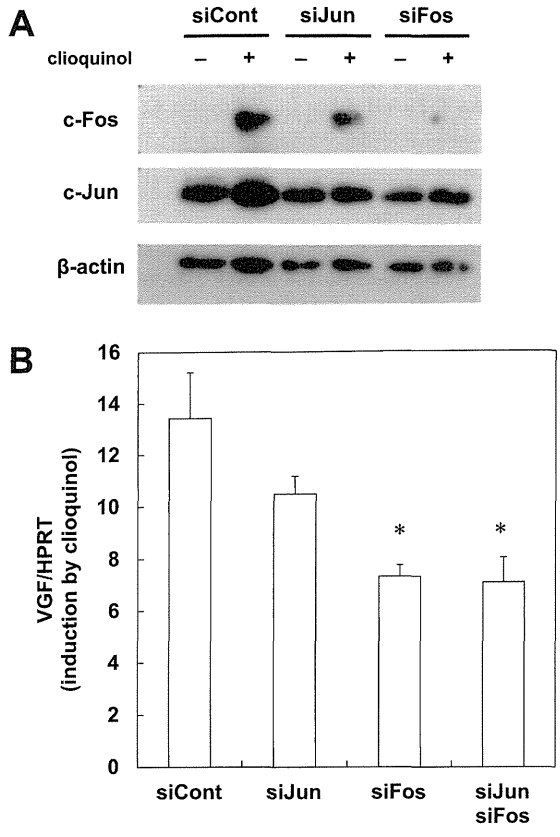

Fig. 5. Gene silencing of c-Fos attenuated the clioquinol-induced expression of VGF mRNA. A: The expression of c-Jun and c-Fos in SH-SY5Y cells transfected with anti-c-Jun or anti-c-Fos siRNA. siRNAs were transfected to SH-SY5Y cells at a final concentration of 50 nM. These cells were cultured for 24 h and then stimulated with 20 μM clioquinol for 24 h. Whole cell lysates (10 μg) were subjected to western blot analysis. Membranes were stripped and re-hybridized with an anti-β-actin antibody. B: The transfection of anti-c-Fos siRNA significantly suppressed VGF mRNA levels. Transcription levels were measured by quantitative PCR and normalized to the level of HPRT mRNA. Levels were expressed as "fold of DMSO". Bars represent means ± S.E. (N = 3). *$P < 0.05$ vs. control siRNA.

Discussion

The main findings of this study are that 1) VGF mRNA levels were significantly increased by the clioquinol treatment; 2) clioquinol-induced transcriptional activation of the *VGF* promoter was dependent on the AP-1 site-like sequence at −1374/−1368; 3) clioquinol induced the expression of the AP-1 transcription factors, c-Jun and c-Fos; 4) clioquinol enhanced the binding of c-Jun and c-Fos to the AP-1 site–like sequence at −1374/−1368 in the *VGF* promoter; and 5) RNA interference against c-Fos significantly suppressed clioquinol-induced VGF mRNA expression. These results suggest that the clioquinol-induced expression of c-Fos mediates the induction of VGF expression.

SMON is characterized by the subacute onset of sensory and motor disturbances in the lower extremities and visual impairment preceded by abdominal symptoms (2, 3). Although pathological studies demonstrated axonopathy of the spinal cord and optic nerves (4), the underlying mechanisms of clioquinol toxicity have yet to be elucidated. As we described previously, the concentration of clioquinol used in this study (20 – 50 μM) is compatible with its plasma level in SMON patients (15, 16).

VGF is a neuropeptide precursor, the gene of which was originally identified to be nerve growth factor (NGF)-responsive (17). Its transcriptional regulation has mainly been focused on induction by NGF; and the proximal promoter region containing the cAMP-response element, CCAAT element, E-box, and G(S)G element was shown to be essential for its expression (18 – 20). We demonstrated for the first time that the expression of VGF is induced by clioquinol in a manner that is dependent on the distal AP-1 site in the promoter.

The expression of VGF is limited to neurons in the central and peripheral nervous systems and to various endocrine cells. VGF-derived peptides were shown to exhibit various biological activities (21). Among them, an increase in the mRNA and protein levels of VGF was shown in dorsal root ganglia following sciatic nerve transection (22) or in the surrounding area after spinal cord injury (23). Thus, elevations in VGF levels have been implicated in neuropathic pain. Several C-terminal peptides derived from VGF were previously reported to cause pain responses. A peripheral injection of TLQP-21 (residues 557 to 576 of VGF) was shown to increase the pain-related licking response in a mouse model (24). The intrathecal application of TLQP-62 (C-terminal 62 amino acids of VGF) to naive rats was found to cause long-lasting mechanical and cold behavioral allodynia (25). AQEE-30 and LQEQ-19, corresponding to the last 30 and 19 amino acids of VGF, respectively, were also shown to evoke thermal hyperalgesia in rats (26). Thus, the induction of VGF may be involved in clioquinol-induced mechanical hyperalgesia and cold allodynia (11).

We focused on c-Jun and c-Fos among members of the AP-1 transcription factors because their expression levels were markedly increased in SH-SY5Y cells. In RNA interference experiments, the contribution of c-Fos to the induction of VGF expression appeared to be greater than that of c-Jun (Fig. 5B), and this was attributed to differences in the efficiencies of siRNAs (Fig. 5A). Thus, the contribution of c-Jun to the induction of VGF expression cannot be excluded because c-Fos is known to require Jun family proteins for its

functional expression through the formation of heterodimers. The induction levels of c-Jun and c-Fos were much lower in IMR-32 cells than in SH-SY5Y cells (Fig. 3). This coincides with the induction level of VGF mRNA being markedly lower in IMR-32 cells than in SH-SY5Y cells (Fig. 1). The induction of c-Fos by clioquinol was also reported in vivo. An i.p. injection of clioquinol to rats and mice was shown to induce c-Fos expression in the hippocampus and telencephalon (27). Further analyses are required on the level of c-Fos in SMON patients administered with clioquinol.

In conclusion, clioquinol, the causative compound of SMON, induced the expression of VGF, the precursor of neuropeptides involved in pain reactions, by inducing c-Fos expression.

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2012 SMON examination in Tokushima

Takao Mitsui , M.D.[#1], Kazuyuki Kawamura , M.D.[#1], Toshio Inui , M.D.[#1], Yutaka Matsuka , M.D.[#2], Masako Matsumoto, R.N.[#3], Yukiko Inoue , R.N.[#3], Yasuo Taichi , PT.[#4], Yasunori Saito.[#5], Kaori Morita.[#5], Aiko Tokunaga.[#5], Hiromi Sato .[#5]

#1 . Department of neurology, Tokushima National Hospital, National Hospital Organization, 1354 Shikiji, Kamojima, Yoshinogawa, Tokushima 776-8585 Japan

#2. Department of orthopedics, Tokushima National Hospital, National Hospital Organization, 1354 Shikiji, Kamojima, Yoshinogawa, Tokushima 776-8585 Japan

#3 . Nursing department, Tokushima National Hospital, National Hospital Organization, 1354 Shikiji, Kamojima, Yoshinogawa, Tokushima 776-8585 Japan

#4 . Department of rehabilitation, Tokushima National Hospital, National Hospital Organization, 1354 Shikiji, Kamojima, Yoshinogawa, Tokushima 776-8585 Japan

#5 . Tokushima public health center

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Abstract

A medical examination of the SMON in Tokushima of 2011 was reported. There were 37 testees this year. Twenty-seven of them had a medical checkup in a group, seven had a medical checkup at home, and three had a medical checkup in Tokushima National Hospital. This was a similar group of medical examination testees to an average year. There were six elderly people aged over 90. One was over 100 years old. A medical examination testee decreases gradually with aging of SMON patients. Measures to increase the number of medical examinations by arranging visits are necessary. A future problem may be that many patients are reluctant to be visited at home.

Keywords: SMON in Tokushima, medical checkup, Tokushima National Hospital

Introduction

The sale of chinoform was halted 42 years ago. Subsequently, no new SMON cases were reported. Also, the number of SMON patients decreases with the course. The weathering measures of the SMON are performed as activity such as "gathering workshops of the SMON" 4). We have been checking on the SMON patients in Tokushima every year for many years. In this study, the results for 2012 are reported. Subjects and methods. The subjects were patients with SMON who are resident in Tokushima and enrolled in an SMON investigation individual vote. We conducted a mass checkup and at-home examinations. Furthermore, we checked on the patients hospitalized in Tokushima National Hospital and outpatients of the hospital. We went in the large meeting room of the Tokushima-shi handicapped persons interchange plaza. Three examination areas, each with a medical examination desk and an examination couch were prepared in the meeting room. An electronic height measuring instrument, a set of scales and a sphygmomanometer were prepared for physical measurement. The

Correspondence to: Takao Mitsui , M.D., Tokushima National Hospital, National Hospital Organization, 1354 Shikiji, Kamojima, Yoshinogawa, Tokushima 776-8585 Japan Phone: +81-883-24-2161 Fax : +81-883-24-8661

physical situation and the present social conditions were described by the SMON patients. Also, a neurological medical examination was conducted.

Results

Thirty-four people received a medical examination in 2012. They comprised 11 men and 26 women. The average age was 80 years old. The average age at which the disease was contracted was 43 years. The mass checkup covered 27 people. Nine people had a medical examination during an at-home visit. The testees in the Tokushima National Hospital outpatient department numbered two people. The hospitalized patients were alone.

Time of contraction of disease. As shown in Table 1, the age of the patients who had a medical checkup at home was the highest. The age of the patients who had a medical checkup in a group was the second highest. The patients who had outpatient consultations were the youngest. The Barthel Index (42 points) of the patients who had a medical checkup at home was the lowest. Most of the patients who received home care had family medicine. Frequent complications included cataract, hypertension, and arthropathy. The number of patients with a BMI (Body Mass Index) of 25 or more was six this year. Many patients were aware of forgetfulness but in four patients this was complicated by obvious dementia. There were seven elderly people older than 90 years. There were two patients with early onset (onset at 18 years old). Two women patients were 61 years old. One had a part-time job; the other was uneasy about single life in the future.

Table 1. Patients with SMON that received a medical examination

	Men	Women	Total	Mean age
Mass checkup	9	18	27	78
Checkup at home	2	7	9	86
Outpatient department	0	2	2	62
Hospitalization	0	0	0	—

Discussion

Forty-five years have passed since the sale of the chinoform agent was halted in (1970) in 1970 [1]. As a result, it is over 41 years since SMON patients began to contract the disease. The average disease contraction time of SMON patients in Tokushima prefecture is 43 years. The average age of the testees was 78.

The number of patients in 1972 when a meeting (patients association) of the Tokushima SMON was organized was 155. The medical examination results that we examined corresponded to the national tendency of the average year. Most patients had family medicine. Even if the patients were living alone, a nearby doctor could be contacted in an emergency. Seven patients were over 90 years old. One was over 100 years old. Three people used nursing care insurance. Furthermore, they received close support from family members. There were two women with young onset (18 years old). The Barthel Index scores for them were 95 and 100 points. The degree of their disorder was very mild. As well as support in terms of food, clothing and shelter, mental support seemed to be needed. The weathering measures of the SMON are performed as activity such as "gathering workshops of the SMON" positively in this study squad. The number of medical examination testees of the aging is shown in Table 1. A mass checkup in the Tokushima public health center began in 1990. More than forty people participated constantly from 1999. In 2011, the number of the people having an examination decreased. This may be associated with a decrease in the number of testees to have changed a place in a medical examination this year. However, a decrease in the number of testees due to aging will be a main factor. The number of medical examinations conducted at home should be increased.

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《短　報》

スモン患者の咳嗽力に関する検討

川上途行[*1]　里宇明元[*1]　堀江温子[*1]
辻川将弘[*1]　前島早代[*1]　大高洋平[*1]
藤原俊之[*1]　辻　哲也[*1]　木村彰男[*1]

Peak Cough Flow in Patients with Subacute Myelo-optic Neuropathy

Michiyuki KAWAKAMI,[*1] Meigen LIU,[*1] Atsuko HORIE,[*1] Masahiro TSUJIKAWA,[*1]
Sayo MAESHIMA,[*1] Yohei OTAKA,[*1] Toshiyuki FUJIWARA,[*1]
Tetsuya TSUJI,[*1] Akio KIMURA[*1]

Abstract　Purpose : This study aims to measure the peak cough flow (PCF) in patients with subacute myelo-optic neuropathy (SMON) and study its relation with muscle strength, functional ability and vocal cord function. Methods : We performed a cross-sectional study in 7 patients with SMON (2 men and 5 women, mean age (SD) 81.6 (7.2) years) and in 7 age- and gender-matched patients with orthopedic problems as a control group. Their PCF, ability to walk, the Barthel Index, grip strength and maximum phonation time were assessed. Results : Mean PCF was 218.6± 66.2 L/min (110–300) for the SMON group and 267.1±76.3 L/min (170–360) for the control group (ns). The PCF was correlated with the maximum phonation time ($r = 0.91$; $p < 0.01$), but not with grip strength, the Barthel Index or the ability to walk scale. Conclusion : The PCF in patients with SMON tended to be lower compared to the control group. Therefore, evaluating PCF is suggested to be necessary to assess the risk of pneumonia. (**Jpn J Rehabil Med 2013 ; 50 : 654–657**)

要　旨：外来通院中のスモン患者7名（男性2名，女性5名，平均年齢81.6±7.2歳）を対象に咳嗽力の評価として，peak cough flow（以下PCF）を測定し，年齢，性別をマッチした対照群と比較した．歩行機能，Barthel Index，握力，発声持続時間も併せて測定し，PCFとの関連をスピアマンの順位相関係数およびピアソンの相関係数を用いて検討した．スモン患者群のPCFの平均値は218.6±66.2 L/min（110～300），対照群は267.1±76.3 L/min（170～360）であり，患者群で低い傾向を認めた．PCF低値の症例は，スモン患者7名中5名（71%）であった．110 L/minの症例は陳旧性肺結核の既往例であった．最長発声持続時間とPCFには強い相関を認めた．【結論】スモン患者の咳嗽力はやや低い傾向を認め，定期的な呼吸機能，咳嗽力の評価，および呼吸器合併症のリスクの軽減のための呼吸リハビリテーションの必要性が示唆された．

Key words : スモン（subacute myelo-optic neuropathy），咳（cough），筋力（muscle strength），最長発声持続時間（maximum phonation time）

はじめに

以前より咳反射の低下が肺炎の危険因子であると報告されている[1]が，近年，咳の力＝咳嗽力の低下も肺炎の危険因子として注目されている[2,3]．肺炎のリスクのある患者に対し，咳嗽力を評価することは重要である．

スモン（亜急性脊髄視束神経症，subacute myelo-opticoneuropathy：SMON）は腹痛・下痢などの腹部症状に引き続いて，特有のしびれ感が足先よりはじま

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[*1] 慶應義塾大学医学部リハビリテーション医学教室/〒160–8582 東京都新宿区信濃町35
Department of Rehabilitation Medicine, Keio University School of Medicine
E-mail : michiyukikawakami@hotmail.com

り，下肢全体あるいは胸・腹部にまで上行する神経疾患である[4]．1970年に整腸剤キノホルム（chinoform, clioquinol）の副作用が原因とする説が提唱され，中央薬事審議会によって同剤の使用が禁止されてから新たな患者の発生はなくなった．患者のキノホルム服用歴などより，疫学的にはスモンの原因は本剤であるのは明らかであり，1972年末までの患者数は9,249人で，1万2千人以上に達したと推定されている[4]．キノホルムの販売停止（1970年9月8日）より40年以上が経過した現在，新たな患者の発生はなくなったものの，症状が慢性固定化した多くの患者が未だ後遺症に苦しんでいる．薬害であるスモン患者の恒久対策として，厚生労働省難治性疾患克服研究事業「スモンに関する調査研究班」は，従来より毎年1,000人前後の患者検診を続けてきており，当院はその一翼を担っている．2011年4月1日現在健康管理手当を受給しているスモン患者数は，全国で1,956名であり，年齢は70歳代が最も多く，65歳以上が91.6%を占めている．

高齢化が進み，また嚥下障害の合併も報告されているスモン患者は肺炎のリスク群であり，咳嗽力の評価の必要性が示唆されるが，渉猟しえた範囲では報告は見当たらないため，スモン患者の咳嗽力を調査した．また，咳嗽力と筋力や声帯機能との関係を調べるために，握力および最長発声持続時間と咳嗽力との関係を検討した．

対象と方法

対象は当院リハビリテーション（以下，リハ）科にてスモン検診を実施したスモン患者全例である．対象患者は7名（男性2名，女性5名，平均年齢81.6±7.2歳）である．5名は当院外来を受診し，2名は往診にて評価を行った．

咳嗽力の評価として，peak cough flow（以下PCF）を測定し，年齢，性別をマッチさせた対照群（整形外科術前に当科を受診した群，男性2名，女性5名，平均年齢80.2±5.7歳）と比較した．スモン患者と対照群の間で体格（身長，体重，body mass index），握力，呼吸器疾患合併例の有無について比較を行った．PCFの測定にはピークフローメーター（ASSESS：レスピロニクス社製）を用い，測定肢位は端座位とし，3回測定を行い，最大の値を採用した．一般的なPCF低値とされる270 L/min未満をPCF低値例とし[5]，その割合を調べた．

スモン患者では，歩行機能（スモン現状調査個人票による9段階評価，1．不能，2．車椅子（自分で操作），3．要介助，4．つかまり歩行（歩行器など），5．松葉杖，6．一本杖，7．独歩（かなり不安定），8．独歩（やや不安定），9．ふつう，の9段階），Barthel Index，握力，最長発声持続時間も合わせて測定し，PCFとの関係をスピアマンの順位相関係数およびピアソンの相関係数を用いて検討した．最長発声持続時間は被験者に最大吸気をさせた後，自然な話声位でできるだけ一定の強さで「アー」と可能な限り長く持続発声を行わせ，その持続時間を測定した[6]．また，既往歴（特に呼吸器に関するもの）の情報を聴取した．

（倫理面への配慮）

データは，スモン検診受診時の診察および「スモン現状調査個人票」から得ており，「データ解析・発表に同意した」患者データのみを使用した．また，対照群のデータ使用については，当大学医学部の倫理委員会の承認を得ている．

結　果

両群で体格，握力，呼吸器疾患合併例の割合につき明らかな差を認めなかった（**表1**）．スモン患者群のPCFの平均値は218.6±66.2 L/min（110～300），対

表1　スモン患者群と対照群のプロフィール（平均値および中央値）

	スモン患者群	対照群	Mann-Whitney検定
年齢（歳）	81.6±7.2（83）	80.2±5.7（77）	$p=0.61$
身長（cm）	153.2±10.1（152）	156.0±8.8（155）	$p=0.48$
体重（kg）	49.3±9.2（48）	51.0±10.0（47）	$p=0.89$
BMI	20.9±3.1（21.1）	21.1±4.6（22.0）	$p=0.85$
握力（kg）	18.6±5.0（18）	17.2±4.1（17.4）	$p=0.65$
呼吸器疾患合併例	陳旧性肺結核1例	COPD 1例	

BMI：body mass index，COPD：慢性閉塞性肺疾患

表2　スモン患者のPCF，握力，歩行機能，BI，最長発声持続時間

年齢（歳）	性別	Peak cough flow (L/min)	握力 (kg)	歩行機能	Barthel Index	最長発声持続時間（秒）
90	女	270	16	2	75	18
76	男	240	28.6	9	100	17
69	女	250	19.2	8	100	13
88	女	160	17.6	8	95	4
83	男	110	19	8	100	5
84	女	200	12	4	90	11
81	女	300	18	8	100	17

表3　PCFと握力，歩行機能，BI，最長発声持続時間との相関

	相関係数	p値
握力	0.09	$p=0.84$
歩行機能	−0.07	$p=0.86$
Barthel Index	−0.21	$p=0.64$
最長発声持続時間	0.91	$p<0.01$

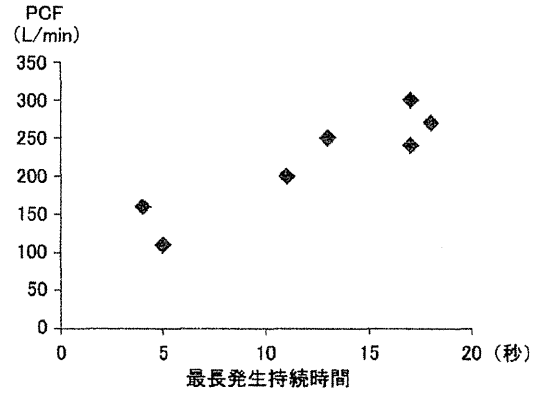

図　PCFと最長発声持続時間との関係
PCFと最長発声持続時間は強い正の相関を認めた．

照群は267.1±76.3 L/min（170～360）であり，両群で統計学的な有意差は認めなかった（Mann-Whitney検定，$p=0.22$）．PCF低値の症例の割合は，スモン患者7名中5名（71%），対照群は7名中3名（43%）であり，統計学的には有意差を認めなかった（Fisherの正確確率検定，$p=0.30$）．110 L/minの症例は陳旧性肺結核の既往例であった．

スモン患者，全例のPCF，握力，歩行機能，BI，最長発声持続時間の値を表に示す（表2）．

歩行機能やADL，握力とPCFとは相関を認めなかったが，最長発声持続時間とPCFには強い相関を認めた（表3，図）．

考　察

肺炎，特に誤嚥性肺炎の危険因子として，嚥下反射の低下，咳反射の低下が知られているが，近年，咳嗽力の低下が肺炎の危険因子として注目されている．Bianchiら[2]は，慢性期脳卒中患者を中心に行った調査で，PCFの低値が肺炎の発症に関連したと報告しており，前島ら[3]も多くの疾患を含む嚥下障害患者を対象に同様の結果を報告している．

咳嗽力の評価として，PCFは神経筋疾患を中心に広く用いられている手法である[7]．ピークフローメータを用いて，咳嗽の流速を測るものであり，喉頭を閉めて胸腔内圧を高める分ピークフローより高い流速が得られる．過去にスモン患者におけるPCFの報告はなく，今回の結果は，今後のスモン患者の診療において，参考となる結果であると考える．

PCFの基準値については，明確なものはまだないが，神経筋疾患患者を中心とした報告で，有効な咳となるためには160 L/minが，喀痰の排出には270 L/minが必要になるとされている[5,8]．今回のスモン患者の結果ではPCF低下例を多く含んでいることが確認された．また，入院中の高齢者を対象とした過去の報告では，自己排痰可能例（平均年齢68.7±11.3歳）のPCFは385.0±167.8 L/minであり[9]，それと比較してもスモン患者のPCFは低い値であるといえるだろ

う．スモン患者の死因として肺炎による死亡割合が高いという報告[10,11]があるが，咳嗽力の低下が関与しているかもしれない．

咳嗽力を規定する因子に関してはまだ報告が少ない．咳嗽とは，気道内の異物を咳受容体が感知し，求心性神経（舌咽神経，上咽頭神経）を介し，延髄咳中枢に伝えられ，遠心性神経（迷走神経，下咽頭神経，横隔膜神経）を介して，横隔膜や胸郭の筋肉に伝えられ，声門の閉鎖を伴う急激な胸腔内圧の上昇とその急激な解放によって生じる強力な呼気であるが，呼吸機能，筋力，声帯機能などが咳嗽力を規定していると予測される．呼吸機能は咳嗽力に関連するという報告[12,13]はいくつかあり，肺活量やピークフローなどが咳嗽力を規定する重要な因子の1つであると考えられている．スモン患者における呼吸機能は加齢に伴い，%肺活量（%VC），一秒率（$FEV_{1.0}$%）は低下すると報告されており[14]，呼吸機能の低下が咳嗽力の低下を招いた可能性はある．

最長発声持続時間は，耳鼻咽喉科領域で一般的に用いられる評価法であり[15]，日常生活に必要な発声能力の測定の1つである．呼気量とその呼気が喉頭調節によりどの程度効率よく声の音源に変換されるかを示している．すなわち呼吸機能と喉頭，声帯の動きの評価である．スモン患者では最大発声持続時間とPCFが高い相関を認めていた．しかし，呼吸器疾患を対象とした過去の報告では最大発声持続時間とPCFは相関しないという報告もあり，今回の結果がスモン患者に特徴的なものなのか，今後検討する必要がある．今回のスモン患者では最大発声持続時間が比較的短い症例が含まれていることが特徴的であり，この原因の検索（肺活量の低下例なのか，声帯機能低下例なのか）と解析結果への影響を慎重に検討する必要がある．

本研究の限界としては，少数症例での検討であること，呼吸機能検査が行えておらず，呼吸機能とPCFの比較ができていないことである．呼吸機能，特に肺活量がPCFと強く関連していることが予測され，今後検証する必要がある．

肺炎のリスクが高いと判断された症例では，呼吸リハの導入によりそのリスクを軽減させることが期待できる．排痰訓練，呼吸筋訓練，全身調整訓練などを用いた呼吸リハは，咳嗽力の低下している患者群の肺炎リスクの軽減に有用と考えられ，今後，スモン患者において，肺炎の発生率を減少させることができうるかどうか，検討する必要がある．

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スモンに関する調査研究班
研究代表者　小長谷　正明
三重県鈴鹿市加佐登3-2-1
国立病院機構鈴鹿病院
印　　刷　株式会社　一誠社
TEL（052）851-1171㈹