Subacute myelo-optic neuropathy, beriberi, and HTLV-I-associated myelopathy: elucidation of some neurological diseases in Japan

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Introduction
Throughout my research life, I discovered the causes of some neurological diseases occurring in Japan. This paper reviews my experience and results in this field.

Subacute myelo-optic neuropathy
Since early 1960s, a peculiar neurological disease, subacute myelo-optic neuropathy (SMON), became prevalent in many regions of Japan, and later turned into a pandemic. In the years 1963–1964, I experienced the outbreak of this disease, mainly in the summer, in the Toda city adjacent to the northern border of Tokyo. The disease affected more than 50 patients. By the end of 1970, the number of patients in Japan had increased to more than 10,000.

Clinical signs and symptoms
SMON had the following clinical features: the onset was rather subacute, sometimes with relapses; abdominal symptoms (abdominal pain, diarrhea, etc.) usually preceded the neurological ones; the main neurological symptoms included symmetrical paresthesia and hypoesthesia, predominantly in the distal parts of the lower extremities without any clear upper margin (in severe cases, the upper extremities are also involved); slight motor disturbance of the lower extremities; bladder and colon disturbances in severe cases; pyramidal signs with decreased Achilles tendon reflexes in many cases; visual disturbance in 20% of the cases; no signs of infection and no abnormal findings in blood and cerebrospinal fluid suggesting infection; rare in children; both men and women were equally affected; death occurred sometimes preceded by cerebral symptoms.

At the beginning, this new disease was named “nonspecific encephalo-myelitis” by the research group of Professor Maekawa from the Kyoto University, but due to its complexity, the name of SMON was proposed by Professor Yasuo Toyokura (Department of Neurology, University of Tokyo) and became widely accepted. The name was derived from the mode of disease onset and pathological findings, which were characterized by pseudo-systemic degeneration of the long tracts of the spinal cord, along with the involvement of the visual and peripheral nervous systems.

The endeavor to elucidate the cause of subacute myelo-optic neuropathy
We were involved in research on the causes and management of the new disease, but the findings had remained obscure for several years. In 1970, Dr Inoue from the Kyoto University suggested that a virus might be the responsible pathogen in patients with SMON, but there was no supportive evidence. It was a surprising observation that many patients with SMON became despaired to commit suicide.

In contrast to the virus hypothesis, we were convinced that SMON was not an infectious disease, and our suggestion was based on the clinical and pathological findings. In the same year, we observed high incidence of the characteristic green tongue fur (FIGURE 1) in patients with SMON. Green feces were also a typical sign. By chance,
in 1970, green color of urine was observed in 2 patients with SMON. Based on these findings, we suspected that the green pigment might have been the causative substance in SMON. The chemical analysis conducted by Tamura and Yoshioka confirmed that the green pigment in urine was clioquinol (5-chloro-7-iodo-8-quinolinol, chinoform) excreted in combination with the coexisting ferric ion (FIGURE 2). Clioquinol was the most popular antidiarrheal agent (known in the form of Enterovioform, Mexaform, and other preparations). In patients excreting green-colored urine, iron tablets were coincidently given for the treatment of anemia at the same time as clioquinol administration. It was surprising that clioquinol was found in urine because it had been clearly stated in all medical textbooks at that time as clioquinol being not absorbed in the intestine. These descriptions were proven later to be wrong, because more than 70% of orally administered clioquinol was found to be absorbed.

Green-colored urine was shown in exceptional cases only because excreted clioquinol appeared colorless and turned green under the presence of the coexisting iron ion. Through this coincidental and serendipitous discovery, clioquinol was for the first time nominated as a possible causative agent of SMON. Following this discovery, I confirmed, in a private hospital, that SMON occurred in 43.6% of 78 patients who received clioquinol, while no SMON occurred in 77 patients who did not receive clioquinol.

Professor Tadao Tsubaki from the Department of Neurology at the Niigata University also became independently confident that clioquinol was the causative agent of SMON, and he directly recommended the Ministry of Health and Welfare of the Japanese Government to ban the use of clioquinol in Japan. Needless to say, I agreed with his proposal, which was later accepted by the Central Drug Affairs Council of the Japanese Government.

After that, the epidemiological studies in Japan were undertaken by a nation-wide research group, but the hot discussions concerning the cause of SMON continued. In this situation, I continued to report additional data to support the clioquinol intoxication hypothesis. One of the questions was why clioquinol was a causative agent of SMON when it was administered to patients to treat abdominal symptoms. It was clarified that the abdominal symptoms observed in patients had 2 stages, the earlier stage consisted of nonspecific abdominal symptoms and they were the cause for the initiation of clioquinol therapy and the latter stage included symptoms induced by the toxic effect of clioquinol and appeared as autonomic dysfunctions.

As for the rarity of SMON in children, I found that the duration of clioquinol medication in children was in almost all cases short, usually limited to 3 days. This was the main reason why the syndrome was so rare in children. On the contrary, clioquinol administration to adult diarrheal patients typically lasted 4 weeks. It was the reason why SMON occurred mainly in adults. In addition, the higher dose of more than 0.5 g/day was also common in adult patients according to the recommendation of pharmaceutical companies in the drug leaflet, namely, that “higher dosage will be more effective”. As to the dose-response relationship, our clinical data confirmed that the low dosage and the short duration of administration (lower than 0.5 g/d, as a daily dosage and within 4 weeks) did non induce SMON. This finding clearly explained the reason why SMON occurred so rarely in the European countries where clioquinol was widely used with strictly regulated doses and duration of medication.

Additionally, we succeeded to experimentally induce the peripheral nerve lesions in rabbits by intravenous injection of clioquinol emulsion, and the alteration seen in the animal model was in all respects similar to SMON.

**General agreement** Despite our convincing data, the final agreement could not be reached for a long time. In this situation, Dr Ishidate, the president of the Central Drug Affairs Council of the Japanese Government, decided to stop the marketing of clioquinol in Japan. Immediately after this initiative, the occurrence of SMON suddenly stopped (FIGURE 3). This was considered as the final proof of clioquinol intoxication. In 1972, the SMON Research Commission of the Japanese Government, of which I was also a member, finally announced...
which reached a brilliant conclusion within 3 years. This success stimulated the general sentiment that any intractable diseases could be settled if ample research funds were issued to or‑ganize a nation‑wide research group. This countermeasure was inaugurated in 1972, following the decision of Prime Minister Kakuei Tanaka, so that a new policy for several intractable dis‑eases started, along with the financial support to cover treatment‑related costs. These counter‑measures still operate today, and excellent results have been achieved. Indeed, many intractable diseases were settled and numerous new effec‑tive drugs were introduced owing to the achieve‑ments of the nation‑wide research groups. This policy is inter‑nationally unique and is now highly evaluated in other countries. We are proud of this political decision, which greatly contributed to the progress in medical research, especially in the field of neurology.

FIGURE 3 New subacute myelo‑optic neuropathy (SMON) patients/by month; continuous outbreak of SMON in Japan stopped in September 1970 after the sale of clioquinol had been banned

that SMON was nothing more than clioquinol intoxication.2,3

History of clioquinol Clioquinol was synthesized in Switzerland in 1899 and used for the treatment of amoebic dysentery. Later, it became widely used in diarrheal patients and was also given to prevent traveler’s diarrhea throughout the world. In Japan, it was used for amoebic dysentery in the Japanese Army before and during the Second World War. It came back again to be widely used as a safe drug in 1960s, as a partial replacement of antibiotics, which were overused at that time. In this situation, clioquinol was import‑ed or produced again in Japan as a generic drug. Unfortunately, high dosage and long administra‑tion were rather common in Japan as mentioned above.2,3,10

Aftermath of clioquinol intoxication theory After the ban of clioquinol, SMON entirely disappeared, and no recurrence has been reported so far (FIGURE 3). Due to the result of this large‑scale “tragic experiment”, the clioquinol intoxication theory became widely accepted throughout the world.

In 1972, roughly 7000 patients with SMON accused pharmaceutical companies in trials asking for the compensation of their health damage in several courts in Japan. After several years, all trials were settled by reconciliation in the courts, accepting the clioquinol intoxication theory.

In addition, a new policy to relieve patients suffering from numerous intractable diseases was started by the Japanese Government. Following the petition of the SMON Patient Association, the government issued ample funds to organize a nation‑wide research group in 1969, which reached a brilliant conclusion within 3 years. This success stimulated the general sentiment that any intractable diseases could be settled if ample research funds were issued to organize a nation‑wide research group. This countermeasure was inaugurated in 1972, following the decision of Prime Minister Kakuei Tanaka, so that a new policy for several intractable diseases started, along with the financial support to cover treatment‑related costs. These counter‑measures still operate today, and excellent results have been achieved. Indeed, many intractable diseases were settled and numerous new effective drugs were introduced owing to the achievements of the nation‑wide research groups. This policy is internationally unique and is now highly evaluated in other countries. We are proud of this political decision, which greatly contributed to the progress in medical research, especially in the field of neurology.

Aftermath of SMON outbreak The history of SMON affair is presented here from the beginning to the end, in which I was at the center. The history of nation‑wide research on SMON was an invaluable lesson showing that any effective drugs could have a harmful effect on the human body. The settlement of SMON affair was a big event in Japanese medical practice, considering that Japanese practitioners and researchers identified the disease themselves and explained its pathomechanism in a considerably short period of time. The success should be regarded as a milestone in the development of Japanese medicine.

Resurgence of beriberi (1973–1975) Beriberi is a disease caused by thiamine (vitamin B1) deficien‑cy. Since the Edo era (1603–1867), beriberi had...
become gradually prevalent in Japan, especially among rich people. At least 2 Shoguns (the Governors of Japan in the Tokugawa period) died of beriberi. In the Meiji and Taisho era (1868–1926), beriberi was a nation-ruining disease, together with tuberculosis and syphilis. Along with the progress of medicine and through the nation-wide endeavor against these diseases, beriberi disappeared entirely by the end of the Second World War, so that physicians in the 1950s knew beriberi only from textbooks and had rarely encountered with beriberi patients in daily practice.\textsuperscript{11-13} Therefore, it was surprising to experience the unexpected resurgence in the years 1973–1975 in Kagoshima (FIGURE 4).

**Outbreak of beriberi** I personally experienced the resurgence of beriberi in the early 1970s in Japan. In the years 1973–1975, we encountered many young patients with swollen legs. At first, the etiology of edema could not be identified and it appeared to be a new disease. The clinical features were as follows (FIGURE 5): leg edema, sometimes also on the face; sensory disturbance of the distal extremities with decreased tendon reflexes, sometimes associated with perioral dysesthesia; calf pains; low diastolic blood pressure and tachycardia with heart dilatation (FIGURE 6); no signs of inflammation; no leukocytosis.

Later, the cardiac examination revealed high cardiac output in these patients. Theoretically, high cardiac output could be symptomatic of beriberi, hyperthyroidism, and a number of other conditions. Since other conditions, except beriberi, were excluded by clinical and laboratory findings, we decided to check whether it was beriberi or not.

Based mainly on clinical findings, I became confident that this disease could be the long-forgotten beriberi. In addition, all clinical, biochemical, and nutritional data pointed to beriberi, i.e., serum thiamine levels were low, the thiamine pyrophosphate effect on transketolase was marked, and pyruvic acid levels in the blood were high (FIGURE 7).\textsuperscript{12} Nutritional tests showed that the intake of thiamine was low compared with that of carbohydrate. After the definite diagnosis had been established, I started an epidemiological study in Kagoshima to investigate the spread of the disease. According to our study, more than 130 cases of beriberi were identified in 1973–1975, particularly in men, and mainly among young people, especially high-school students. All symptoms disappeared immediately after the administration of thiamine.

**Background of the resurgence of beriberi** Until the end of the Second World War, the Japanese people had a traditional custom of eating mainly well-polished rice, of which the thiamine-rich mantle had been scraped off. This custom was the cause of large beriberi outbreak at that time. After the war, due to food shortage, many people suffered from malnutrition that overwhelmed the manifestations of beriberi.

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**FIGURE 4** Beriberi resurgence in Kagoshima, 1973–1975; many beriberi patients were identified in Kagoshima

**FIGURE 5** Symptoms of beriberi; the incidence of each symptoms among patients in Kagoshima, 1973–1975

Abbreviations: ATR – Achilles tendon reflex, DBP – diastolic blood pressure

**FIGURE 6** Chest X ray of a patient with beriberi, before and after the thiamine treatment; heart dilatation was reversed after thiamine treatment
Although beriberi had been forgotten, still thiamine intake was low compared with that of carbohydrate even in recent years without any overt signs and symptoms of beriberi. In addition, sweets containing artificial sweetener were forbidden in 1972 due to the danger of inducing cancer, so that real carbohydrate content in soft drinks became higher. Instant noodles, in which thiamine content was clearly lower compared with carbohydrate content, became also widely consumed at the time. For example, some young men living alone had instant noodles for every meal, and within a few months developed beriberi.

Aftermath of the resurgence of beriberi in Japan

Faced with this situation, I treated patients with thiamine and achieved excellent results. Also, to prevent the outbreak of beriberi, I launched a large-scale campaign to disseminate information about beriberi and raise the awareness of people in Kagoshima. After we recommended to the city authorities that they revise the regulations concerning soft-drink vending machines and replace sugar-containing soft drinks with fruit juice, milk, and tea, beriberi gradually disappeared. Since the outbreak of beriberi in Kagoshima, similar endemic findings were also reported in Kumamoto, Tottori, Tokyo, and many other regions of Japan. At the same time, the majority of the Japanese population became aware of the outbreak. As long as we eat well-polished rice as our main food, we should remember about the threat of beriberi.

Studies in the Asian countries

To compare the resurgence of beriberi in Japan with that in other countries, I performed epidemiological studies on the prevalence of beriberi in several Asian countries (Philippines, Indonesia, Thailand, and Taiwan) where rice is consumed as the main food. The studies revealed that there was no pure form of beriberi but that a large number of patients were malnourished. Indeed, the average thiamine content in rice available in those countries was higher than that in Japan. Therefore, I became confident that beriberi was rather specific for the Japanese who ate mainly well-polished rice.

Studies on beriberi in Japan

Until the Meiji era (1867–1912), the cause of beriberi remained obscure, though its prevalence was high. During that period, the development of modern medicine started in Japan under the guidance of German professors who came to Japan. The professors tended to believe in the importance of the then flourishing bacteriology, so they suggested that beriberi in Japan might have been caused by a specific bacillus. Thus, many Japanese leaders, especially in the army and national medical schools, followed the suggestion of the German professors and assumed that there in fact might have been a specific beriberi bacillus, and numerous reports seemed to confirm this finding.

However, Dr Kanehiro Takaki, who was the head of the medical department of the Japanese Navy and later the founder of the Jikei Medical School, insisted that beriberi must have been induced by a diet-related factor, based on a large-scale experiment conducted in the navy in 1884. In 1983, a warship “Ryuyo” made a voyage to Sidney, Chili, and Hawaii, in which the crew was fed with a traditional Japanese diet, and more than half of the crew suffered from beriberi. Knowing this fact, Dr Takaki planned a similar voyage by a warship “Tsukuba” with a European-style diet. As he expected, only a few beriberi patients were reported. Therefore, he reached a conclusion that beriberi was caused by traditional Japanese diet. After the diet had been modified according to the European style, beriberi disappeared from the navy.

However, other medical leaders, including Dr Mori, the head of the medical department in the Japanese army, continued to believe that beriberi was an infectious disease and refused to accept Takaki’s food theory. Japanese soldiers in the army were fed with a typical Japanese diet consisting mainly of polished rice, which was considered a real treat. Although more than 10 years passed since the food theory was proposed by Dr Takaki, many soldiers in the army died of beriberi (the number was comparable to that of the victims in the Russian-Japanese war, 1904–1905), whereas no deaths from beriberi were reported in the navy.

In 1896, Eijckman succeeded in inducing beriberi in chickens by feeding them with polished rice and confirmed the curing effect of rice bran, a constituent of rice that was later clarified into a vitamin (thiamine) by a Polish biochemist, Casimir Funk, in 1912.
It should be stressed that Dr Umetaro Suzuki was one of the discoverers of vitamin B₁. After the role of vitamin B₁ in beriberi was internationally accepted, all Japanese leaders became convinced that beriberi was caused by thiamine deficiency. Thus, the Japanese government tried to suppress the outbreak of beriberi by launching an education program for dieticians. Following this initiative, the occurrence of beriberi gradually diminished until the disease was finally wiped out. We should never forget the outstanding results of an epidemiological experiment supervised by Dr Takaki, in order to avoid the resurgence of beriberi in the future.

**Human T-lymphotropic virus type I-associated myelopathy – a new disease of the spinal cord** The history of human T-lymphotropic virus type I (HTLV-I)-associated myelopathy (HAM) began 40 years ago. When I became the professor at the Department of Internal Medicine at the Kagoshima University, I promptly started epidemiological studies of all neurological diseases in the Kagoshima prefecture and sporadic spastic paraparesis was noted. Our research was thus started to elucidate the cause of this particular disease, but it remained unknown for many years.

**Symptoms of HTLV-I-associated myelopathy** The characteristic features of HAM were as follows: gradual onset followed by slow progression, sporadic spastic paraparesis, adult-onset without any hereditary transmission, prominent pyramidal tract signs and mild sensory and sphincter disturbances, no cerebral symptoms, and no signs of inflammation.

The prevalence rate of this new disease was estimated to be 55/1,700,000 in the Kagoshima prefecture, while that of the most common muscle degenerative disease, i.e., Duchenne muscular dystrophy, was 29/1,700,000. We immediately realized that it was a new disease.

**Research into the cause of HTLV-I-associated myelopathy** Since the 1970s, a peculiar type of lymphoma had been known to be prevalent in southern Kyushu including Kagoshima. This lymphoma was characterized by proliferation of malignant cells in peripheral blood with the coexistence of lymphomas of various size. It was named “cauliflower-like leukemia”, after the appearance of the nucleus of the proliferated lymphocytes as reported by the Cancer Research Institute of the Kagoshima University. Independently of this report, Dr Takatsuki from the Kyoto University, observed that some patients who were born in Kagoshima suffered from similar lymphoma in Kyoto. He noticed that the lymphoma was of T-cell origin and was identical with that reported in Kagoshima. He named it “adult T-cell lymphoma/leukemia” (ATL).

Following this discovery, Professor Hinuma, a virologist from the Kyoto University, and Dr Yoshida identified the causative virus – HTLV-I. In 1984, we noticed by chance the presence of ATL-like cells in the blood and cerebrospinal fluid (CSF) of patients with the above neurological disease, without any signs of malignant proliferation and lymphoma (Figure 8). In addition, we found that the titer of the antibodies against HTLV-1 in the blood and CSF was significantly increased. “Our disease” seemed, however, to be different from ATL not only hematologically but also clinically. This fact enabled us to conclude that our disease and ATL were different entities both occurring among the carriers of HTLV-I.

In 1987, our first report was based on the data obtained from 85 patients – 58 men and 19 women.
old Mongolian (Johnmon, who immigrated to Japan from Eurasia before the glacial age), and Neo-Mongoloid (Yayoi, who immigrated to Japan about 2000 years ago after the glacial age).

HTLV-1 was preserved mainly in the Johnmon group by transmission through lactation from HTLV-I seropositive mothers, who lived predominantly in southern Japan, while the Yayoi group inhabited the central and northern Japan. This could explain the geographic difference in the prevalence of HAM and ATL within the Japanese population.

Transmission of HTLV-I through blood transfusion It was also suggested that a certain group of patients with HAM underwent blood transfusion before the onset of the disease (FIGURE 11).22,23 Based on our suggestion that the incidence of HAM might be related to blood transfusion, the Japanese government stopped transfusion from seropositive donors, and the transmission of the disease through blood transfusion has now been stopped completely.

Mother-child transmission Our studies suggested that HAM was transmitted from mother to child. Furthermore, it became clear that HTLV-I was transmitted through mothers’ milk.17 Currently, it is strongly recommended to HTLV-I seropositive mothers not to breastfeed their children.24

Association between HTLV-I-associated myelopathy and multiple sclerosis Since several reports in the 1980s suggested that the antibody against HTLV-1 could be found in some patients with multiple sclerosis, HTLV-1 became the hottest topic in the world, because multiple sclerosis is the most common neurological disease in Western countries.20 However, this hypothesis was later disproved by many researches. The pathomechanism of HAM has now been clarified, especially from the neuroimmunological perspective, and the name of HAM is now internationally recognized.25

Aftermath of HTLV-I-associated myelopathy outbreak Looking back at the history of our investigations into HAM, I have a strong feeling that, owing to our studies, a locally observed and minor condition became an important and widely recognized disease. This is a good example of our saying “to keep in mind to send message of scientific progress from the local area to the international stage”. Detailed studies on the pathomechanism of HAM and its treatment are now in progress, conducted by the research group of the former Professor Mitsuhiro Osame from the Kagoshima University.

Conclusions In this paper, I described my personal experience with several neurological diseases in Japan and our attempts to elucidate their causes. To sum up, SMON, a peculiar neurological disease prevalent in Japan since the early 1960s,
was found to be caused by intoxication with clioquinol, an antidiarrheal drug. The discovery was made after the chemical analysis of characteristic green urine, and was a hot issue in the history of Japanese medicine.

In the early 1970s, I encountered many young patients in Kagoshima who suffered from edema and polyneuropathy. Finally, the disease turned out to be the long-forgotten beriberi, which seemed to have disappeared several decades earlier. The resurgence was caused by the consumption of well-polished rice.

In 1972, we observed a group of patients with sporadic paraparesis in Kagoshima. Twenty years later it was confirmed to be induced by HTLV-I. We named the disease “HTLV-I associated myelopathy”. The discovery was important in that we re-identified that the causative virus of ATL could induce completely different diseases in terms of the clinical course and pathological features. It was also proved that HAM was identical with TSP, which was prevalent in many tropical areas.

The above experiences are good examples of our saying “to keep in mind to send message of scientific progress from the local area to the international stage”.

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ARTYKUŁ POGŁĄDOWY

Podostrá neuropatia rdzeniowo-wzrokowa, beri-beri mielopatia związana z zakażeniem wirusem HTLV 1 – omówienie niektórych chorób neurologicznych w Japonii

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SŁOWA KLUCZOWE
beri-beri, mielopatia związana z zakażeniem wirusem HTLV 1, podostra neuropatia rdzeniowo-wzrokowa

STRESZCZENIE
Artykuł przedstawia osobiste doświadczenia i udział autora w wykryciu przyczyn i patomechanizmu oraz w opracowaniu zasad leczenia i metod zapobiegania podostrej neuropatii rdzeniowo-wzrokowej, nawrotu występowania epidemicznego choroby beri-beri i mielopatii związanej z zakażeniem wirusem HTLV 1.

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