,[2,3] there still may be unknown genetic factors both in Japanese and Western populations. The database may be useful not only for determining MH prevalence in Japanese but also for suggesting the existence of other undetected MH mechanisms. Further studies should be conducted to elucidate other etiologies of MH in any population.

Our results also showed that men were three times more likely to contract MH than women. The prevalence of MH was relatively high in patients aged younger than 30 yr compared with those older than 30 yr. These results coincide with recent Japanese and American reports.[23,24]

In the current study, the patient fatality rate was 5.9% (1 of 17 patients). The patient fatality rate in MH in the 1970s was approximately 70%,[8] whereas a recent North American study reported that of 291 events from 1987 to 2006, 8 (2.7%) resulted in cardiac arrest and 4 (1.4%) resulted in death.[25] In Japan, the patient fatality rate decreased over time, from 42.3% during 1961–1984 to 15.0% during 1985–2004.[23] A possible explanation for the recent decrease in the death rate after MH is the improved system of monitoring and treatment. Widespread use of end-tidal carbon dioxide monitors and continuous body temperature measurement, with improved availability of dantrolene, could have resulted in early detection and improved clinical consequences of MH.[6] In the current study, dantrolene was given to only 11 of 17 MH patients. One possible reason is the availability of dantrolene in Japanese facilities. A previous Japanese study reported that 22.5% of hospitals had no stock of dantrolene in their operating rooms and 3.0% of hospitals had no stock on their premises.[6] Another reason may be that six patients might have responded to other therapies (*e.g.*, active cooling of the body), resulting in successful improvement without dantrolene use. That there were no in-hospital deaths in the six MH patients treated without dantrolene might support this possibility.

MH Risk of Anesthetic Agents

In contrast to the New York database[7] and others,[18] the unique advantage of the DPC database is that it can provide comprehensive information on all drugs given to all inpatients. We could identify the drugs given during anesthesia not only in MH patients but also in all patients undergoing general anesthesia. Therefore, the database enabled us to make a statistical comparison of the rates of MH between users and nonusers of problematic anesthetic agents.

Suxamethonium is a well-known triggering agent of MH. After exposure to this agent, deterioration of calcium homeostasis in the skeletal muscle cells may lead to muscle contracture, metabolic failure, lactic acidosis, and heat production.[1,8] Suxamethonium had commonly been used in anesthetic induction for decades; however, use of this drug has gradually decreased, and use of vecuronium and rocuronium has gradually increased. Our results showed that suxamethonium was used in only 1.6% of all patients who underwent general anesthesia, and the association between suxamethonium and MH could not be assessed because no MH patient was found among suxamethonium users.

As well as suxamethonium, volatile anesthetics also are considered triggering agents of MH. *In vitro* experiments, animal models, and human case series reports showed the potential risk of sevoflurane for MH.[9,10] Our data showed that sevoflurane was widely used and other volatile agents were rarely used in Japan. Our epidemiologic study indicated a relatively but not significantly high prevalence of MH in sevoflurane users. There was no MH case with volatile anesthetics other than sevoflurane.

Nondepolarizing muscle relaxants are now considered to be much safer than suxamethonium. However, limited evidence suggested a possible MH risk with nondepolarizing muscle relaxants. Several case reports suggested that severe masseter muscle rigidity might have been occasionally induced by administration of a nondepolarizing muscle relaxant.[26,27] Severe masseter muscle rigidity was identified as an early sign of generalized muscle rigidity and one of the signs for evaluating the likelihood of MH.[28] In practice, 32.7% of Japanese MH patients showed severe masseter muscle rigidity,[29] and 50% of Western patients with severe masseter spasms were subsequently confirmed to be MH-susceptible from muscle biopsies and contracture testing.[30–32] Based on these limited data, in the current study, we hypothesized a relationship between nondepolarizing muscle relaxants and MH. The prevalence of MH in vecuronium users was relatively low, and no MH patient was found among the pancuronium users. Furthermore, use of rocuronium also was not statistically or significantly associated with MH. Our results thus supported the conventional consideration that nondepolarizing muscle relaxants are safe; however, the current study did not definitely eliminate a possible association of increased MH occurrence with rocuronium because of a relatively increased risk of MH. Our data might be useful in suggesting to anesthesiologists the possibility of MH when using rocuronium. We should continuously gather follow-up data on the relationship among nondepolarizing muscle relaxants and MH. Furthermore, future studies will be necessary to investigate the direct relationship by means of MH-susceptible muscle biopsy and contracture testing.

Whether propofol can induce MH or not remains controversial.[11–13] Our epidemiologic data showed a relatively low prevalence of MH in propofol users and did not support an association between propofol and MH.

We should consider the possible effect of inhalation of residual volatile agents in the anesthetic circuits. Technical recommendations for the management of patients known to be MH-susceptible include: having clean anesthesia equipment and delivery of 10 l/min oxygen flow through the

equipment for more than 5 min preoperatively; removal of volatile agents from the equipment; and having a fresh carbon dioxide absorbent in the canister or nonrebreathing system.[33] We found three MH patients without exposure to suxamethonium and any volatile anesthetics. It is possible that they might have been accidentally exposed to residual volatile agents in the anesthesia equipment.

Limitations

Several limitations should be acknowledged. The first limitation is related to the use of an administrative claims database. Generally, the recorded diagnoses in such databases are less well validated than those in planned prospective surveys. However, several advantages of the data submission processes in the DPC database, such as physician-dependent diagnosis reporting, requirement of data entry *via* a strict data format, and mandatory submission linked with reimbursement, maximized the accuracy and consistency of reporting. Second, given the anonymous nature of the database, it is not possible to determine whether the same individual has been noted to have MH more than once during multiple admissions. Third, the database does not include information on patients' signs and symptoms or laboratory data; thus, we could not evaluate the validity of MH diagnosis and the severity of each individual MH episode. Underreporting or biased reporting (withholding sensitive cases) could lead to underestimation of MH events. Fourth, although the database included 40% of acute-care inpatients in Japan, participation in the DPC system was voluntary for each hospital, and patient selection was not based on a random sampling method. The database only included data between July and December, and such a time restriction will cause inaccurate estimation of the incidence of several diseases that show seasonal variation. However, to our knowledge, the occurrence of MH is unlikely to show seasonal variation, and this time restriction should have little affect. Finally, it was not possible to perform a multivariate analysis to examine the concurrent effect of multiple factors, including patient characteristics and drugs used, because of the extreme rarity of MH occurrence. Data should be continuously compiled, and further analysis with larger numbers of cases is necessary.

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Case Report

Complex Regional Pain Syndrome Revived by Epileptic Seizure Then Disappeared Soon during Treatment with Regional Intravenous Nerve Blockade: A Case Report

Masahiko Sumitani,[1] Arito Yozu,[2] Toshiya Tomioka,[1] Satoru Miyauchi,[3] and Yoshitsugu Yamada[1]

[1] *Department of Anesthesiology and Pain Relief Center, The University of Tokyo Hospital, Tokyo 113-0033, Japan*
[2] *Department of Rehabilitation Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan*
[3] *Kobe Advanced ICT Research Center, National Institute of Information and Communications Technology, Kobe 651-2492, Japan*

Correspondence should be addressed to Masahiko Sumitani, sumitanim-ane@h.u-tokyo.ac.jp

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We present a case of complex regional pain syndrome (CRPS), in which symptoms, including burning pain and severe allodynia, were alleviated by using a regional intravenous nerve blockade (Bier block) combined with physiotherapy, but reappeared following an epileptic seizure. Symptoms disappeared again following control of epileptic discharges, as revealed by single-photon emission computed tomography (SPECT) and electroencephalography (EEG) results. Although systemic toxicity of a local anesthetic applied by Bier block was suspected as a cause of the first seizure, the patient did not present any other toxic symptoms, and seizures repeatedly occurred after Bier block cessation; the patient was then diagnosed as having temporal symptomatic epilepsy. This case suggests that symptoms of CRPS may be sustained by abnormal brain conditions, and our findings contribute to the understanding of how the central nervous system participates in maintaining pain and allodynia associated with CRPS.

1. Introduction

Complex regional pain syndrome (CRPS) causes extreme pain. Dysfunctions of the peripheral nervous system, including the sensory and sympathetic nervous systems, are typically considered to sustain CRPS. The central nervous system (CNS) has also been reported to play an important role in CRPS emergence and maintenance [1]. Although many clinical studies on CRPS and studies using animal models have been conducted, the pathophysiological mechanism of CRPS is not yet clear [2–5]. Here, we report a case of a CRPS patient whose pain was improved by a regional intravenous nerve blockade combined with physiotherapy; however, CRPS relapsed into intolerable pain and severe allodynia following an epileptic seizure. Recurrent CRPS then rapidly improved through the control of epileptic discharges. During epileptic episodes, we investigated the CRPS patient using single-photon emission computed tomography (SPECT) and electroencephalography (EEG). Our findings may contribute to the understanding of how the CNS participates in maintaining CRPS-related pain and allodynia.

2. Case Report

A 65-year-old woman with aortic regurgitation following infectious endocarditis had undergone twice aortic valve replacement procedures within 2 months. After the second operation, more than 3 weeks were required before she could be weaned from intensive treatment, including artificial ventilation and sedative drug administration. Following recovery from heart failure, sedative drug administration was discontinued. The patient's clouded consciousness persisted for several days, but she did not show signs of epilepsy. At that time, a computed tomography (CT) scan of the brain showed a diffuse lacunar infarction but no distinct lesion. As the patient's consciousness increased, she complained of intense pain and allodynia originating from the neck and radiating to

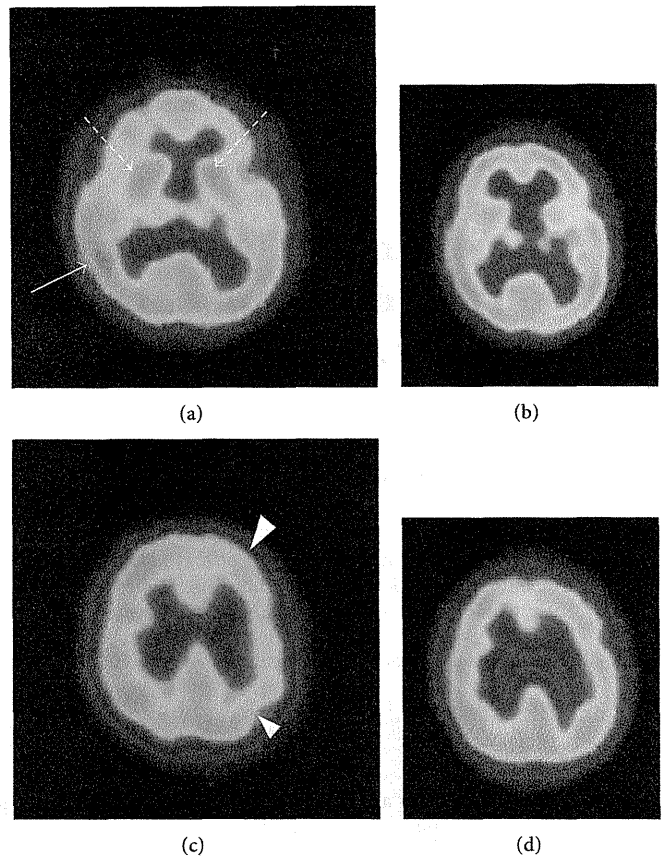

FIGURE 1: 99^m-HMPAO-SPECT images acquired during a seizure and 10 days later. (a) and (c) show relative hyperperfusion in the right parietal lobe (arrow) and both thalami (dotted arrows) and relative hypoperfusion in the left prefrontal and parietal lobes (arrow heads) during a seizure. (b) and (d) are the same axial slices as (a) and (c), respectively, obtained 10 days after the final seizure. In (b) and (d), relative hyperperfusion and hypoperfusion are not noted, as bilateral symmetrical cerebral perfusion has been normalized.

her left hand. The patient was treated with oral nonsteroidal anti-inflammatory drugs, but no favorable effects were observed. Her pain worsened, and she consulted our pain clinic 3 months after the second operation. She showed no signs and symptoms of neurological complications, except for pain and allodynia, before and after the cardiovascular surgeries.

During the first examination at our pain clinic, she complained of spontaneous burning pain and severe allodynia from her neck to her hand; her left hand was swollen, pale, and hot. We diagnosed her condition as complex regional pain syndrome (CRPS) [6] and began treatment, although the initiating injury was unknown. Because she was being administered anticoagulant therapy, many of the available neural blockades could not be used, except for a regional intravenous nerve blockade (Bier block, with 20 mL of 0.5% lidocaine). This neural blockade was performed 4 times per week concurrently with oral administration of a tricyclic antidepressant, nortriptyline (20 mg); this treatment resulted in the gradual reduction of pain and allodynia, which allowed the patient to receive physiotherapy. One month after treatment, pain and allodynia symptoms were nearly eliminated and swelling had also diminished. Additionally, her upper limb motor disturbance was significantly improved.

One hour after the 18th Bier block, the patient suddenly experienced a major epileptic seizure and lost consciousness during physiotherapy. This was the first time in the patient's life that a seizure episode had occurred. Intravenous administration of diazepam followed by thiamylal was used to control the seizure. An emergency CT scan of the brain showed no distinct lesions, which was confirmed by magnetic resonance imaging (MRI). The following day, the patient regained consciousness and complained of burning pain and severe allodynia localized in her left upper limb; subsequently, there was a recurrence of other CRPS symptoms (swelling, skin temperature escalation, and paleness). Despite regular intravenous administration of phenytoin, seizures occurred several times over the following 3 days, which occasionally required additional administrations of intravenous diazepam or thiamylal, and consciousness was again lost. When the patient was partially asleep due to intravenous anticonvulsants, she executed escaping movements for noxious stimulations on various healthy body parts but did not respond to noxious and tactile stimulations

on the left upper limb, suggesting an absence of hyperalgesia and allodynia. After 3 days, her consciousness was fully recovered and no seizure episodes occurred. The patient had no further complaints of burning pain or allodynia. SPECT examinations, using 99^m-Tc-hexamethyl-propylene amine oxime (HMPAO), were performed during the seizure period and 10 days later (Figure 1). The first image, obtained during a seizure, showed relative hyperperfusion in the right parietal lobe and both thalami and relative hypoperfusion in the left frontal and parietal lobes (Figures 1(a) and 1(c)), which improved after 10 days (Figures 1(b) and 1(d)). Electroencephalography (EEG) examinations were also carried out immediately following a seizure and 2 weeks later. EEG readings immediately following a seizure showed irregular and sporadic spiked waves in the left temporal lobe, followed by spikes in both the temporal lobes. Clinically, the patient showed an intermittent left upper limb spasm, although obvious epileptic discharges were not noted on EEG readings after the 3-day seizure episodes. Although postictal EEG readings occasionally displayed irregular spiked waves in the left posterior parietal and temporal lobes, the patient did not show epileptic symptoms. Clinical symptoms suggested that spiked waves were not related to the intermittent left upper limb spasm. On the basis of the SPECT and EEG findings, our neurologist diagnosed the patient as having temporal symptomatic epilepsy focused in the right parietal lobe. Her recovery was uneventful, and pain and allodynia nearly disappeared, although her skin color remained pale and her hand remained hot.

We obtained her consent to report her progress in accordance with the Declaration of Helsinki.

3. Discussion

The initiating injury causing CRPS symptoms in our patient was unknown. We speculated that an unconfirmed brachial plexus injury induced by a median sternotomy [7] and/or prolonged immobilization by sedative drug administration [8, 9] may have been a trigger. Furthermore, pain and allodynia may have been derived from disturbed cerebral function, possibly related to the use of heart-lung machines on 2 occasions and for many hours, and infectious endocarditis, which can induce epileptic seizures. Ictal pain related to an epileptic seizure has been noted in approximately 3% of reported epilepsy cases, typically involving an entire limb, a part of a limb, or hemibody [10–12]. Ictal allodynia-related epileptic seizures have been reported in only 2 cases, and both were in children [13, 14].

This is the first known case of successfully treated CRPS revived by an epileptic seizure. Following the first seizure, we suspected systemic toxicity of the local anesthetic (lidocaine, 100 mg) applied by Bier block. However, the anesthetic may not have been responsible for the seizures because the first seizure occurred one hour after Bier block, and the patient did not present symptoms of systemic toxicity to local anesthetics (e.g., change in speech pattern, lightheadedness, dizziness, or agitation) before the seizure, and seizures recurred several times for 3 days following Bier block cessation. The patient's SPECT and EEG abnormal findings were primarily concentrated to the temporal and parietal lobes, whereas epileptic discharges induced by systemic toxicity of local anesthetics are known to generally originate from nonspecific regions of the brain. The patient was therefore diagnosed with temporal symptomatic epilepsy.

A previous report of a brain tumor case suggested that epileptic discharges involved in the main pain pathways (i.e., primary and secondary somatosensory cortices (SI, SII), insula, and amygdale) can cause ictal pain and allodynia [13]. A congenital epilepsy case report suggested that deregulation of pain control established by relative hypoperfusion in the thalamus may play an important role in causing ictal pain and allodynia [14]. Furthermore, acute CRPS is reported to be related to hyperperfusion in the thalamus [15]. On the basis of these findings, we considered that the epileptic discharges noted on the EEG readings and subsequent hyper- and hypoperfusion in the specific brain regions, as revealed by 99^m-HMPAO SPECT, originated from the right parietal lobe, which includes the two main pain pathway regions (i.e., SI and SII); hyperfusion and hypofusion then spread over the entire brain, including other regions in the pain pathways (i.e., thalamus, anterior cingulate cortex, insula, and amygdala), during the seizure. This abnormal brain condition likely resulted in pain and allodynia. Further, recent advancements in functional brain imaging revealed that the anterior insula, which is strongly associated with autonomic nervous function, is reorganized in CRPS patients [16]. For our patient, abnormal autonomic-like symptoms (i.e., edema, skin discoloration, and skin temperature asymmetry) were revived by epileptic seizures. This may be related to reorganization of autonomic cerebral regions. In the present case, the second episode of CRPS symptoms occurred immediately after the first epileptic seizure episode and then rapidly disappeared with the control of epileptic discharges, although we administered antiepileptic medications, which has little potential to improve neuropathic pain. We therefore concluded that epileptic discharges relapsed into CRPS. Alternatively, we speculate that repeated seizures contributed to improvement of the second bout of CRPS symptoms. For epileptic seizure and pain relief, it has been reported that electroconvulsive therapy (ECT) can be used as an alternative treatment for chronic neuropathic pain [17]. In ECT, epileptic seizures are necessary for pain relief, as fewer seizures are related to a reduced analgesic effect. A possible mechanism of ECT for pain relief may involve alteration of neurotransmitter levels in cerebrospinal fluid, resulting in pain perception modulation. Therefore, we cannot completely rule out the possibility that repeated seizure episodes may have improved the second occurrence of CRPS symptoms.

In conclusion, the present case suggests that a pathophysiological condition(s), such as epileptic discharge and/or abnormal brain perfusion, can repeatedly trigger ictal pain, allodynia, and other signs and symptoms of CRPS when brain regions participating in pain perception have been sensitized. However, why abnormal autonomic-like symptoms of CRPS remain after controlling epileptic discharges and improvement of pain and allodynia is unclear.

4. Conclusion

We present a case of CRPS in which the symptoms of burning pain and severe allodynia were once resolved but returned following an epileptic seizure. These symptoms disappeared following the control of epileptic discharges. This suggests that CRPS symptoms may be sustained by abnormall brain conditions, and our results contribute to the understanding of how the CNS participates in maintaining pain and allodynia associated with CRPS.

Acknowledgments

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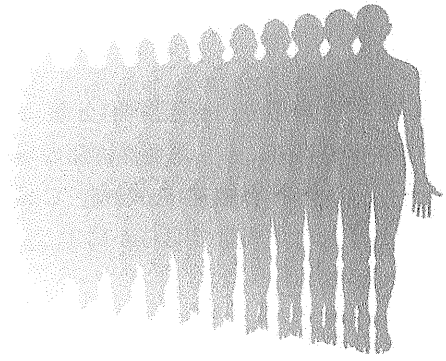
【テーマ①】

痛みの質的評価



1：東京大学医学部附属病院麻酔科・痛みセンター，2：東京大学医学部附属病院整形外科・脊椎外科

住谷昌彦[1)]，竹下克志[2)]，原　慶宏[2)]，山田芳嗣[1)]

はじめに

「痛み」(Pain)は“組織の実質的ないし潜在的な傷害と関連した，あるいはこのような傷害と関連して述べられる不快な感覚的かつ情動的体験”と国際疼痛学会(International Association for the Study of Pain；IASP)によって定義されているとおり，主観的な身体経験である．このような主観的な経験を臨床的に，なおかつ科学的に正しく扱うことを目的として，疼痛の量的評価とともに質的評価も行われてきた．

疼痛の量的評価としては，疼痛強度を数値化するvisual analogue scale(VAS)やnumerical rating scale(NRS)が主に用いられている．このような量的評価尺度は重症度評価や治療効果の判定を簡便に行えるが，痛みという主観的身体経験を表すためには不十分である．われわれが日常的に経験する痛みを例に挙げると，皮膚を鋏で切ったときの痛みと筋肉が攣ったときの痛みが同じ強さであったとしても疼痛の性質は大きく異なり，さらに，これらの疼痛に対する生体反応は皮膚に対する疼痛刺激では交感神経系が興奮(血圧や脈拍が上昇)する一方で，筋骨格系に対する疼痛刺激では交感神経系がむしろ抑制される傾向にあることが知られ[1)]，疼痛の量的評価(強度)だけでなく疼痛の質的評価も重要である．

疼痛の質的評価方法では，マギル疼痛質問票(McGill pain questionnaire)が最も有名で国際的にも非常に広く用いられている[2)]．マギル疼痛質問票には78個の痛みの性質を表す単語(例：ズキズキ，切り裂かれるような，灼かれるような，圧迫されるような，など)が列挙されており，それぞれの単語が20の特徴(例：空間的，時間的，温度的，など)に分類され，さらにそれぞれの特徴を4つの要因(感覚的，情動的，評価的，その他)に大別することができる．疼痛は不快な感覚的かつ情動的身体経験であるため，感覚面のみならず情動面についても質的に評価できるマギル疼痛質問票はその臨床的有用性が非常に高く，さらに，78単語から選択された単語の合計数や単語に付与された点数の合計得点から，疼痛の質的評価だけでなく量的評価も網羅的に行うことができる．

痛みの性質を利用した疼痛疾患の診断

がんが内臓に浸潤したがん疼痛患者の多くは“重苦しい”や“ズキズキした”痛みの性質を訴える一方，肺がんによる腕神経叢浸潤の患者は“電気が走るような”や“ビリビリした”痛みの性質を訴えることが多い．このように疼痛の発症機序に応じて痛みの性質が異なることが示唆されており，マギル疼痛質問票を用

いて疼痛疾患の病態解明(分類)が行われている[3]．がん疼痛以外にも，虚血性疼痛の病態解明や侵害情報を伝達する神経線維(Aδ線維，C線維)ごとの障害をマギル疼痛質問票で明らかにする試み[4]などが報告されている．

このような，痛みの性質から疼痛疾患の病態を推測する方法論の可能性から，われわれは疼痛発症機序がいまだ不明瞭なcomplex regional pain syndrome (CRPS) type I患者の疼痛が，炎症性疼痛であるか神経障害性疼痛であるかを判別することを試みたが，疼痛の性質からは明確な結果を得ることはできなかった．このことから，CRPS患者の発症機序が炎症性疼痛と神経障害性疼痛の両機序を併せもつ混合性疼痛機序に起因することが考えられる．

痛みの性質を利用した神経障害性疼痛のスクリーニング

さまざまな疼痛疾患のなかでも，神経障害性疼痛の性質は詳細に調査されており，マギル疼痛質問票の78単語のうち，神経障害性疼痛患者がしばしば訴える疼痛の性質(いいかえると，疼痛専門医が神経障害性疼痛と診断した患者からしばしば聴取される疼痛の性質)が明らかにされている．マギル疼痛質問票では78単語についての煩雑な調査を必要とするため，より簡便に神経障害性疼痛に特徴的な5〜7単語だけを調査する神経障害性疼痛スクリーニング質問票が各国で開発されており，本邦独自のスクリーニング質問票も存在する[5]．いずれのスクリーニング質問票も内容は類似しており，神経障害性疼痛に特徴的な痛みの性質が列挙されており，それらを点数化して神経障害性疼痛であるか否かをスクリーニングできる．臨床現場では，患者の訴える痛みを神経障害性疼痛か否か(つまり体性感覚系の損傷あるいは疾患が存在するか否か)の二者択一で判断するのは時として困難であるが，スクリーニングツールでは神経障害性疼痛の可能性がきわめて高い，可能性が高い，要素が含まれている，可能性がほとんどないという臨床に即した段階的なスクリーニングを行うことができるため，神経障害性疼痛(体性感覚系の障害)の要素を含む可能性を議論することは比較的容易であり，続く治療方針の決定に対する有用性が期待できる．実際，ドイツのグループが開発したPainDETECT(図1)はこれまで筋骨格系の機械的刺激や炎症がその主病態とされてきた慢性腰痛にも神経障害性疼痛の要素が含まれていることを明確に示し[6]，神経障害性疼痛に対する治療薬の導入が容易に図れるようになった．

痛みの性質に応じた神経障害性疼痛の重症度評価と治療効果判定

これまでわれわれは，四肢切断後の幻肢痛や脊髄損傷後疼痛患者に対して鏡を用いた神経リハビリテーション治療(鏡療法)を行い，“ナイフで刺されているような”，“電気ショックのような”など，皮膚表面で感じているような痛みの性質には鏡療法は無効である一方，“関節を捻られるような”，“筋肉を絞られるような”など，深部組織で感じているような痛みの性質にはきわめて有効であることを明らかにした[7]．痛みの性質の違いはその病態に起因しているため，痛みの性質に応じて治療効果が異なることは妥当であると考えられる．このような観点から，神経障害性疼痛患者に特徴的な痛みの性質10個それぞれについての重症度を点数化し，それらを合計することによって総合的な重症度を評価する神経障害性疼痛に特化した質問票(neuropathic pain symptom inventory；NPSI)も開発されている(図2)[8]．われわれは，自己免疫性脊髄炎による神経障害性疼痛をNPSIで評価すると疼痛の性質によって治療効果が異なることを経験している[9]．このように，NPSIを用いて神経障害性疼痛治療の知見を蓄積することによって，痛みの性質に応じて特異的に有効な治療方法の発見や，神経障害性疼痛の病態解明に繋がる可能性があると考えられる．

painDETECT™

痛みの質問票

日付		名前	

いま現在のあなたの痛みは 10 点満点でどの程度ですか？

0 1 2 3 4 5 6 7 8 9 10
なし 最大

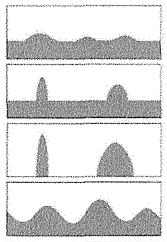
過去 4 年間で最も激しい痛みはどの程度でしたか．

0 1 2 3 4 5 6 7 8 9 10
なし 最大

過去 4 年間の痛みの平均レベルはどの程度ですか．

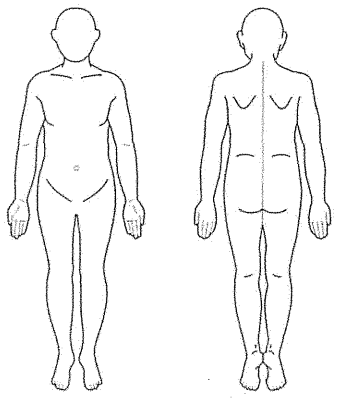
0 1 2 3 4 5 6 7 8 9 10
なし 最大

あなたの痛みの経過を表す図として，どれが最もあてはまりますか？
□印にチェックを付けてください．



- 持続的な痛みで，痛みの程度に若干の変動がある □
- 持続的な痛みで，ときどき痛みの発作がある □
- 痛みがときどき発作的に強まり，それ以外のときは痛みがない □
- 痛みがときどき発作的に強まり，それ以外のときも痛みがある □

痛みのある場所を図に示してください．



痛みはほかの部位にも広がりますか？
□はい □いいえ

はいと答えた方は，その場所と広がり方も書いてください．

痛みのある部位では，焼けるような痛み(例：ヒリヒリするような痛み)がありますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

ピリピリしたり，チクチク刺したりするような感じ(蟻が歩いているような，電気が流れているような感じ)がありますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

痛みがある部位を軽く触れられる(衣服や毛布が触れる)だけでも痛いですか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

電気ショックのような急激な痛みの発作が起きることはありますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

冷たいものや熱いもの(お風呂のお湯など)によって痛みが起きますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

痛みのある場所に，しびれを感じますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

痛みがある部位を，少しの力(指で押す程度)で押しても痛みが起きますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

一度もない	ほとんどない	少しある	ある程度ある	激しい	非常に激しい
□×0=0	□×1=□	□×2=□□	□×3=□□	□×4=□□	□×5=□□

総数 □□ (最大 35 点)

図 1 PainDETECT 日本語版

painDETECT

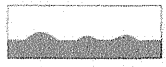
痛みの質問票のスコア

日付		名前	

「痛みの質問票」の総スコアをここに書き写してください．

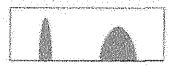
総計 □□

該当する痛みの経過のパターンと痛みの広がりの有無に応じて，以下の数値の合計を出し，それを総計スコアに加算して最終スコアを出してください．

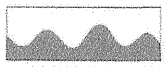


持続的な痛みで，痛みの程度に若干の変動がある　0

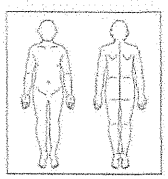
持続的な痛みで，ときどき痛みの発作がある　−1　（これに印をつけた場合）



痛みがときどき発作的に強まり，それ以外のときは痛みがない　+1　（これに印をつけた場合）



痛みがときどき発作的に強まり，それ以外のときも痛みがある　+1　（これに印をつけた場合）

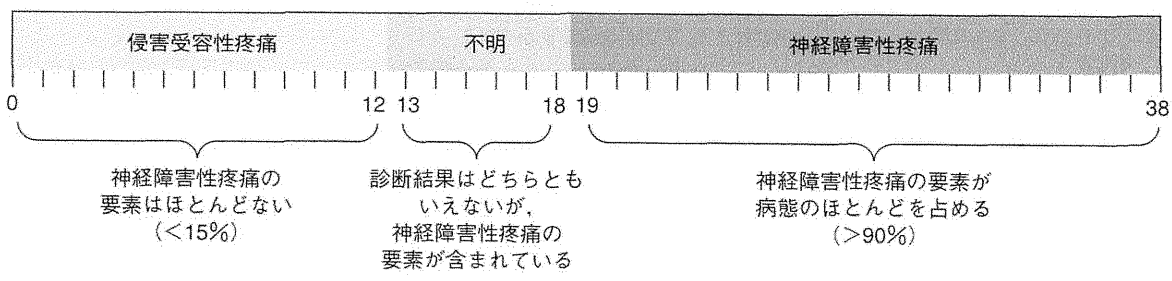


痛みの広がり　+2　（はいの場合）

最終スコア □□

スクリーニング結果

最終スコア



このシートは医師の診断に代わるものではありません．
神経障害性疼痛の要素についてのスクリーニングに使用してください．

Curr Med Res Opin 2006；22：1911-20 を改変
責任監訳：東京大学医学部附属病院麻酔科痛みセンター　住谷昌彦

PainDETECT は慢性腰痛症のうち神経障害性疼痛（神経根障害による腰痛）をスクリーニングするために開発され，ドイツでその妥当性・有用性が検証されたものである．ここに示した PainDETECT 日本語版は筆者が和訳後，日英 2 言語使用の一般人が英訳して和訳に不適切な箇所がないかを検証したものである．PainDETECT 日本語版の妥当性・有用性は検証中である．　（文献 6 から改変して引用した図を文献 10 から許可を得て掲載）