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ELSEVIER

Clinical analysis of longstanding subacute myelo-optico-neuropathy: sequelae of clioquinol at 32 years after its ban

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Abstract

One thousand and thirty-one longstanding patients with subacute myelo-optico-neuropathy (SMON; 275 males, 756 females; mean age ± S.D., 72.9 ± 9.6 years; age at onset 37.6 ± 9.8 years; duration of illness 35.3 ± 4.0 years) were examined in 2002, 32 years after banning of clioquinol. At onset, 66.7% of patients were unable to walk, and 4.7% complete blindness. At present time, about 41% of patients were still difficult to walk independently, including 15.8% of completely loss of locomotion. One point six percent of patients were in complete blindness and 5.8% had severe visual impairment. The majority (95.6–97.7%) of patients exhibited sensory disturbances including superficial and vibratory sensations and dysesthesia. Dysautonomia was observed as leg hypothermia in 79.8%, urinary incontinence in 60.7%, and bowel disturbance in 95.3%. As complication, high incidence was revealed with cataract (56.2%), hypertension (40.2%), vertebral disease (35.5%), and limb articular disease (31.5%). These results indicate the serious sequelae of clioquinol intoxication, SMON. © 2003 Elsevier B.V. All rights reserved.

Keywords: Subacute myelo-optico-neuropathy; SMON; Clioquinol; Intoxication

1. Introduction

Subacute myelo-optico-neuropathy (SMON) is a disease characterized by subacute onset of sensory and motor disorders in the lower half body combined with visual impairment, which are preceded by abdominal symptoms. In addition, in some cases, bulbar palsy due to brainstem impairment leads to death [1–4]. A large number of SMON were observed throughout Japan and the total number of cases reached nearly 10,000 by the end of

1970. Based on the results of extensive epidemiological study by SMON Research Group, SMON was confirmed to be caused by ingestion of clioquinol (5-chloro-7-iod-8-hydroxyquinoline), an intestinal antibacterial drug. Patients who developed SMON had a daily intake of more than 0.6 g of clioquinol for 14 days, and with larger amounts, the symptoms appeared within several days [5]. After the governmental banning of the use of clioquinol in September 1970, there was the dramatic disappearance of new cases of SMON. Afterward, the number of patients decreased with time, and in 2002, there were 2936 people receiving health management allowances from the Organization for Adverse Drug Reaction Relief. It is estimated that the number of patients slightly exceeds

that number. The clinical condition has not progressed after the certain recovery from the acute stage, but there are no effective treatments for the remaining symptoms.

The pathological findings of SMON are symmetrical demyelination of the lateral and posterior funiculi of the spinal cord, optic nerve, and peripheral nerves [2,6]. There have been some hypothesis for the neurotoxicity of clioquinol such as the contribution of heavy metals like iron and zinc [7], tissue damage due to radical oxygen and lipid hyperoxidation [8,9], and vitamin B12 metabolic abnormalities [10]; however, none of these theories has been established.

Meanwhile, recent attention has focused on the chelating activity of clioquinol to reduce β-amyloid plaques, and some trials have been reported for possible treatment in Alzheimer's disease [11,12]. However, in the light of the appalling damage that has been caused by this drug, caution must be given in its use [13]. Thirty-two years have now passed since the banning of clioquinol in Japan, and in the present paper, we would like to report the current state of SMON patients as an aid to the consideration of the revival of clioquinol.

2. Patients and methods

The subjects were 1031 SMON patients (275 males, 756 females; mean age ± S.D., 72.9 ± 9.6 years; age at onset 37.6 ± 9.8 years; duration of illness 35.3 ± 4.0 years) who were examined in 2002 by the SMON Research Committee, supported by the Ministry of Health, Labor, and Welfare of Japan.

Symptoms were identified based on the medical check-up records of the research group [14]; stages were appropriately grouped according to the medical check items, and four stages were set as a rule. Patients were divided into four groups by level of dysbasia at the time of examination. These were the abasia group, clinging walking group, cane walking group, and independent walking group. According to visual impairment, the patients were also divided into four groups: the completely blind group, severely impaired group with visual acuity less than counting fingers, mildly impaired group, and nearly normal group.

Table 1
Current visual impairment and dysbasia

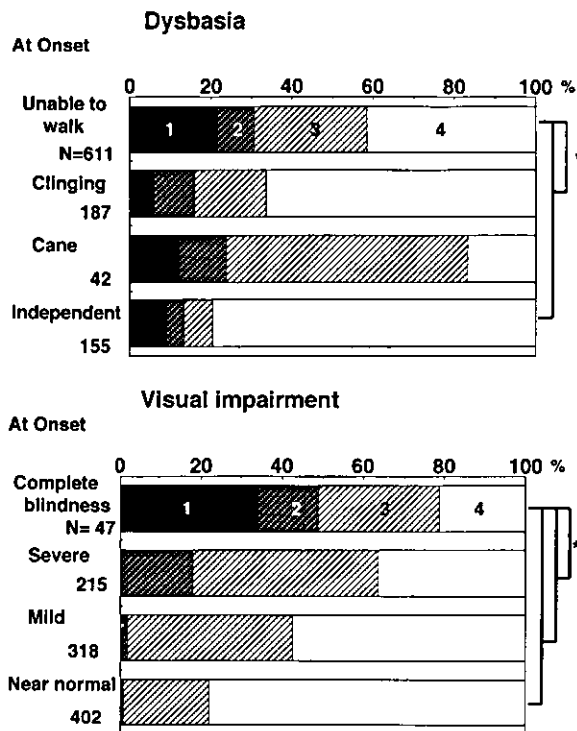| Dysbasia	Unable to walk	Clinging	Cane	Independent	Total
Visual impairment					
Complete blindness	14	1	0	1	16
Severe	26	11	10	11	58
Mild	71	38	104	123	336
Nearly normal	47	39	126	375	587
Total	158	89	240	510	997

Fig. 1. Change of impairments. Above: Dysbasia. (1) Unable to walk at present time; (2) walking with clinging; (3) walking with cane; (4) independent walking. *: Significantly change in proportion of unable to walk, $p < 0.01$. Below: Visual impairment. (1) Complete blindness at present time; (2) severe impairment; (3) mild impairment; (4) near normal. *: significantly change in proportion of complete blindness, $p < 0.01$.

Change in symptoms from the onset till the present: investigation of the proportion of patients by severity of dysbasia and visual impairment. Current visual impairment and dysbasia: the groups were compared for each symptom including leg motor symptoms, sensory disorder and dysautonomia, activities of daily living (ADL) scale, and recuperation.

The number of unknowns for each item was excluded from the statistical study, and the population parameter differed for each investigated item. In the statistical tests [15], the differences in mean values between the groups were examined with Bonferroni's population mean multiple comparison method and the differences in proportion by Bonferroni's population rate multiple comparison method.

Table 2
Symptoms of lower extremities

Impairments	Severe	Moderate	Mild	Normal	Total
Weakness	144	282	384	192	1002
Amyotrophy	58	145	308	493	1004
Spasticity	66	184	274	459	1003

3. Results

3.1. Dysbasia and symptoms in lower extremities

Dysbasia was investigated in 997 people, of whom 15.8% were unable to walk, 9.0% walked while clinging, 24.1% walked with a cane, and 51.1% walked independently. In the present day, there is a significantly higher proportion of people unable to walk in the groups with stronger visual impairments (Table 1, $p < 0.001$). Of the people able to walk independently, 29% were judged to be unstable. Dysbasia improved in 64.8%, unchanged in 29.8%, and worsened in 5.3% (Fig. 1). Of 611 people unable to walk at the onset, 130 remained the same ability, 57 walked while clinging, 170 walked with a cane, and 254 walked independently.

Motor symptoms in lower extremities were found in 80.8% of patients, including 14.4% with severe motor weakness, 50.9% with amyotrophy (severe in 5.8%), and 54.2% with spasticity (severe in 8.6%) (Table 2). In the groups with severer dysbasia, there were also significantly larger proportions of people with other lower extremity symptoms ($p < 0.001$).

3.2. Visual impairments

In an investigation of the present visual impairment in 997 patients, 1.6% were in complete blindness, 5.8% in severe impairment, 33.7% in mild impairment, and 58.9% in nearly normal vision (Table 1). Forty-seven patients were completely blind at onset, and at present, 16 remain complete blindness, 7 have severe impairment, and 14 have mild impairment. The group with complete blindness at onset shows significantly larger proportions of complete blindness or severe impairment in the present examination compared with other groups (Fig. 1). The visual impairment improved in 39.8% of patients, unchanged in 9.7%, and worsened in 9.7%. The improvement ratio in visual impairment was significantly lower than that in dysbasia ($p < 0.001$).

3.3. Sensory impairment

Superficial sensory impairment was seen in 982 patients, and the distal dominancy was observed in 90% of these patients. The region affected was above the breast level in

3.3%, below the breast in 13.0%, below the navel in 31.5%, below the groin in 29.0%, below the knee in 17.4%, and below the ankle in 5.0%. Tactile sensation disorders were hypesthesia in 86.3% and hypersensitivity in 9.3%, and algesthesia were hypoalgesia in 74.7% and hyperalgesia in 21.7% (Table 3).

Impaired vibratory sensation in the lower extremities was observed in 95.9% and was severe in 36.0%. In the groups with stronger dysbasia, there were also significantly larger proportions of people with severely impaired vibratory sensation ($p < 0.001$), except comparison between the group unable to walk and clinging groups. Six hundred forty-six out of 858 examined cases were positive Romberg's sign.

Dysesthesia was present in 97.6% of patients and severe in 23.3%. This included the adherent sensation to sole in 48.1%, girdle sensation or cramp in 46.6%, tingling sensation in 20.3%, pain in 47.2%, and psychroesthesia in 37.2%. The course of dysesthesia from the onset was worsened in 13.0%, unchanged in 19.5%, improved mildly in 29.3%, and improved considerably in 33.7%. The proportion of patients in whom the conditions improved was significantly lower than in the severe dysesthesia group than in the moderate or mild dysesthesia groups. The proportion of group with severe dysesthesia was larger in the groups with poorer walking ability, except comparison with the clinging and cane groups (Fig. 2).

3.4. Autonomic disorders

Lower extremity hypothermia was observed in 79.8% of patients. Incontinence of urine was seen in 60.7% and incontinence of feces in 32.7%. Diarrhea was present in 27.0% of patients, constipation in 49.3%, and alternating diarrhea and constipation 18.9%, so that altogether, 95.3% complained of bowel disturbance.

3.5. Complications

Complications were present in 93% of patients. Complications with high incidence were cataract in 56.2%, hypertension in 40.2%, vertebral disease in 35.5%, limb articular disease in 31.5%, digestive disorders other than in the hepatocystic system in 31.5%, and cardiac disease in 22.8%. Bone fractures were reported in 14.9%. Mental

Table 3
Sensory symptoms

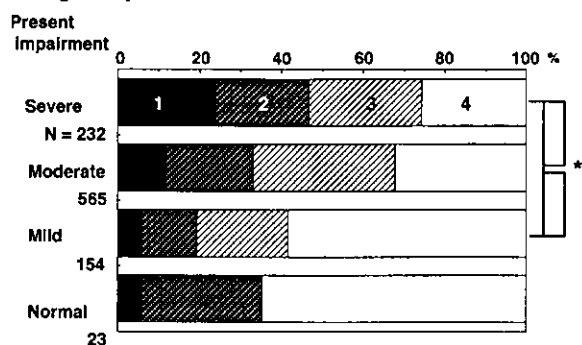| Impairments	Severely decreased	Moderately decreased	Mildly decreased	Hypersensitive	Normal	Total
Tactile sensation	113	421	330	93	44	1001
Algesthesia	120	350	276	217	36	999
Vibratory sensation	356	342	249		1	968
	Severe	Moderate	Mild		Normal	Total
Dysesthesia	232	565	154		23	994

Change of Dysesthesia

Fig. 2. Change of severity of dysesthesia from the onset. (1) Worsened; (2) not changed; (3) slightly improved; (4) remarkably improved. *: significantly changed the population of slightly improved + remarkably improved, $p < 0.01$.

symptoms were seen in 51.8% and dementia in 4.3% (Table 4).

3.6. Severity in illness

The degree of the general severity was very severe in 4.5%, severe in 19.7%, moderate in 43.0%, mild in 24.9%, and very mild in 5.1%. These were caused by SMON in 36.3%, SMON plus complications in 52.7%, complications in 11.1%, and SMON plus aging in 7.2%. The mean Barthel Index [16], an indicator of ADL, was 81.9 ± 22.4, and the severe group had a significantly lower Barthel Index than

Table 4
Complications

|	Severe to moderate	Mild	Total	Percentage (%)
Physical complications			962	93.0
Cataract	146	436	582	56.2
Hypertension	95	321	416	40.2
Cerebrovascular diseases	29	85	114	11.0
Cardiac disease	45	191	236	22.8
Hepato-cystic disease	34	121	155	15.0
Gastrointestinal disease	75	211	286	27.6
Diabetes mellitus	38	78	116	11.2
Respiratory disease	24	80	104	10.0
Bone fracture	48	106	154	14.9
Vertebral diseases	108	259	367	35.5
Limb articular diseases	104	222	326	31.5
Uro-genital disease	49	130	179	17.3
Parkinsonism	4	7	11	1.1
Dyskinesia	2	2	4	0.4
Malignancy	15	40	55	5.3
Other complications	125	348	473	45.7
Psychiatric complications			536	51.8
Irritation	80	208	288	27.8
Neurosis	42	99	141	13.6
Depression	53	152	205	19.8
Memory loss	43	214	257	24.8
Dementia	16	28	44	4.3
Other complications	10	27	37	3.6

Dysbasia

Visual impairment

M ± SD
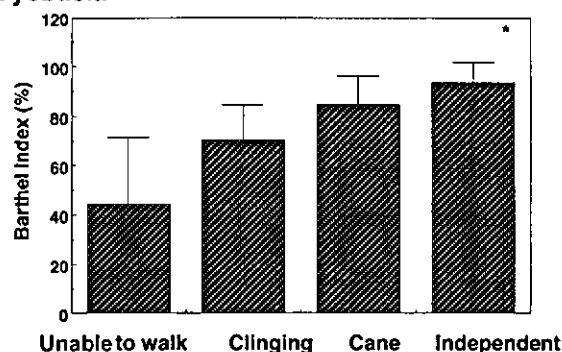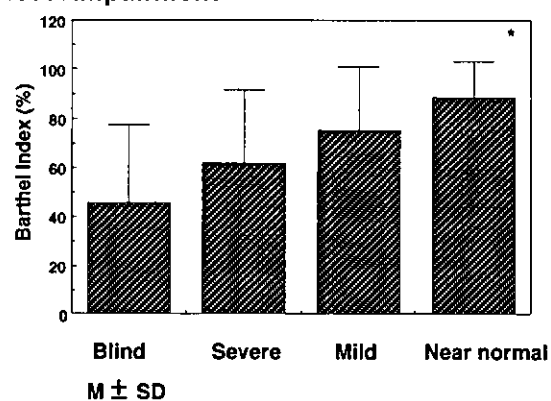
Fig. 3. Barthel Index and impairments. Above: Dysbasia. Below: Visual impairment. *: Significantly change in each comparison, $p < 0.01$.

the milder groups in both investigation of walking and visual impairment ($p < 0.01$) (Fig. 3).

3.7. Long-term care

Sixty-four patients were under the long-term hospitalization, 190 were hospitalized at intervals, and 748 lived at home. Twenty-five percent of completely blind patients and 28.5% of those patients unable to walk were under the long-term hospitalizations.

In daily life, 45 of the 1031 patients were confined to bed, 32 to the hospital room, and 268 to indoors, while 682 could go out of doors.

4. Discussion

The results of the present study are summarized as follows. The severities of impairments in vision, walking, and sensation are overall milder than those at the onset. But in the present study, at more than 32 years after clioquinol intoxication, about 41% of patients were still unable to walk independently, including 15.8% who could not walk at all. In terms of vision, 1.6% of patients were

totally blind and 5.8% had severe visual impairments with visual acuity below the level of counting fingers. Moreover, the majority of patients showed sensory disturbances and other difficulties, so it is clear that serious sequelae of clioquinol intoxication have remained. Considering the likelihood that some patients with severe conditions were not examined, the proportion of seriously harmed patients are assumed to be a little higher than in the numbers given here.

Besides the severe motor dysfunction, many of those patients with severe dysbasia showed strongly impaired vibratory sensation and severe dysesthesia in the lower half body. So the dysbasia in SMON is thought to be from a combined disorder in the motor and sensory systems. The ratio of the patient unable to walk has remarkably reduced of 60% at onset to 20% at present, which indicates a considerable improvement of injury in the spinal cord and peripheral nerve in the large population of SMON patients. On the other hand, about 5% of patients showed a poorer walking ability today than that at onset because of the complications such as joint and vertebral diseases and apoplexy.

Thirty five percent of patients with complete blindness at onset still remained blindness at the present examination, which indicates the less restorative ability of the visual system than the motor system. The high proportion of blindness and severe visual impairment in those patients unable to walk seem that the patients with optic nerve damage also have severe damage in the lateral and posterior funiculi of the spinal cord. It is as a matter of course that the patients with severe visual handicap are in poor states of ADL [17]. About 10% of the patients demonstrated decreased visual ability since the onset, and this is thought to be from the contribution of other ophthalmologic complications such as cataract and hyperopia [14,18].

Sensory disorders were present in nearly all patients, and in addition to decreased sensitivity, many patients also complained of hypersensitivity of the tactile and pain sensations. About 80% of patients complained of dysesthesia and paresthesia in the lower extremities, which are characteristic symptoms in SMON [1]. However, 65% of patients had improvements in the severity of dysesthesia. While the major symptoms were thus ameliorated over the long term, it is not clear whether it was due to the various treatments given soon after the onset (ACTH, steroids, vitamins, ATP, agents to improve blood circulation, hyperbaric oxygen therapy, etc.) or due to natural course of the disease.

Among dysautonomia, high incidence was observed in hypothermia, urinary incontinence, and bowel disturbance. A detailed investigation by Matsuoka and Konagaya [19] revealed that the incidence of urinary incontinence in SMON patients was increased to six times of that in the general elder population in 2000. Urinary incontinence in SMON patients was suggested mainly due to central and peripheral nervous system disorders by clioquinol intoxica-

tion. The aging process may play a role in the development of the symptom.

There is an increase in various complications year by year [14,18], and a previous investigation showed a higher incidence of cataract in SMON patients than in a general group matched for age. The increases in vertebral and limb articular diseases are expected to exacerbate the original dysbasia of SMON, which may bring an increase of fractures. The mutual influence of the aging process and SMON seems to cause the complications and worsening the clinical states year by year.

The marked deterioration in ADL was demonstrated in patients with severe walking and vision disorders. Considering the patients who were not examined, there may be more number of patients in serious state today. In the study of mortality in SMON patients, the presence of severe walking disturbance and low ADL level was reported to associate with significantly high risk of death [20,21].

Since no de novo cases after clioquinol banning and the nature of no progression, SMON has fallen out of the spotlight in both medical and social society and seems to have faded. However, in current attempts of clioquinol to Alzheimer's disease, the neurotoxicity of the substance and its sequelae should be noticed.

Acknowledgements

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