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The history of the Japanese Society for Neuro-infectious Diseases: Foundation, objectives, and legacy

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SUMMARY The Japanese Research Group for Neuro-infectious Diseases was founded in August 1996, and by 2004 it had evolved into the Japanese Society for Neuro-infectious Diseases. The Society focuses on neuroinfectious conditions (*e.g*., encephalitis/encephalopathy, myelitis, and meningitis), providing a venue for academic presentations and exchanges. Clinical guidelines for major neurological infectious diseases are also published by the Society, in order to meet the social demands of each era. Although the threat of herpes simplex encephalitis has declined due to acyclovir's introduction, the frequency of encephalitis or peripheral neuropathy caused by varicella-zoster virus is increasing. In Japan, prion disease, human T-cell leukemia virus-1 (HTLV-1)-associated myelopathy (HAM), subacute sclerosing panencephalitis (SSPE), and progressive multifocal leukoencephalopathy (PML) are designated as intractable diseases. The incidence of prion disease is 1.8/1,000,000 individuals, with the sporadic type accounting for 80%. Prion disease is fatal, and effective medications are awaited. HAM's prevalence is ~3/100,000 individuals, with a male-to-female ratio of 1:2–3. HAM is common in western Japan, including Kyushu and Okinawa. The prevalence of PML is rising with the spread of both immunosuppressive therapy for transplantation and treatment for multiple sclerosis. From late 2019 through 2020, the world faced a global outbreak of coronavirus disease 2019 (COVID-19) due to virus mutations, and the threat of new mutations persists. Close attention should be paid to the emergence of new neurological infections that could arise from abnormal weather patterns and/or a decline in immune function due to aging.

Keywords herpes simplex encephalitis, influenza encephalopathy, Creutzfeldt-Jakob disease/prion disease, HTLV-1 associated myelopathy, clinical guideline

1. Introduction

Neuro-infectious diseases including acute and subacute forms of encephalitis, encephalopathy, myelitis, and meningitis are not common but they are intractable conditions in which delays in diagnosis and treatment can result in prolonged illness, severe complications, or death. Prion disease, human T-cell leukemia virus-1 (HTLV-1)-associated myelopathy (HAM), subacute sclerosing panencephalitis (SSPE), progressive multifocal leukoencephalopathy (PML), and Bickerstaff brainstem encephalitis are designated as intractable and rare diseases, *i.e*., *nanbyo* in Japanese.

Herpes simplex encephalitis (HSE) or influenza encephalopathy was a threat in the early 1990s (*1,2*), and disparities in its diagnosis and treatment initiation across facilities led to medical lawsuits (*3*). To address this problem, the first research meeting of the Japanese Research Group for Neuro-infectious Diseases was convened in 1996. At the eighth research meeting in 2003, the Research Group was revised as the Japanese Society for Neuro-infectious Diseases. The Research Group and the Society both issued clinical practice guidelines in response to the societal needs of each era and have provided useful resources for general practitioners.

The current incidence of HSE remains unchanged at 3/1,000,000 individuals (*4*), but the threat posed by HSE declined with the introduction of acyclovir. Conversely, the incidences of the HSE-related diseases anti-N-methyl-D-aspartate (NMDA) encephalitis and paraneoplastic encephalopathy are increasing. The incidence of prion disease, a fatal disorder, is 1.8/1,000,000 individuals, with 80% being sporadic cases; the development of an effective treatment for prion disease is awaited (*5*). The lifetime incidence of HAM among HTLV-1 carriers is 0.3%, and adult T-cell leukemia/lymphoma (ATL) is diagnosed when abnormal lymphocytes exceed 5% in

white blood cells of peripheral blood (*6*). The incidence of PML is increasing with the widespread use of immunosuppressive therapy for transplantation and with the treatment of multiple sclerosis (MS) (*7*).

From late 2019 to 2020, the global outbreak of coronavirus disease 2019 (COVID-19) (*8*), primarily a respiratory infection, led to the postponement of the Society's 25th Congress to 2021, and the Congress was successfully held up to its 27th edition in October 2023. We reflect on the approximately 30-year journey of the Japanese Research Group and Society for Neuro-Infectious Diseases.

2. Overview of the Japanese Neuro-infectious Disease Research Group and Society

Table 1 summarizes the history of the Research Group and Society from the first issue of the Research Group's journal to the Society's journal, up to "Neuroinfection No. 23". We review the work of the Group and Society by dividing the history from 1996 to 2023 into three periods: *i*) the Japanese Neuro-infectious Diseases Research Group, 1996–2002; *ii*) the Japanese Society for Neurological Infectious Diseases, 2003–2012; and *iii*) the Japanese Neurological Infectious Diseases Society, 2013–2023, focusing on the president's lectures, special lectures, and clinical guidelines. This review was conducted in accord with the principles of the Declaration of Helsinki and was approved by our Hospital's Ethics Committee (Ron 23-104).

The titles of the Chairman's Lectures and Special Lectures from the 1st Research Group meeting to the 27th Society meeting reveal 10 titles concerning prion disease, six about viral encephalitis pathology, four for viral encephalitis, four for influenza encephalopathy, three regarding HAM, three concerning AIDS encephalopathy, single lectures about human herpesvirus-6 (HHV-6), SSPE, and PML, respectively; and others.

3. 1996–2002: The Japanese Neuro-infectious Disease Research Group

In February 1996, the first research meeting was hosted by Professor Toshiaki Takasu in Tokyo (*9*). It featured 94 members, approximately 160 participants, 34 general presentations, and two special lectures on "Influenza Encephalitis" and "Infectious Pathology of AIDS Encephalopathy". In 1999, the 4th Research Meeting took place under the leadership of Prof. Yasuto Itoyama in collaboration with Prof. Tetsushi Kitamoto of the Japan Neuro-virus Research Group. Notably, the two research groups merged in Sendai, the city credited with the discovery of the Sendai virus. The highlight of the 7th conference, orchestrated by Prof. Makoto Iwata in October 2002, was a significant international symposium titled "Emerging and Re-Emerging Infectious Diseases of the Nervous System". The conference also featured lectures on "Japanese Encephalitis" by Dr. S. Pradhan from India (*10*), "Nipah Virus Encephalitis" by Prof. Chong Tin Tan from Malaysia (*11*), and lectures on dengue fever and Hansen's disease.

4. 2003–2012: The Japanese Neuro-infectious Diseases Society

In 2003, our Research Group evolved into an Academic Society during its 8th meeting held in October in Ube City, under the leadership of Prof. Susumu Furukawa. The society boasted 300 members, approximately 200 participants, and 68 general presentations. Since 1996, there had been discrepancies among facilities regarding the diagnosis and treatment of HSE, leading to frequent medical lawsuits due to severe complications from delayed diagnoses (*3*), and there was thus an urgent need to establish medical guidelines. At the 9th conference in 2004, a workshop was organized to develop clinical practice guidelines for HSE, resulting in the publication of the HSE guidelines in an academic journal. This was followed by the release of a book that highlighted the importance of early acyclovir administration in suspected cases (*12*).

In 2007, the guideline for bacterial meningitis was published, overseen by Prof. Itoyama, and PDFs of guidelines for neurological infectious diseases that posed societal challenges such as influenza encephalopathy, prion disease, SSPE, and PML were released. These evidence-based clinical practice guidelines were developed in collaboration with The Health Labour and Welfare Science Committee, the Japanese Society of Neurology, and the Japanese Society of Pediatrics. These guidelines have been made available in PDF format, with

Table 1. Overview of the history of the Japanese Society of Neuro-infectious Diseases

1996	1st Japanese Neuro-infectious Diseases Group, Tokyo
1999	Co-sponsored by the 4th Research Group and Neuro-virus Research, Sendai
2003	8th Japanese Neuro-infectious Diseases Society, Ube City; 300 members, 200 participants, 68 general presentations
2014	19th Annual Meeting, co-hosted by the Japanese Neuro-immunology Society, Kanazawa City
2015	Herpes Simplex Encephalitis Clinical Guideline, Nankodo Co., 2017
2019	HTLV-1 Associated Myelopathy Clinical Guideline, Nankodo Co., 2019
2019	COVID-19 outbreak, pandemic
2020	Prion Disease Guideline (PDF) released
2021	Suspended due to the coronavirus pandemic
2022	27th Japanese Neuro-infectious Diseases Society, Yokohama City; 541 members, 393 registered participants, 48 general presentations

revised editions incorporating new findings published every three years.

5. 2013-2023: The Japanese Society for Neuroinfectious Diseases

The 18th Meeting, chaired by Prof. Hiroyuki Nunoi, featured a keynote lecture on the "Science of Virus and Host Reactions in Influenza Encephalopathy". The clinical practice guidelines developed during this period emphasized the importance of supportive care to maintain patients' general condition, with the aim of alleviating hypercytokinemia and recommending the administration of steroid hormone for cytokine storms. At the 22nd conference, Prof. Satoshi Kamei, chair of the organizing committee, discussed the "HSE Clinical Practice Guideline 2017" (*13,14*), which stipulated that acyclovir treatment should be started within 6 hours of symptom onset. The Guideline also mentioned the adjunctive use of corticosteroids to suppress inflammatory cytokines, in a short-term combination with antiviral drugs. Prof. Kamei also added the clinical features of a related disease NMDA limbic encephalitis associated with ovarian tumor, and Dr. Makoto Hara explained the pathophysiology of new nerve-cell surface antibodies in various types of immune encephalitis (*15*).

At the 23rd meeting in 2018, a special lecture was given by Prof. Hidehiro Mizusawa on the "Current Status and Prospects of Prion Diseases" (*5*). The frequency of sporadic prion disease in Japan at that time was 1.8/1,000,000 individuals per year. Prion diseases can be divided into familial, iatrogenic, and sporadic cases, with sporadic cases accounting for 80%. The special lecture highlighted two points: *i*) the conversion mechanism from normal prion protein to abnormal prion protein remains unknown, and *ii*) understanding the aggregation mechanism could offer insights into neurodegeneration. There is no specific treatment for prion diseases, and the development of such treatments is considered urgent.

The COVID-19 pandemic that began in December 2019 led to the postponement of the Society's 2020 conference. Although pneumonia was the primary concern in the early days of the pandemic, various neuromuscular complications including cerebrovascular disorders, meningoencephalitis, and myositis associated with COVID-19 have been reported (*16*).

The 25th meeting held in October 2021 and organized by Prof. Tetsushi Yoshikawa highlighted the practical use of real-time polymerase chain reaction (PCR) for the primary screening of several herpes genus species. In the 2024 educational lecture, Prof. Yoshikawa noted that the frequencies of encephalitis and encephalopathy due to HHV-6B reactivation during hematopoietic stem cell transplantation are 2%–3%, and the involvement of Epstein-Barr virus and cytomegalovirus in MS was described (*17*). Discussions held at the meeting revealed an increasing frequency of herpes zoster limbic encephalitis or varicella-zoster virus neuropathy (unpublished data, *18*). The 26th conference, led by Chairman Prof. Hiroshi Takashima, focused on how metagenomic analyses using next-generation sequencing could identify a new type of archaeal encephalitis (*19*), with symptoms improved by sulfamethoxazole and trimethoprim (ST) drug treatment.

The 27th meeting hosted in 2023 by Prof. Yoshihisa Yamano, saw the creation of a national HAM patient registry (HAM Net). The lifetime incidence of HAM among HTLV-1 carriers is 0.3%, and the prevalence of HAM is approx. 3 persons/100,000 people, with a male-to-female ratio of 1:2–3; HAM is common in western Japan, including Kyushu and Okinawa. Prof. Yamano's lecture entitled 'New Future of Neuroinfectious Diseases Revealed through HAM Research' delved into new pathophysiological insights (Figure 1) (*20*).

In conclusion, over its 30-year history, the Japanese Society for Neuro-infectious Diseases, through its journal *Neuroinfection* and academic conferences, has served as a platform for research and exchange on neuro-infectious diseases. Prion disease has been a focal point of attention, underscoring the urgent need for therapeutic drug development for this deadly disorder. With the impacts of abnormal weather and a super-aging population, further vigilance is warranted for various neurological infections. We hope that this legacy will

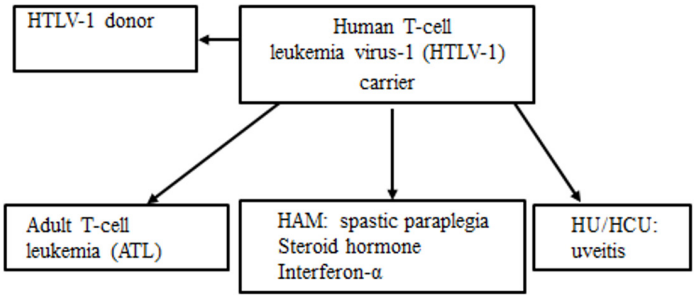

Figure 1. HAM and related disorders and current therapy. HAM patients exhibit signs of stiffness and spastic paraplegia in both lower limbs. The HTLV-1 antibody is positive in cerebrospinal fluid (CSF), and current treatments include steroids or interferon-alpha (IFN-α). Adult T-cell leukemia/lymphoma (ATL) is diagnosed when abnormal lymphocytes exceed 5% in white blood cells of peripheral blood. For HTLV-1-assciated uveitis (HU/HAU), steroids are effective. If an HTLV-1-positive individual is an organ transplant donor, testing for the HTLV-1 antibody is recommended.

continue for future generations as part of the history of the Japanese Society for Neuro-infectious Diseases.

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