表1　スモン調査研究協議会発足時のスモンの概要

Ⅰ感染説を示唆する所見
1）地域に数年にわたって流行的に発生する．
2）家族内発生がまれでなく，家族集積性がある．
3）院内流行では病棟集積性を示した例がある．
4）家族内または院内発生において患者発生間隔は平均2.5カ月で，発生が連鎖的である．
5）夏期に好発する傾向があり，下痢，腹痛などをともなう．
6）多発地では患者年齢に浸染度前進現象がみられる．
7）発生に逐域伝播を思わせる地域がある．
8）職業的に医療職，事務職に罹患率が高い．
9）発生は特定の工場，鉱山などと関連しない．

Ⅱ感染説では説明が難しい所見
a）疫学所見
1）患者に小児がきわめてまれで，中年とくに女性に多い．
2）散発発生地域においては伝播を思わせる知見がない．
3）日本に特有な疾患で，昭和30年以降に出現した．
b）臨床所見
1）発熱を欠くことが多い．
2）血液像，髄液に炎症を思わせる所見がない．
c）病理組織学的所見
1）軸索変性，脱髄が主病変で，炎症性病変を欠く．

表2　スモン臨床診断指針

必発症状

1. 腹部症状（腹痛，下痢など）：おおむね神経症状に先立っておこる．
2. 神経症状
a．急性または亜急性に発現する．
b．知覚症状が前景に立つ．
両側性で，下半身，ことに下肢末端につよく，上界は不鮮明である．とくに異常感覚（ものがついている，しめつけられる，ジンジンする，その他）をともない，これをもって初発することが多い．

参考条項

（必発症状と併せて，診断上きわめて大切である）

1. 下肢の深部知覚障害を呈することが多い．
2. 運動障害
a．下肢の筋力低下がよくみられる．
b．錐体路徴候（下肢腱反射の亢進，Babinski現象など）を呈することが多い．
3. 上肢に軽度の知覚・運動障害をおこすことがある．
4. 次の症状をともなうことがある．
a．両側性視力障害
b．脳症状，精神症状
c．緑色舌苔，緑便
d．膀胱・直腸障害
5. 経過はおおむね遷延し，再燃することがある．
6. 小児にはまれである．

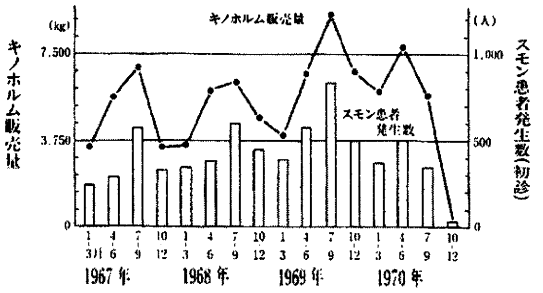

図3　キノホルム販売量と3カ月ごとのスモン患者発生数

ホルムと3価の鉄イオンとのキレート化合物が検出され，本剤の関与が強く示唆された．なお，この緑色結晶は看護婦が気づいたことが発端となっている．他の緑色の生体材料からも同様の分析結果が得られた．

ただちに新潟大学神経内科の椿忠雄らは7病院（新潟6，長野1）のスモン患者171名の疫学調査を行い，次のような結果を得た[3]．

1）97%の患者が神経症状発現時にキノホルムを服用しているのに対して，他の薬剤は多いものでも50%である．
2）神経症状発現時期とキノホルム服用時期との間に密接な関係がある．
3）一日服用量の多い症例は短期間の服用で発症する．
4）服用量と重症度との間に相関関係がみられる．
5）病院のキノホルム使用量と患者発生の頻度との間に関連がある．
6）患者の多発した病棟においてのみキノホルムが長期投与された．

これらの事実を根拠に，8月6日椿は新潟県衛生部を通じてキノホルム原因説を厚生省に報告し，同省は9月7日に中央薬事審議会に諮問し，その答申を得て9月8日にキノホルム剤販売中止処置をとった．なお，学会での正式発表は9月5日の日本神経学会関東地方会である[18]．

ほぼ同時期に，吉武と井形[19]は腹部手術後にSMONを発症した患者にキノホルム製剤が使われていたことを報告する論文を投稿した（8月12日受付）．

スモン調査研究協議会はただちに全国調査を行い，調査可能だった890例では85%にキノホルム製剤服用歴が明らかとなり，11月13日に報告された[20]．残りの15%になお曖昧さが残されてはいたが，キノホルム禁止後に新規発症患者は激減し，本剤とスモンの関係がさらに強く示唆されていった（図3）．

後日の検証では[3,4]，病院間においてキノホルム使用量とスモン患者数に有意な正の相関性がみられている．局地的な伝染性や，院内発症が疑われる事例でも，本剤処方の傾向が強い医師の存在があり，その医師の転任によってスモン患者が発生する病院も移動していた．製薬会社の営業担当者の転勤によっても同様の現象があったという．臨床経過においても，大量のキノホルムは腸管の蠕動障害をおこし，腹痛や鼓腸などの腹部症状を増強させてから神経症状が出現することが明らかになった．中にはスモンの感染症説に基づいて，発症後にさらにキノホルムを投与し続けたケースもあった[4,5]．また，夏期にスモン患者発生が多い現象も，食中毒等の消化器疾患が多発する季節であり，したがってキノホルムの使用量も増加したためと説明ができた．

動物実験では，井形ら[21]は家兎にキノホルムを静注し，下肢の麻痺と坐骨神経の軸索変性を確認した．立石ら[22]はビーグル犬8頭にキノホルムを経口投与したところ，3頭は急性中毒で死亡し，4頭で投与後20-28日に後肢が麻痺した．病理所見は脊髄ゴル束の軸索変性や髄鞘の変性，末梢神経の軸索腫大や断裂等のスモンに一致する変化が認められた．

1972年3月，スモン調査研究協議会は「疫学的事実ならびに実験的根拠から，スモンと診断された患者の大多数はキノホルム剤の服用によって神経障害をおこしたものと判断される」と総括し[23]，治療指針を示した（にもかかわらず，完全治癒例は少なく，現在も重篤な後遺症が続いている）．同年4月，厚生省衛生局企画課に特定疾患対策室が設置され，スモンを始め，ベーチェット，重症筋無力症，SLE，多発性硬化症，再生不良性貧血，サルコイドーシス，難治性感疾患が特定疾患に指定され，調査研究班が発足した．スモンが難病研究の原点といわれる理由はここにある．

キノホルムの歴史

キノホルム（5 chloro-7 iodo-8 hydroxy-quynoline）は，キニーネを構成するキノリン核に水酸基やヨード，塩素等が結合した殺菌力の強い化学物質で，1899年にスイスのバーゼル化学工業（後のチバガイギー）で開発された．翌年「外用防腐創傷剤」，つまり「ぬり薬」ヴィオフォルムとして販売を開始

された[5]．1920年代になって，本剤の殺菌力の強い飲み薬としての可能性が検討され，33年にアメーバ赤痢に有効な薬剤として報告された．日本へは1913年に輸入され，24年に陸軍によって製造された．内服薬としての試用は1929年で，腸結核，大腸カタル，赤痢，アメーバ赤痢に有効で副作用はないと治験報告がなされている[3]．

しかしながら，1935年にアルゼンチンでキノホルムの神経毒性を疑わせる症例の発生があり[24]，薬学的実験根拠なしの投与容量が原因と批判を受けた．スイスは本剤を劇薬指定し，36年には日本もこれにならった．38年には日本国内でもキノホルム投与後に下肢にしびれが出現した3症例が出現したという[25]．ところが，39年にわが国では本剤の劇薬指定が取り消され，戦時薬局方に記載され，軍需用に国内で生産が拡大していった．

キノホルムを使用したのはアメリカも同様だったようだが，動物実験で非水溶性でも投与後に腸管から吸収されること，神経毒性があることを明らかにし，使用する上での注意が喚起されていた[3]．1945年には，David[26]はJAMAに，次のように記載している．「アメーバ症治療薬の乱用で中毒がでている．キノホルム等は毒性が強いから10-14日を限度とし，2-3週間休薬すること，アメーバが発見されなかったら使用しないことが大切である」．さらに60年には米国食品衛生局（FDA）も医師の処方せんが必要でアメバー赤痢への限定使用とし，この旨を製薬会社のチバガイギー（45年にバーゼル化学工業より改称）にも通告した．

一方，敗戦直後の混乱期の日本で，消化器感染症の蔓延は容易に想像できる．1948年にはキノホルムの生産が再開され，また，厚生省の薬事審議会は内外の薬局方に収載されている薬品を一括承認し，本剤も含まれていた[3)-5)]．その後も，安全で無害な薬剤として広く使われ，61年の健康保険制度が完成してからは，使用量が増加した．エンテロヴィオフォルムに関していえば，53年から61年の間に220倍にのびている．当初は1日0.6gであった常用使用量も，2.0-3.0gと大幅に増加し，家庭への配置販売薬（いわゆる“富山の薬”）の整腸剤としても認められた．キノホルム含有薬剤は173品目にも及び，93社が販売していた[5]．

なお，近年キノホルムは抗認知症剤や抗悪性腫瘍剤の可能性が言われている．かつて重篤な薬害をきたしたことを念頭に置き，有用性有益性を考えるべきである．

薬害事件

スモンの原因がキノホルム剤であることは，国によって使用が認可されていた薬剤による重篤な副作用，薬害事件であり，国とキノホルムに関わった製薬会社の責任が強く問われることになる．すでに1971年5月には東京地方裁判所にスモン患者による損害賠償請求訴訟がなされ，次いで各地で集団訴訟がおこり，社会的問題としてのスモンは別の様相を呈することになる．最終的には6,476人が提訴した．

1971年4月にTsubaki[27]がキノホルムによる神経症状の論文をLancetに発表すると，チバガイギー側がただちに反論[28]，これらへの反論やTateishi ら[29]がキノホルムの動物実験のデータを示し，Lancet誌上でスモンの病因説が再び争われた．これを通じて日本国内での発症が海外に知れ渡り，また，スウェーデン，デンマーク，イギリス，オーストラリアなどからキノホルム剤服用によるスモン類似症例が報告された[3]．

国と日本チバガイギー，武田製薬，田辺製薬のいわゆる製薬三社，患者団体との訴訟は，キノホルムと井上ウイルスを軸に長期化した．1953年の東京地方裁判所での勝訴も患者側は内容を不満として控訴したが，1980年までには徐々に和解が進んだ．和解においてスモン患者との認定のために，祖父江逸郎を団長とする15名の鑑定団が組織され，当時の国立病院からは国立病院医療センターの越島新三郎，国立東京第二病院の片岡喜久雄，呉病院の大村一郎が参加している．1979年に，薬害被害者救済を目的に『医薬品副作用被害者救済基金法』が制定され，被害者と認定された人には重症度に応じた損害賠償金と，製薬会社の拠出金による薬害救済基金からの健康管理手当・年金が支給された．

恒久対策として，原因追及と治療法の開発，検診等で予後追求と健康管理を行うことになり，厚生省特定疾患「スモン調査研究班」，あるいは厚生労働省難治性疾患対策事業「スモンに関する調査研究班」で事業が引き継がれてきており，平成20年度からは筆者が研究代表者を務めている．

また，同様の事件を再びおこさないように，1979年に薬事法が改正され，行政の医薬品安全性確保義務が初めて明文化された．

教　訓

上記のように，戦後の混乱期を脱したばかりの日本に現れた奇病スモンは，多くの研究者たちの努力と解明への熱意で，汎用されていた整腸剤キノホルムによる薬害と確定した．その1970年の研究や推論の発表は，『医学のあゆみ』や『日本医事新報』で，海外に論争が移った時は『Lancet』という具合に速報性のある週刊ないしは旬刊医学雑誌で行われた．Internetのない時代の速報競争というよりは，一刻も早くこの疾患の蔓延を止め，社会正義を実現するための情熱の現れだったとうかがえる．

スモンが社会問題となる直前，1962年頃にアザラシ肢症の催奇形性の鎮静剤サリドマイドの薬害事件があった．サリドマイドが新薬であり，また因果関係が容易に確定できたのに対し，キノホルムは太平洋戦争前から安全だといわれて使われてきた薬剤だったのと，症状や経過から感染症ないしは傍感染性疾患が疑われた点が，スモンの病因確定に時間を要し，被害の一層の拡大を来してしまった．

戦後混乱期は医薬行政も体制が整わず，応急的に精査せずに薬品を薬局方に収載し，行政機能が落ち着いてからも再審査されることなく，安全性に疑いをもたれずに使われ続けていた．また，戦前から戦後しばらくまでは国際的孤立が続き，海外の医学情報が十分に入ってこず，仮に情報が入ったとしても受け止めて対応するだけの人的資源がなかったこと等が災いしていた．さらに，医学知識や医療情報・技術も現在よりは均てん化されておらず，薬剤の用量用法でも，医師の経験や主観によることが多かった点も背景にあった．

スモン研究の過程では，椿より前にも，国立病院研究班のようにキノホルム製剤に疑いを持った医師は少数ながらもおり，また，楠井の初報告例でのエンテロヴィオフォルム投与など，スモンの症例報告論文にも使用薬剤にキノホルム製剤が記載されていたことも確認されている．国内でのなんらかの医薬品副作用の情報収集と解析のシステムがなかったことも災いしている．

椿によってキノホルム剤が原因薬剤と指摘されてから，厚生省による同剤の販売禁止までは1カ月であり，当時としては迅速な決断であったように思える．当然ながら，企業側の反発や，それ以前の過程や井上ウイルス説が脚光をあびているなどと，病因が確定していなかったことを考えると，リスクは大きかった．意思決定する側の葛藤もあり，本来ウイルス学者だったスモン調査研究協議会会長の甲野禮作は，「キノホルム説とウイルス説のどちらもまちがっているとして，どちらが患者を苦しめるか」を考えて判断したという．

しかし，医薬品が重篤な健康被害を引きおこしている疑いがあるとしても，製品回収を命じるだけの法的根拠もなかった．結果的にキノホルム販売中止後にスモン発症がなくなったので，疫学的に原因として確認されたが，そうでなかった場合はどういう展開になったのだろうか？必要な行政措置を速やかにとり，もし違っていたならば国がきちんと対応するシステムが必要となった．

このようなキノホルムやサリドマイド等の薬害事件を教訓として，1979年に改正された薬事法には，次のような点が盛られている．

1）薬局方収載品についても承認申請の義務づけ，安全性確保のための承認基準を明記した．
2）承認6年後の再評価を義務づけ．承認済みでも必要に応じて再評価を課した．
3）新薬に限らず有効性，安全性に関する情報の収集と報告を業者に義務づけた．
4）患者への臨床試験基準を省令で制定．事前に厚生大臣に計画提出を義務づけた．
5）薬事法違反でなくとも，重大な健康被害発生の恐れがあるときの販売の一時停止など，厚生大臣に緊急措置命令権を付与．
6）再評価時に基準不合格が判明した場合の承認取り消し，回収命令などを明記．

などなどである．

これにより，薬剤の治験基準は強化され，内外の有害情報の報告や収集，副作用情報が発信されるようになったのは周知のごとくである．筆者の専門の神経内科領域ではカルシウム拮抗剤によるパーキンソニズムが問題になったし，2007年にはパーキンソン病の治療薬である麦角アルカロイド系のドパミン受容体アゴニスト製剤が弁膜障害をきたす報告が海外であったとして厚生労働省より注意情報が流された．薬事法の適用は医薬部外品，化粧品，医療器具にも及んでいる．

医薬品の有害情報に関するこのようなシステムができたにもかかわらず，血液製剤によるAIDS，硬膜移植によるクロイツフェルト・ヤコブ病，アルブミン製剤によるC型肝炎と，重篤な薬害事件がしばしばおこっている．内外から情報が入っても，そ

れを判定するのは人間である．薬害事件を繰り返さないためには，要路の人はもちろん，医療にたずさわる個々の医師にも冷静な目と，時に応じて果敢な判断力が必要とされている．

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PO10-TU-82
Characteristics of subacute myelo-optico-neuropathy (SMON) patients with hip fracture

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Purpose: The aim of this study was to investigate the incidence of hip fracture and neurological symptoms contributing hip fracture in subacute myelo-optico-neuropathy (SMON) patients.
Method: The subjects consisted of 3,269 SMON patients with 24,187 examinations from 1979 through 2007. Case control study with 80 hip-fracture patients and 160 without hip-fracture patients was examined incidence and severity of clinical signs, visual acuity, motor and sensory signs, dementia, and depression.
Results: Two hundreds and thirty hip fractures occurred in 208 patients with a man-to-woman ratio of 21:187. Annual incidence per 10,000 women stratified by age showed twice to three times higher incidences were revealed in ages under 70 years compared with those of Japanese women population. Gait with assistance or crutch was seen in 57.5% in the Hip-fracture group and 40.6% in the No-hip-fracture group, indicating a significant difference ($p < 0.05$). Sevère impairment of leg vibratory sensation was 51.9% in the Hip-fracture group and 32.0% in the No-hip-fracture group indicating a significant difference ($p < 0.02$). Other clinical signs examined showed no significant changes in variance between two groups.
Conclusions: SMON patients with significant gait disturbance due to sensory ataxia are more likely to fall and have hip fractures.

PO10-TU-83
The dynamic of neurologic disturbances in patients suffering a multiple sclerosis after high-dosage immunoablative therapy with autologous stem cell transplantation

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Among the new methods of treating multiple sclerosis (MS), high-dosage immunosuppressive therapy with Transplantation of blood Stem cell (HDIT+ASCT) is used.
Purpose: To study the dynamic of neurological disturbances in patients suffering a (MS) at different duration of time after administration of HDIT+ASCT.
Material and Methods: 79 patients have been examined, among them 36 males and 43 females. The median age of patients was about 30±4 years. Among the patients examined, 46% had relapsing-remitting MS, 28% had secondary-progressive MS, 18% primary-progressive MS, 9% had progressive-relapsing MS. The median disease duration was about 7.62±4.93. The preceded treatment with traditional therapy showed inadequate effect in all patients. The degree of expression of neurological deficiency at the time of first visit by EDSS scale was 3.99±1.72 scores and 78.52±10.89 scores by SCRIPPS scale. The autologous stem cell mobilisation protocol has been executed out according to EBMT recommendations. Evaluation of neurological state was done before starting HDIT + ASCT, after 3, 6, 12 months after infusion of blood stem cells.
Results: Results of the research showed that in majority of the patients after HDIT + ASCT expressed positive dynamic in neurological status of 19% (0,75 scores, from 3,99 to 3,24) by EDSS scale, 8% (5,96 scores, from 78,52 to 84,48) by SCRIPPS scale in comparison to initial state.
Conclusion: The positive dynamic neurological disturbances in patients with MS after HDIT + ASCT showed the effect of this method of treatment.

PO10-TU-84
Total tau and phospho-tau (Thr181) in cerebrospinal fluid of MS patients and healthy individuals

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Purpose: Tau proteins belong to the family of microtubulin associated proteins and are mainly localized in neurons. The aim of the study was to examine tau and phospho-tau as a possible markers of axonal damage, in cerebrospinal fluid of MS patients and healthy control group.
Materials and Methods: CSF of 66 MS patients was drawn to establish levels of total tau (t-tau) and phospho Thr181 tau (p-tau) proteins. Results were compared with protein levels of 120 healthy individuals. Mean age (MS 37.3±10.2 years, healthy 44.0±12.8 years) did not differed significantly. T-tau and p-tauThr181 was assayed with ELISA method with commercial kits from Innogenetics. Data were analysed with Mann-Whitney test due to lack of normal distribution. Results were expressed as medians. $P < 0.05$ was considered significant.
Results: There was significant difference in total-tau and phospho-tau concentrations between both groups (t-tau: healthy 146.3 pg/ml vs MS 171.3 pg/ml, $p = 0.04$, p-tau: healthy 38.86 pg/ml vs MS 56.84 pg/ml, $p = 0.001$). In contrast there was no difference in p-tau/t-tau ratios. After 7 extreme values of t-tau (outliers in probability density function, >SD) were excluded there was no difference in t-tau concentrations (146.3 pg/ml vs 158.8 pg/ml), but significant difference in p-tau/t-tau ratios was observed (healthy 0.23 vs MS 0.35, $p = 0.006$).
Conclusions: T-tau seems to be a useful marker in MS but its reliability depends upon disease activity. In stable patients t-tau does not differentiate MS patients from healthy individuals. In contrast phospho-tau concentrations differs significantly regardless MS activity and should be considered as a possible potent marker in MS pathology. Elevated levels of p-tau with normal t-tau in stable stage of MS suggest axonal loss may be accompanied by disturbed tau metabolism and abnormal phosphorylation.
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PO11 – Stroke: experimental studies

PO11-TU-01
Platinum nanoparticle rescues brain damage in rat middle cerebral artery occulusion/reperfusion models by quenching reactive oxygen species

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Platinum nanoparticles were prepared by an alcohol reduction method and complementarily stabilized with polyacrilic acid (PAA-Pt). The average diameter of PAA-Pt was about 2nm. They were well dispersed in water and became colloidal solution. PAA-Pt efficiently quenched superoxide anion (O_2^-). This quenching activity against ROS persisited like catalysis such as SOD or catalase. Therefore. PAA-Pt may be a useful scavenger which is effective on medical treatment of oxidative stress diseases. The left middle cerebral artery occlusion stroke model were prepared accoding to the method of Koizumi, using rats (Slc:Wistar, 8weeks old, male, 170-210g, n = 10). After one hour occlusion, PAA-Pt were injected to the rats at reperfusion, and the brains were removed at 24 hours or 72 hours after the start of reperfusion. Each brain wre cut into 6 slices of 2 mm width each, the slice were photographed with digital camera, and the images obtained were input into a computer system with an image analyzing software for measurement of each

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Original Article

Activities of Daily Living, Functional Capacity, and Life Satisfaction of Subacute Myelo-Optico-Neuropathy Patients in Japan

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ABSTRACT

Background: Patients with subacute myelo-optico-neuropathy (SMON) suffer from a number of serious neurological symptoms that adversely affect their activities of daily living (ADL). However, the effects of these neurological symptoms on functional capacity and life satisfaction have not been reported.

Methods: We analyzed data from 1,300 SMON patients aged 55–94 years that was obtained at medical check-ups carried out by the SMON Research Committee in 2004–2006 in Japan. The neurological symptoms investigated were visual impairment, dysbasia, symptoms of the lower extremities, and sensory symptoms. Neurological symptoms were classified by severity. The Barthel Index, the Tokyo Metropolitan Institute of Gerontology Index of Competence, and the participant's response to the question "Are you satisfied with life?" were used to evaluate ADL, functional capacity, and life satisfaction, respectively. Data were analyzed using a proportional odds model with the scores for these items as ordinal dependent variables.

Results: For most neurological symptoms, scores for ADL, functional capacity, and life satisfaction were significantly lower in participants with severe or moderate neurological symptoms than in those with nearly normal results upon examination. The odds ratio for life satisfaction due to superior functional capacity was significant after adjustment for sex, age, and ADL score.

Conclusion: The presence of neurological symptoms in SMON patients was associated with low functional capacity, life satisfaction, and ADL. Our results suggest that the life satisfaction of SMON patients can be increased by improving their functional capacity.

Key words: subacute myelo-optico-neuropathy; SMON; activities of daily living; functional capacity; life satisfaction

INTRODUCTION

Subacute myelo-optico-neuropathy (SMON) is a disease caused by clioquinol intoxication, and is characterized by subacute onset of sensory and motor disorders in the lower half of the body and visual impairment.[1,2] In Japan, there are a large number of SMON patients.[3] The incidence of SMON rapidly diminished after clioquinol was banned in 1970. In 2005, approximately 2,600 people with SMON were still receiving health management allowances as relief for an adverse drug reaction.[4]

Some studies have reported that a number of serious neurological symptoms have remained as sequelae of clioquinol intoxication among SMON patients, and that these symptoms are strongly associated with limited activities of daily living (ADL).[4–6] However, both life satisfaction and functional capacity—which includes instrumental self-maintenance, intellectual activities, and social role—play an important role in the life of older SMON patients, and these are yet to be reported.[7] In the present study, we examine the associations between neurological symptoms, ADL, functional capacity, and life satisfaction in SMON patients.

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Table 1. Number of participants included in analysis, by sex and age

Age (years)	Men		Women		Total	
	No.	%	No.	%	No.	%
55–64	39	11.9	138	14.2	177	13.6
65–74	152	46.2	318	32.7	470	36.2
75–84	115	35.0	366	37.7	481	37.0
85–94	23	7.0	149	15.3	172	13.2
Total	329	100.0	971	100.0	1,300	100.0

PARTICIPANTS AND METHODS

Participants

We analyzed data from medical check-ups performed by the SMON Research Committee with the support of the Ministry of Health, Labour and Welfare of Japan.[5,6] Our study participants were SMON patients aged 55 to 94 years who underwent medical check-ups in the years 2004 to 2006. Of 1,326 participants, we excluded 11 who did not consent to the use of their medical check-up data for analysis, and 15 with missing data on ADL, functional capacity, or life satisfaction. Table 1 shows the number of participants eligible for analysis by sex and age. Of a total of 1,300 SMON patients (329 males and 971 females), 73% were between 65–84 years old.

Neurological symptoms

A standardized record was used in the medical check-ups for SMON patients.[5,6] The record included visual impairment (completely blind, visual acuity insufficient to count fingers, mildly impaired, or nearly normal), dysbasia (abasia, clinging while walking, walking with a cane, or independent walking), symptoms of the lower extremities (severe, moderate, mild, or nearly normal), and sensory symptoms (severely diminished, moderately diminished, mildly diminished, or nearly normal). These levels were recorded as "severe," "moderate," "mild," and "nearly normal," respectively. Symptoms of the lower extremities were weakness, spasticity, and amyotrophy. Sensory symptoms were tactile sensation, algesthesia, vibratory sensation, and dysesthesia. Tactile sensation and algesthesia were divided into the 4 abovementioned levels plus "hypersensitive."

ADL, functional capacity, and life satisfaction

The Barthel Index was used to measure ADL.[8] Scores ranged from 0 to 100, with a higher score denoting higher ADL. The Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG Index) was used to measure functional capacity[9,10] and ranged from 0 to 13, with a higher score indicating higher capacity. Life satisfaction was evaluated using the response to the question, "Are you satisfied with life?" Participant responses were grouped into 5 categories: "dissatisfied," "slightly dissatisfied," "slightly satisfied," "satisfied," and "other." We assigned scores of 1, 2, 4, 5 and 3, respectively, to these categories.

Statistical analyses

ADL, functional capacity, and life satisfaction were compared among the severity groups for neurological symptoms by using a proportional odds model, which is a logistic model for ordinal dependent variables which assumes that the odds ratios for falling above a category versus those for falling within, or below, a category of ordinal dependent variables for independent variables are common across those categories.[11,12] ADL, functional capacity, and life satisfaction were ordinal dependent variables. The model included sex, age, and one of the neurological symptoms (a dummy variable) as independent variables. The associations between ADL, functional capacity, and life satisfaction were examined using the proportional odds model with life satisfaction as an ordinal dependent variable and sex, age, ADL, and functional capacity as independent variables. Statistical analyses were conducted using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Ethical review

This study was approved in December 2005 by the Ethical Review Board for Epidemiological and Clinical Studies of the Fujita Health University School of Medicine.

RESULTS

Table 2 shows the distributions of neurological symptoms. The proportions of participants with severe symptoms were 1.5% for visual impairment, 16.4% for dysbasia, 5.4–14.0% for symptoms of the lower extremities, and 10.1–35.3% for sensory symptoms. The proportions of participants with nearly normal results were 59.3%, 48.8%, 19.2–49.7%, and 3.0–4.3%, respectively.

Figures 1, 2, and 3 show the distributions of the scores for ADL, functional capacity, and life satisfaction, respectively. The scores for ADL and functional capacity were widely distributed. For ADL, the proportion of participants scoring 70 or less was 22.1%. A functional capacity of 11 or less was noted in 71.8% of participants. With respect to life satisfaction, 23.2% of participants were "dissatisfied" or "slightly dissatisfied" and 49.1% were "slightly satisfied" or "satisfied".

Tables 3, 4, and 5 show the respective mean scores and odds ratios for ADL, functional capacity, and life satisfaction for the groups of neurological symptoms. For all neurological symptoms, mean scores were lower in the severe and moderate groups than in the nearly normal group. For most neurological symptoms, after adjustment for sex and age, the differences in scores between the groups were statistically significant in analysis using the proportional odds model. The

Table 2. Distribution of neurological symptoms

Neurological symptoms	No.	Proportion (%)				
		Severe	Moderate	Mild	Hyper-sensitive	Nearly normal
Visual impairment	1247	1.5	6.8	32.4	-	59.3
Dysbasia	1249	16.4	9.7	25.1	-	48.8
Symptoms of lower extremities						
Weakness	1215	14.0	28.1	38.8	-	19.2
Spasticity	1212	7.1	16.9	26.3	-	49.7
Amyotrophy	1212	5.4	13.6	32.4	-	48.5
Sensory symptoms						
Tactile sensation	1211	10.2	41.5	34.5	9.4	4.3
Algesthesia	1211	10.1	34.3	28.3	23.1	4.2
Vibratory sensation	1205	35.3	35.4	24.9	-	4.4
Dysesthesia	1207	20.3	57.5	19.2	-	3.0

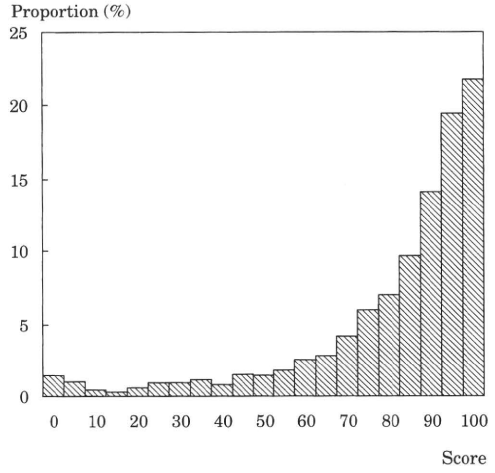

Figure 1. Distribution of activities of daily living scores

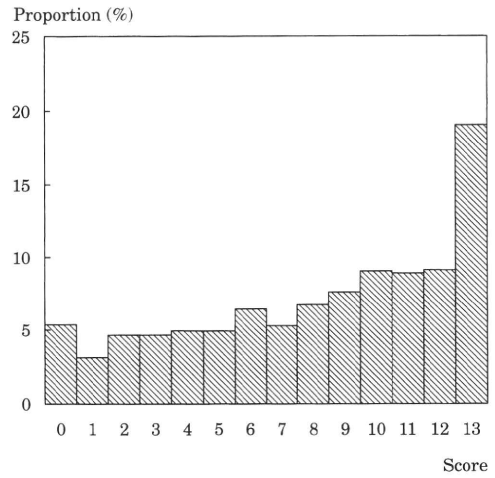

Figure 2. Distribution of functional capacity scores

odds ratios for participants in the severe groups, as compared with the respective nearly normal group, were between 0.00 and 0.49.

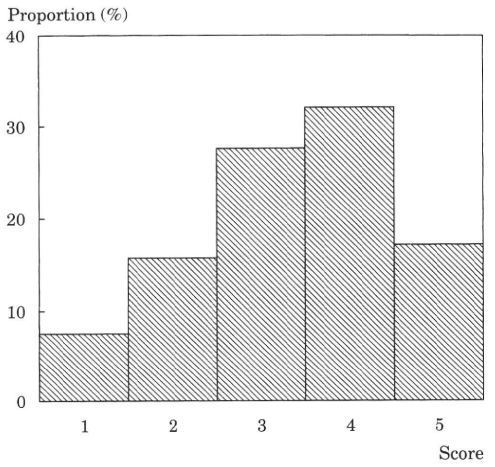

Figure 3. Distribution of life satisfaction scores

Table 6 shows the odds ratios for independent variables in the proportional odds model with life satisfaction as the ordinal dependent variable. The odds ratio for functional capacity—after adjustment for sex, age, and ADL—was significantly higher than 1.

DISCUSSION

We observed that the scores for ADL, functional capacity, and life satisfaction among SMON patients were strongly associated with the severity of neurological symptoms. The odds ratios of the severe group were much lower than those of the nearly normal group. These associations are not surprising, given that the neurological symptoms included visual impairment, dysbasia, symptoms of the lower extremities, and sensory symptoms. Some previous studies on ADL in SMON patients reported results similar to ours.[5,6] We found that more than 70% of SMON patients had limited functional capacity (a score of ≤ 11 on the TMIG Index).[13] Functional capacity includes instrumental self-maintenance, intellectual activities, and social role, and is likely to be an accurate

Table 3. Mean scores and odds ratios for activities of daily living by severity of neurological symptoms

Neurological symptoms	Severe		Moderate		Mild		Hypersensitive		Nearly normal		*P* value†
	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	
Visual impairment	40.0	0.02	63.5	0.12	75.6	0.37	-	-	87.7	1.00	<0.001
Dysbasia	44.1	0.00	73.9	0.05	85.5	0.22	-	-	93.4	1.00	<0.001
Symptoms of lower extremities											
Weakness	49.2	0.01	77.6	0.13	89.5	0.45	-	-	94.5	1.00	<0.001
Spasticity	66.5	0.14	73.0	0.25	83.1	0.65	-	-	85.7	1.00	<0.001
Amyotrophy	38.9	0.02	65.4	0.09	81.9	0.39	-	-	90.6	1.00	<0.001
Sensory symptoms											
Tactile sensation	67.9	0.15	78.7	0.38	88.5	0.93	83.6	0.52	84.5	1.00	<0.001
Algesthesia	69.8	0.17	77.5	0.35	87.8	0.81	85.1	0.58	84.7	1.00	<0.001
Vibratory sensation	75.4	0.22	82.3	0.42	88.9	0.74	-	-	89.3	1.00	<0.001
Dysesthesia	72.6	0.24	82.6	0.57	88.8	1.18	-	-	81.7	1.00	<0.001

* Mean activities of daily living score.
† Odds ratio and *P* value from the proportional odds model with activities of daily living as an ordinal dependent variable and sex, age, and a neurological symptom as independent variables.

Table 4. Mean scores and odds ratios for functional capacity by severity of neurological symptoms

Neurological symptoms	Severe		Moderate		Mild		Hypersensitive		Nearly normal		*P* value†
	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	
Visual impairment	1.6	0.01	4.2	0.06	6.7	0.28	-	-	9.7	1.00	<0.001
Dysbasia	3.4	0.03	5.3	0.08	8.0	0.25	-	-	10.5	1.00	<0.001
Symptoms of lower extremities											
Weakness	3.8	0.04	7.2	0.17	9.3	0.48	-	-	10.9	1.00	<0.001
Spasticity	6.8	0.31	7.1	0.36	8.3	0.72	-	-	8.8	1.00	<0.001
Amyotrophy	2.7	0.03	5.5	0.13	7.8	0.38	-	-	9.9	1.00	<0.001
Sensory symptoms											
Tactile sensation	5.9	0.25	7.8	0.59	9.5	1.17	8.3	0.69	8.5	1.00	<0.001
Algesthesia	6.0	0.26	7.6	0.54	9.4	1.10	8.7	0.78	8.7	1.00	<0.001
Vibratory sensation	7.2	0.47	8.3	0.69	9.6	1.11	-	-	9.7	1.00	<0.001
Dysesthesia	7.0	0.35	8.3	0.60	9.4	0.95	-	-	8.7	1.00	<0.001

* Mean functional capacity score.
† Odds ratio and *P* value from the proportional odds model with functional capacity as an ordinal dependent variable and sex, age, and a neurological symptom as independent variables.

Table 5. Mean scores and odds ratios for life satisfaction by severity of neurological symptoms

Neurological symptoms	Severe		Moderate		Mild		Hypersensitive		Nearly normal		*P* value†
	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	Mean score*	Odds ratio†	
Visual impairment	2.2	0.16	3.0	0.46	3.2	0.66	-	-	3.5	1.00	<0.001
Dysbasia	3.1	0.42	3.2	0.47	3.2	0.56	-	-	3.5	1.00	<0.001
Symptoms of lower extremities											
Weakness	2.9	0.27	3.3	0.47	3.4	0.61	-	-	3.6	1.00	<0.001
Spasticity	3.1	0.63	3.2	0.68	3.2	0.67	-	-	3.5	1.00	0.002
Amyotrophy	2.9	0.33	3.1	0.53	3.3	0.67	-	-	3.5	1.00	<0.001
Sensory symptoms											
Tactile sensation	3.2	0.42	3.3	0.48	3.5	0.73	3.3	0.55	3.7	1.00	<0.001
Algesthesia	3.2	0.55	3.3	0.59	3.4	0.79	3.3	0.66	3.6	1.00	0.067
Vibratory sensation	3.3	0.47	3.3	0.45	3.4	0.53	-	-	3.8	1.00	0.021
Dysesthesia	3.2	0.49	3.3	0.54	3.6	0.89	-	-	3.7	1.00	<0.001

* Mean life satisfaction score.
† Odds ratio and *P* value from the proportional odds model with life satisfaction as an ordinal dependent variable and sex, age, and a neurological symptom as independent variables.

Table 6. Odds ratios for life satisfaction with respect to sex, age, activities of daily living, and functional capacity

Independent variables	Odds ratio*	*P* value*
Sex (male/female)	1.51	<0.001
Age (years)	1.05	<0.001
Activities of daily living	1.01	0.109
Functional capacity	1.16	<0.001

* Odds ratio and *P* value from the proportional odds model, with life satisfaction as an ordinal dependent variable.

indicator of the quality of life of older SMON patients.[10,13] Our findings suggest that measures that can remedy the limited functional capacity of SMON patients are of great importance.[4,6]

When asked "Are you satisfied with life?" almost half of participants answered "slightly satisfied" or "satisfied." Although interpreting these responses is difficult, the level of life satisfaction in SMON patients appears relatively low. A national survey in Japan reported that in the general elderly population the proportion of individuals who responded similarly to the same question was over 90%.[14]

In the present study, the level of life satisfaction was significantly associated with functional capacity after adjustment for sex, age, and ADL score, which suggests that life satisfaction among SMON patients might be increased by obtaining a higher level of functional capacity.[15,16] Unfortunately, there are no effective medical treatments to relieve the remaining neurological symptoms in SMON patients.[4,5] Although we did not investigate the factors associated with high functional capacity, our results offer information that should be useful in offering specific and effective assistance to those patients.

There are several limitations and problems in the present study. The participants were examined at medical check-ups carried out by the SMON Research Committee; approximately half of the participants were SMON patients receiving health management allowances for the relief of adverse drug reactions.[4,5] Although the proportions SMON patients with limited ADL, functional capacity, and life satisfaction might be higher in the entire SMON population than in the subset of patients we analyzed, we believe that the associations between neurological symptoms and those indices would not be radically changed. The Barthel Index and TMIG Index used in this study are common tools for measuring ADL and functional capacity, respectively.[7–9] We used the question "Are you satisfied with life?" to measure life satisfaction. Although other indices to measure life satisfaction have been proposed,[17,18] questions similar to ours have been used in several previous studies.[14,19] We used a proportional odds models for ordinal dependent variables of ADL, functional capacity, and life satisfaction, rather than binary logistic models that reduce those variables to just two categories. In proportional odds models, as we describe above, it is assumed that the odds of falling above a category versus those of falling with, or below, the category of ordinal dependent variables for independent variables are common across all categories.[11,12] To take one example from the present study, the odds ratio for participants with severe visual impairment, as compared with those in the nearly normal group, was 0.49 for the dependent variable of ADL. This can be interpreted to mean that SMON patients with severe visual impairment had 0.49 times the odds of a higher, versus a lower, ADL score than those with nearly normal visual impairment. The results obtained from such models lead to important findings regarding the factors related to the distributions of ADL, functional capacity, and life satisfaction. However, their interpretation requires careful analysis and debate.

In conclusion, the neurological symptoms of SMON patients are associated with low levels of functional capacity, life satisfaction, and ADL. Our results indicate that life satisfaction of SMON patients might be increased by improving functional capacity.

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RESEARCH PAPER

Characteristics of disabilities in patients with subacute myelo-optico-neuropathy living at home: Satisfaction in daily life and short form-36

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Abstract

Purpose. The aim of this study was to investigate the characteristics of disabilities in patients with subacute myelo-optico-neuropathy (SMON), and to reveal whether the satisfaction in daily life (SDL) or short form-36 (SF-36) correlated with these disabilities.

Method. The subjects consisted of 97 patients with SMON living at home, who were mailed a questionnaire concerning the patient's profile, SMON severity (disability scale for SMON), basic activities of daily living (self-rating Barthel Index, SR-BI), lifestyle (self-rating Frenchay Activities Index, SR-FAI), SDL and SF-36. A relationship with SDL, SF-36 and disabilities was analysed by using Spearman's rank correlation coefficient.

Results. Fifty-eight out of 97 patients with SMON responded, and their mean age was 76.1 years. The mean of SMON severity was 8.0; SR-BI, 70.8; SR-FAI, 11.1; SDL, 27.3; physical component summary of SF-36 (PCS), 26.3; mental component summary of SF-36 (MCS), 39.5. The SMON group had significantly lower scores for SDL than those for the age- and sex ratio- matched elderly persons. With respect to SDL, a significant correlation was observed with SMON severity, SR-BI, SR-FAI, SDL, and PCS and MCS of SF-36, but no significant correlation was observed regarding SMON severity and either the PCS or MCS.

Conclusions. The subjective domains of the quality of life in patients with SMON were observed to have decreased. SDL was considered to closely reflect the characteristics of the disabilities observed in patients with SMON.

Keywords: *SMON, satisfaction in daily life, SF-36*

Introduction

SMON is the name of a disease, being an acronym for subacute myelo-optico-neuropathy, which has a distinctive clinical course, symptoms and pathological findings, and in Japan, it occurred as drug poisoning in which clioquinol, an intestinal antibacterial drug, was normally the cause [1]. Following the onset of intestinal symptoms, the occurrence of visual impairment, paraparesis, paresthesia in the lower limb, bladder bowel disturbance, and so on, has been reported. The incidence of this disease was clustered from 1955 to 1970, and because a long period of time has passed after the onset of the disease, neurologic abnormalities associated with this disease have already become chronic. The effects of advancing age and its complications make overall disabilities of the patients with SMON more complicated [2]. For this reason, it is important to understand the disabilities, lifestyle, and quality of life (QOL) of the patients with SMON before teaching how to lead a daily life and providing information on welfare services, if rehabilitative intervention is carried out.

SMON is a condition that resembles paraparesis, and the disabilities and lifestyle of the patients with SMON may be appropriately evaluated using the Barthel Index (BI) and the Frenchay Activities Index (FAI) [3]. On the other hand, satisfaction in daily life (SDL) [4] was devised in 1989 as an evaluation of the subjective domain of QOL in SMON which was a simpler method than the sickness impact profile [5] and the Nottingham health profile [6]. SDL had

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seven items on a 5-point scale, and was revised to have 11 items on a 5-point scale in order to make this universally adaptable to elderly persons, based on the results of a random sampling study on the factors involved in the satisfaction of daily living for elderly individuals living at home [7]. Later, we also proved the validity of SDL in using for patients with stroke living at home [8], elderly persons living at home [9] and hemophiliacs [10].

Although there were few reports on the QOL of patients with SMON, Kuriyama et al. [11] and Fujii and Arakawa [12] carried out research using short form-36 (SF-36) [13], and Honaga et al. [14] used SF-8, which was a shortened version of SF-36. From these reports, all SF-36 scores in patients with SMON were lower than those of healthy elderly people. In the present research, the disabilities, lifestyle and QOL of patients with SMON were studied using self-rating Barthel Index (SR-BI), self-rating Frenchay Activities Index (SR-FAI), SDL and SF-36, in order to reveal: (1) what are the features of disabilities, lifestyle and QOL in patients with SMON and (2) whether SDL closely reflects the characteristic disabilities in patients with SMON.

Methods

Ninety-seven patients with SMON residing in Fukuoka prefecture (one of Japanese 47 prefectures, situated in north-eastern Kyushu, with a population of about 5.05 million people as of 1 March 2007) were registered with the Ministry of Health, Labor and Welfare. The study forms were mailed to the 97 patients with SMON, who were asked to fill in the forms and mail them back. Fifty-eight patients with SMON who responded were analysed as the subjects (SMON group), and their age distribution and sex ratio were described as follows: 50–59 years, 3 (males 0/females 3); 60–69 years, 16 (7/9); 70–79 years, 11 (3/8); 80–years, 28 (8/20).

To include age distribution and sex ratio-matched elderly persons as a control, 58 persons (control group) were randomly sampled from the database, using the RANDOM command of a statistical software package (SPSS 8.1J, SPSS Japan, Tokyo). The database derived from the measurements of 748 elderly people who were randomly selected from the list of voters for Yahatanishi-ku, Kitakyushu, to obtain standard values for SR-BI, SR-FAI and SDL [15]. The evaluation items were patient profile (age, sex, living arrangements), SMON severity, activities of daily living (ADL), lifestyle and QOL. Here is an outline of the evaluation items.

SMON severity was classified based on Disability Scale for SMON patients, which was devised by the SMON research committee of the Ministry of Health, Welfare and Labour [16]. The Disability Scale for SMON, consisting of three major neurologic disturbances, namely gait, sensation and vision, indicated a total score of three weighted disturbances as severity (from 0 for no sign to 21 for very severe sign of SMON), and they are considered to be the standard criteria for severity.

SR-BI [17], which was modeled after the Granger version of BI [18] and was a self-rating modification for epidemiological research, was used for evaluation of the personal ADL. The SR-BI consists of 13 items concerning basic daily activities, summed up on a 0–100 scale, and the validity and reliability of the self-entry form have been confirmed.

SR-FAI [19], which is a self-rating modification of FAI [20], was used for evaluation of lifestyle. The SR-FAI consists of 15 items concerning performance of applied ADL in four stages from 0 to 3, for a total of 0–45 points. The validity and reliability of a self-rating version have been confirmed [21].

In the evaluation of QOL, SDL and SF-36 were used. The SDL is an evaluation of the subjective domain of QOL in daily life, and consists of 11 important items shared by the elderly persons living at home (physical health, mental stability, self care, ambulatory mobility, household work, living environment, living arrangements with spouse/family, hobbies/recreation, local/social interaction, pension/income and work), using a 5-stage satisfaction level, from 1 for 'dissatisfied' to 5 for 'satisfied', with the total score being within the range of 11 for the most dissatisfied and 55 for the most satisfied [7].

SF-36 is a standard evaluation indicator of health-related QOL, comprising 36 items generally related to health, as reported by Ware et al. [13] in 1992. These items are arranged into eight sub-scales (physical functioning, role physical, bodily pain, social functioning, general health perceptions, vitality, role emotional and mental health), and are put together into two summary measures (physical component summary (PCS) and mental component summary (MCS)).

A relationship between disabilities, lifestyle and QOL in SMON patients was statistically analysed by using Spearman's rank correlation coefficient (SPSS 8.1J). p-values of less than 0.05 were considered to be significant.

Results

The SMON group comprised 58 patients (18 males and 40 females), and the mean age was 76.1 ± 10.6 years (mean $\pm$ SD). The control group also consisted of 58 (18 males and 40 females), and the mean age was 75.3 ± 8.7. There was no significant difference in age between both groups (NS, t-test).

A total score of the SMON severity was 8.0 ± 4.8 (3.3 ± 2.6 for gait, 2.2 ± 0.9 for sensation and 2.5 ± 2.6 for vision). The living arrangements were as follows: living alone, 11 persons (19.0%); living with a spouse, 13 persons (22.4%); living with a spouse and another family member (son, daughter, daughter-in-law and/or son-in-law), 16 persons (27.6%); living with another family member, 10 persons (17.2%); and other arrangements, 8 persons (13.8%).

The total score and all items of SR-BI of the SMON group were significantly lower than those of the control group (Table I), and the total score and all items, except for preparing meals, washing clothes, and gainful work of SR-FAI were significantly lower than those of the control group (Table II). Table III shows that the total score and all items of SDL of the SMON group were significantly lower than those of the control group. PCS and MCS of SF-36 in the SMON group were 26.3 ± 7.8 and 39.5 ± 11.0, respectively.

Table IV shows the correlation coefficients between SMON severity, SR-BI, SR-FAI, SDL, PCS and MCS. SDL had significant correlations with SMON severity, SR-BI, SR-FAI, PCS and MCS; PCS, with SR-BI and SDL; MCS, with SDL.

Discussion

The number of subjects in this study was not large, but we believe our data reflect the situation for all

Table I. Scores of Self-Rating Barthel Index.

	SMON ($N=58$)	Control ($N=58$)
Self-care		
Eating (0–10)	8.8 ± 2.9*	10.0 ± 0.0
Grooming (0–5)	4.4 ± 1.3*	5.0 ± 0.0
Washing or bathing (0–5)	3.7 ± 1.9*	5.0 ± 0.0
Dressing upper body (0–7)	5.6 ± 2.3*	7.0 ± 0.0
Dressing lower body (0–8)	6.0 ± 2.8*	8.0 ± 0.0
Toileting (0–5)	4.2 ± 1.6*	5.0 ± 0.0
Controlling urination (0–10)	5.3 ± 3.5*	10.0 ± 0.0
Controlling bowel movements (0–10)	6.5 ± 3.7*	9.9 ± 0.7
Mobility		
Getting in and out of chairs (0–5)	3.8 ± 1.8*	5.0 ± 0.0
Getting on and off a toilet (0–5)	4.0 ± 1.8*	5.0 ± 0.0
Getting in and out of tub or shower (0–5)	3.3 ± 2.0*	5.0 ± 0.0
Walking 50 m on level ground (0–15)	10.7 ± 5.2*	15.0 ± 0.0
Walking up/down the stairs (0–10)	4.5 ± 4.4*	9.1 ± 2.4
Total score (0–100)	70.8 ± 28.0*	99.0 ± 2.4

The numbers in brackets are theoretical ranges, and measured values are presented as means ± SD.
*$p < 0.05$, Mann–Whitney test, SMON *vs.* control.

Table II. Scores of Self-Rating Frenchay Activities Index.

	SMON ($N=58$)	Control ($N=58$)
1. Preparing meals (0–3)	0.9 ± 1.2	1.4 ± 1.4
2. Washing up (0–3)	1.0 ± 1.2*	1.9 ± 1.2
3. Washing clothes (0–3)	1.2 ± 1.3	1.7 ± 1.3
4. Light housework (0–3)	1.2 ± 1.3*	2.3 ± 1.0
5. Heavy housework (0–3)	0.6 ± 1.0*	2.0 ± 1.1
6. Local shopping (0–3)	0.9 ± 1.2*	2.2 ± 1.1
7. Social occasions (0–3)	0.8 ± 1.1*	1.9 ± 1.0
8. Walking outside (0–3)	0.9 ± 1.2*	2.5 ± 0.8
9. Actively pursuing hobby (0–3)	0.7 ± 1.1*	1.6 ± 1.3
10. Driving car/bus travel (0–3)	1.2 ± 1.2*	2.1 ± 1.0
11. Travel outings/car rides (0–3)	0.3 ± 0.7*	0.8 ± 0.8
12. Gardening (0–3)	0.3 ± 0.7*	1.1 ± 1.1
13. Household/car maintenance (0–3)	0.2 ± 0.5*	0.7 ± 1.1
14. Reading books (0–3)	0.8 ± 1.2*	1.3 ± 1.3
15. Gainful work (0–3)	0.2 ± 0.6	0.4 ± 1.0
Total score (0–45)	11.1 ± 11.0*	23.9 ± 7.7

The numbers in brackets are theoretical ranges, and measured values are presented as means ± SD.
*$p < 0.05$, Mann–Whitney test, SMON *vs.* control.

Table III. Scores of satisfaction in daily life.

SDL items	SMON ($N=58$)	Control ($N=58$)
Physical health (1–5)	1.6 ± 0.9*	3.2 ± 1.2
Mental stability (1–5)	2.2 ± 1.1*	3.7 ± 1.2
Self care (1–5)	2.4 ± 1.3*	4.4 ± 0.8
Ambulatory mobility (1–5)	2.3 ± 1.3*	4.4 ± 1.0
Household work (1–5)	2.1 ± 1.2*	4.1 ± 1.1
Living environment (1–5)	3.1 ± 1.4*	4.3 ± 1.0
Living arrangements with spouse/family (1–5)	3.5 ± 1.2*	4.4 ± 0.9
Hobbies/recreation (1–5)	2.4 ± 1.1*	3.4 ± 1.2
Local/social interaction (1–5)	2.5 ± 1.2*	3.5 ± 1.0
Pension/income (1–5)	2.4 ± 1.3*	3.3 ± 1.2
Work (1–5)	2.8 ± 0.7*	3.1 ± 0.5
Total (11–55)	27.3 ± 8.6*	41.8 ± 7.0

The numbers in brackets are theoretical ranges, and measured values are presented as means ± SD.
*$p < 0.05$, Mann–Whitney test, SMON *vs.* control.

Table IV. Correlation with SDL and SF-36 in patients with SMON.

	SDL	PCS	MCS
SMON severity	−0.387*	−0.204	0.049
SR-BI	0.464*	0.417*	−0.075
SR-FAI	0.442*	0.343	−0.019
SDL	–	0.373*	0.459*

SMON severity, disability scale for SMON; SR-BI, Self-Rating Barthel Index; SR-FAI, Self-Rating Frenchay Activities Index; PCS of SF-36, physical component summary of short form-36; MCS of SF-36, mental component summary of short form-36.
*$p < 0.05$, Spearman's correlation coefficient (with Bonferroni correction for multiple testing).

patients with SMON living at home to some extent. The officially approved number of patients with SMON in Japan is 2504 in April 2006. Because patients with SMON are receiving a special health allowance from the pharmaceuticals and medical devices agency and all such patients are known to receive the payments, the officially approved number of SMON is presumably accurate. Although Kuriyama et al. [11], Fujii and Arakawa [12], Honaga et al. [14] investigated 23, 17 and 7 patients with SMON, respectively, we examined 58 subjects in this study who were thus equivalent to 2% of all patients with SMON in our country.

We have developed SDL in order to evaluate the subjective domains of QOL in patients with SMON, and have studied the similarities and differences between the measurement concepts of SDL and SF-36 in the patients with stroke living at home and the elderly persons living at home [8]. As a result, we demonstrated that SDL could detect the subjective domains of QOL in patients with stroke that were similar to the psychological scales of SF-36.

As mentioned before, there have been few reports on the QOL of patients with SMON, and moreover, there are no reports of research on disease-specific QOL scales for patients with SMON. In the present study, we have investigated the characteristics of disabilities in patients with SMON based on the research to date, and we have examined the similarities and differences between SDL and SF-36. We found that significant correlations were observed between SMON severity and SR-BI, SR-FAI and SDL. It is believed that the subjective domains of QOL in patients with SMON are reduced, along with a decrease in independence of basic ADL and performance of applied ADL, when the SMON severity is severe. In addition, from the fact that correlations were observed between SDL and SMON severity, basic and applied ADL, and PCS and MCS of SF-36, SDL would reflect well the characteristics of disabilities in patients with SMON. On the other hand, no relationship has been observed between SF-36 and SMON severity.

Significant correlations were observed between SMON severity and SDL, but not between SMON severity and SF-36. SDL was originally developed to evaluate the subjective domains of QOL specific to patients with SMON, and the questionnaire consisted of the items related to satisfaction of elderly people living at home and disabilities of patients with SMON. SF-36 is a comprehensive evaluation scale that does not specify the disease or symptoms, and its items are constructed to broadly measure, across eight areas, comprehensive health concepts. It is believed that SDL reflects the disabilities in SMON better than SF-36. Fujii and Arakawa evaluated patients with SMON using Disability Scale for SMON, BI and SF-36, but reported that no correlation with the PCS and MCS of SF-36 could be found. The reason for this was stated as the possibility that QOL of a patient with SMON is not simply correlated with the extent of the disability, and that other factors are involved [12]. However, the results of our research show that SDL, a QOL scale disease-specific to SMON, can detect subtle changes of living conditions which are difficult to accurately determine using SF-36.

In our previous research which included a comparison between patients with SMON and stroke, patients with SMON showed high values in applied ADL and low values in SDL. Those results also indicated that SDL was able to differentiate the characteristics between patients with SMON and stroke [22].

The limitations of our research can be stated as follows. The first is that 39 non-respondents may have affected the results. The male–female ratio of respondents and non-respondents was about 1:2 in both groups, and there was no disparity. The questionnaires were designed to be anonymous, so there was little information on the non-respondents. Patients with SMON who were bedridden or had very severe disabilities might not have either wanted or be able to respond the questionnaire. However, such patients are less than 5% according to the annual medical checkup administered by the local members of the SMON research committee of the Ministry of Health, Welfare and Labour, and it is unlikely that there was any definite bias toward the respondents. The second is that the values of correlation coefficients with significance were not high. Although the SDL was associated with SMON severity, basic and applied ADL, and QOL, SDL could not explain all of the symptoms and disabilities of patients with SMON, and other factors, including victims of drug poisoning might be involved as Fujii and Arakawa had previously described [12].

In conclusion, the subjective domains of the QOL in patients with SMON were observed to decrease, and SDL was found to closely reflect the characteristics of disabilities in patients with SMON. As a result, SDL is therefore considered to be an appropriate scale for the subjective domains of QOL in patients with SMON.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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LETTERS TO THE EDITOR

キノホルムは特殊な薬ではなかった

〔Clinoquinol was not a special drug.〕

舟川　格

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拝　啓

スモンは1960年代に多発した整腸剤キノホルムによる神経疾患です[1]．1970年にキノホルムの使用が禁止されてから新たな患者の発生はなくなりました．その結果，若い医師がスモンをもはや過去の病気としてとらえているとしても無理のないことなのかもしれません．しかし，少なくとも神経内科医は多くの患者が今もなお存在していることを真摯に受け止める必要があると思います．

スモンに関する調査研究班ではスモン患者の恒久対策として毎年患者検診を行っています．その折，患者さんから耳にすることはこの疾患が風化するのではないか，という恐れにも似た不安感です．実際，看護学生にアンケート調査を行ったところ完全に風化した病気といえる結果を得ました[2]．

谷崎潤一郎の「瘋癲老人日記」は昭和36年(1961年)11月号から翌年5月号の中央公論に掲載された小説です．この時期はまさにスモンの出現と一致しています．この小説には多くの薬剤が登場しますが，その中に次のような文章があります．「二十六日．昨夜冷奴ヲ食ベ過ギタノガ悪カッタト見エテ夜半ヨリ苦シミ出シ二三度下痢スル．エンテロビオフォルムヲ三錠服用シタガマダ止マラナイ．今日一日寝タリ起キタリシテ暮ラス」[3]．エンテロビオフォルムは商品名であり，若い医師にとってキノホルムとは直ちに結びつかないかもしれません．この薬剤については注解があり，そこには次のように記載されています．「スイスのチバ社の下痢止め薬．キノホルムおよびサパミンを含有し，細菌性の下痢に最適」[3]．このように本文や注解をみてもキノホルムは決して医師が構えて処方したような特殊な薬剤ではないことがわかります．また，近所の薬局で簡単に手に入った薬でもありました．つまり，スモンは決して特殊な薬剤によって一部の患者にのみ出現した疾患ではありませんでした．

現在私たちがあまり神経質にならずに使っている薬剤も，一剤だけでなく組み合わせによっては未知なる薬害をひき起こす可能性は十分にあります．検診のたびにスモンは決して風化させてはならない「事件」であると思っておりますので，ご報告させていただきました．

敬　具

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Research Report

Clioquinol inhibits NGF-induced Trk autophosphorylation and neurite outgrowth in PC12 cells

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ABSTRACT

Clioquinol is considered to be a causative agent of subacute myelo-optico neuropathy (SMON), although the pathogenesis of SMON is yet to be elucidated. To investigate the mechanism of neurotoxicity of clioquinol, we used PC12 cell line and focused on nerve growth factor (NGF) signaling through Trk receptor, which is essential for survival and differentiation of neuronal cells. Clioquinol inhibited NGF-induced Trk autophosphorylation in a dose-dependent manner. This inhibitory activity was further confirmed by the data of the inhibition of NGF-induced mitogen-activated protein kinase (MAPK) phosphorylation, which is located in the down stream of NGF-Trk intracellular signaling pathway. Clioquinol also caused neurite retraction induced by NGF and cell death. NGF-stimulated (differentiated) cells were more vulnerable than naïve cells. These results strongly suggest that clioquinol may cause the perturbation of the intracellular survival pathway by inhibiting Trk-initiated signaling pathway.

1. Introduction

Clioquinol or 5-chloro-7-iodo-8-hydroxyquinoline was used as an antibiotic for treating diarrhea and skin infection. It has been considered that clioquinol was a causative agent of subacute myelo-optico neuropathy (SMON), which is characterized by subacute onset of sensory and motor disturbances in the lower extremities with visual impairment (Nakae et al., 1973; Tsubaki et al., 1971). Pathological study demonstrated distal dominant axonopathy of the spinal long tracts and optic tracts (Tateishi, 2000). Over 10,000 patients in Japan were affected by SMON before therapeutic use of clioquinol discontinued in clinical practices in Japan. After the ban of the sale of clioquinol in September 1970, there was a drastic disappearance of new cases of SMON though nearly 3000 patients still suffer from its sequelae in 2002 (Konagaya et al., 2004). Even after 30 years of the outbreak of SMON in Japan, the mechanism of neuronal cell damage by clioquinol is yet to be elucidated.

Recently clioquinol reemerged for the treatment of non-infectious indication including malignancy (Chen et al., 2007), Alzheimer's disease (Cherny et al., 2001; Ritchie et al., 2003), and Huntington's disease (Nguyen et al., 2005). Given the potential reintroduction of oral clioquinol medication for these new indications, a clear understanding of clioquinol neurotoxicity is essential to fully appreciate the potential side effects of this drug.

Neurons are non-dividing cells in vivo and nerve growth factor (NGF) is one of the cardinal growth factors to support neuronal survival and differentiation (Thoenen, 1995). Trk is a

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Abbreviations: SMON, subacute mylo-optico neuropathy; NGF, nerve growth factor

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high-affinity NGF receptor which contains tyrosine kinase activity and its activation represents the initial step in the intracellular signal transduction pathway (Kaplan and Miller, 2000). Following ligand binding, the Trk receptor is activated by homodimerization. The degree of tyrosine autophosphorylation correlates well with the biological effects in responsive cells. In this study, to explore the mechanism of neurotoxicity of clioquinol, we focused on NGF-Trk-dependent signal transduction pathway for cell survival and examine the Trk receptor autophosphorylation in a neuronal cell line. The data clearly indicate the potential novel mechanism for the neurotoxicity by clioquinol.

2. Results

2.1. *Morphological observation*

Morphological effects of clioquinol on NGF-induced neurite outgrowth in PCtrk cells were observed under phase contrast microscope. After 24 h in culture, 1 μM of clioquinol-induced neurite retraction in PCtrk cells as shown in Fig. 1. After 48 h in culture, 100 nM and 1 μM of clioquinol also induced neurite retraction (Fig. 1). We further confirmed the effect of clioquinol on these cells by neurofilament expression by western blotting. Western blotting with anti-neurofilament antibody revealed that clioquinol causes decrease of neurofilament expression after 48 h in culture in a concentration-dependent manner. In contrast, β-actin expressions were not changed (Fig. 2A). We could not detect any changes in the expression of neurofilament after 24 h in culture (data not shown). To further confirm the neurite retraction by clioquinol, the length of neurite was measured. At 24 h in culture, the neurites were significantly retracted at 1 μM concentration of clioquinol as shown in the Fig. 2B.

2.2. *Cell viability assay*

To detect the cell death, trypan blue-dye exclusion assay was performed. As shown in Fig. 3, clioquinol-induced cell death in NGF-stimulated PCtrk cells in a concentration-dependent manner. One micromolar of clioquinol increased cell death drastically in NGF-stimulated cells at 24 h incubation (Fig. 3A). In contrast, naïve cells were significantly resistant to the same concentration of clioquinol (Fig. 3A). Most of the NGF-stimulated cells were dead at 1 μM of clioquinol after 48 h incubation. NGF-stimulated cells (differentiated cells) were more vulnerable than naïve cells (undifferentiated cells; Fig. 3B).

2.3. *Western blotting analysis of Trk autophosphorylation*

A mature form of Trk and its precursor form were recognized as 140 and 110 kDa, respectively. The immunoblot analysis with α-PY revealed a single band at 140 kDa corresponding to Trk (Fig. 4). To examine the effects of clioquinol on NGF-induced Trk autophosphorylation, PCtrk cells were incubated in the presence of clioquinol at various concentrations (from 10 nM to 10 μM) followed by the stimulation with NGF for 5 min. The cells were lysed with lysis buffer. Then, the cell-free lysates were immunoprecipitated with α-Trk and the immunoprecipitates were immunoblotted with α-PY. As shown in the Fig. 4, the inhibition of NGF-induced Trk autophosphorylation became evident at 100 nM clioquinol and it was further decreased in a concentration-dependent manner.

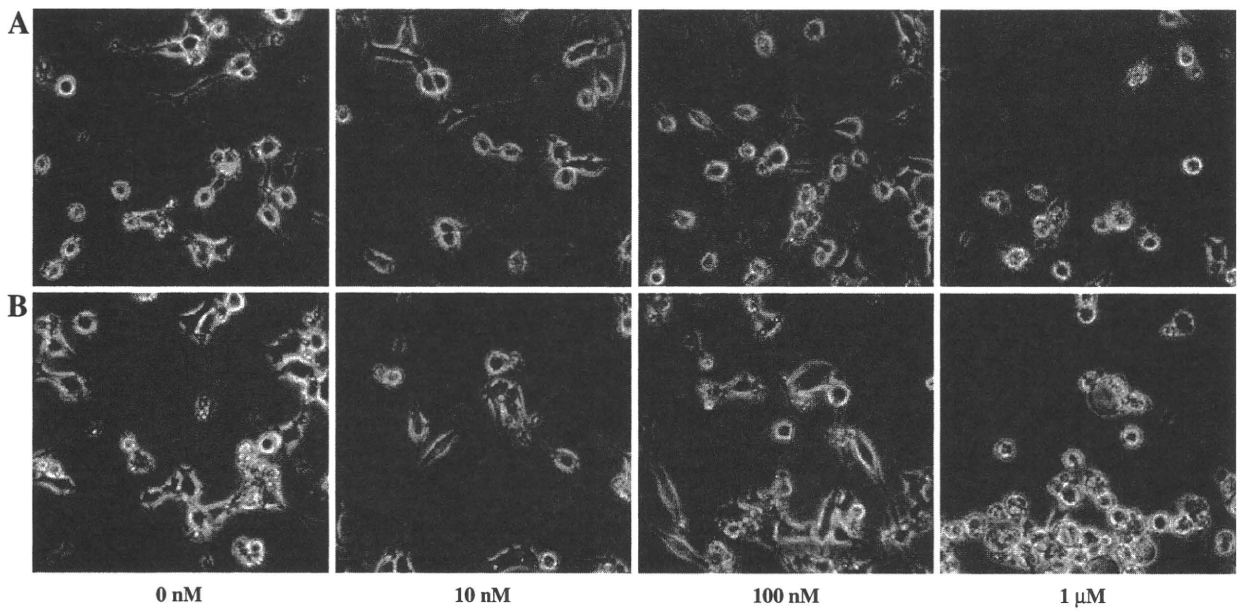

Fig. 1 – Morphological effects of clioquinol on NGF-induced neurite outgrowth. Representative photomicrographs of the cells cultured with various concentration of clioquinol for 24 h (A) and 48 h (B). Note the neurite retraction in (A) 1 μM and (B) 100 nM and 1 μM of clioquinol.