Results

Conventional and immunologic data of the first CSF examination

Conventional and immunologic data of the first CSF examination of 19 and 24 patients before initiation of immunologic treatment were compared with those of disease controls to evaluate their roles in RS. At the first CSF examination, cell counts (3.6 ± 4.4, n = 18), protein levels (28.7 ± 12.1 mg/dl, n = 19), glucose levels (60.3 ± 13.3 mg/dl, n = 15), albumin levels (16.5 ± 5.9 mg/dl, n = 8), and chloride levels (124.6 ± 3.5 mEq/l, n = 12) in RS patients were similar to the levels in disease controls (Fig. 1). On the other hand, IgG levels were higher in RS patients (3.0 ± 1.3 mg/dl, n = 10) than in disease controls (1.6 ± 0.8 mg/dl, n = 11) (Mann-Whitney *U* test, $p < 0.01$) (Fig. 1F).

$CD4^+$ T cells were higher in RS patients (59.3 ± 21.4%, n = 7) than in disease controls (34.7 ± 15.0%, n = 12) (Mann-Whitney *U* test, p = 0.02) (Fig. 2). $CD8^+$ T cells were not significantly different between RS patients (34.8 ± 18.3%, n = 7) and disease controls (23.4 ± 7.0%, n = 11), whereas $CD3^+$ T cells were higher in RS patients (74.8 ± 15.5%, n = 7) than in disease controls (52.5 ± 18.4%, n = 12) (p = 0.01). IFNγ levels were not significantly different between RS patients (11.3 ± 6.0 pg/ml, n = 22) and disease controls (9.6 ± 9.1 pg/ml, n = 26) (Mann-Whitney *U* test, $p > 0.05$). TNFα levels were higher in RS patients (23.7 ± 34.8 pg/ml, n = 17) than in controls (4.0 ± 2.4 pg/ml, n = 13) ($p < 0.01$). Granzyme B levels were higher in RS patients (10.8 ± 15.5 pg/ml, n = 18) than in disease controls (1.2 ± 1.2 pg/ml, n = 13) (Mann-Whitney *U* test, $p < 0.01$). IL-4 and IL-12 levels were similar in RS patients and disease controls.

Clinical evolution and immune molecules in CSF

Evolutional changes of conventional laboratory data and immunologic molecules in CSF were evaluated in 27 RS patients using the data of the initial examination and subsequent follow-up examinations. White blood cell counts in CSF were elevated in two patients around onset, and were within normal limits in samples collected 5 months after onset (Fig. 3). Protein levels and albumin levels were higher in samples collected at the progressed stage, compared with those in the early stage. Half of the patients showed protein levels greater than 40 mg/dl 12.5 years after onset. Albumin levels were higher (>20 mg/dl) in half of the patients 5 years after onset. IgG levels were slightly elevated (>2.5 mg/dl) in two-thirds of patients at all stages of disease evolution.

$CD4^+$ T cell counts were elevated (>50%) in the majority of patients at all stages of disease evolution (Fig. 4). $CD8^+$ T cells were also elevated (>30%) in many patients at all stages of disease evolution, and the elevated levels declined evolutionally. $CD3^+$ T cells were elevated (~70%) in almost all patients at all stages of disease evolution. $CD4^+$ T cells and $CD3^+$ T cells were higher in samples collected at the progressed stage compared with the early stage.

IFNγ levels were elevated (>15.0 pg/ml) in many patients during the early stage, but the majority of patients had the same level as disease controls (~10.0 pg/ml) 5 years after onset (Fig. 5). IL-4 levels were higher in samples from the progressed stage compared with the early stage. IL-12 levels were elevated in several samples during the early stage. TNFα levels were elevated (>7.0 pg/ml) in many patients at all stages of disease evolution (Figure 6). Granzyme B levels were markedly elevated, especially in the early stages, and remained slightly elevated even in the progressed stage.

When patients without immunologic treatment were compared with patients after introduction of immunologic treatment, CD4, CD8, CD3, Granzyme B, IL-4, IL-12, TNFα, and IFNγ showed no statistically significant difference (data not shown, Mann-Whitney *U* test).

Clinical evolution and autoantibodies against GluR ε2 (NR2B) in CSF

Anti-GluR ε2 (NR2B) autoantibodies in the CSF samples collected from a total of 25 RS patients were examined qualitatively by immunoblot, and evolutional changes were evaluated using the positive rates at various intervals after onset. In eight samples from five patients collected within 6 months of epilepsy onset, IgG autoantibodies against GluR ε2 (NR2B) were found in half of patients (50%), and IgM autoantibodies against GluR ε2 (NR2B) were found in one of eight patients (12.5%)

Figure 2.
Cytokines and Granzyme B at the first cerebrospinal fluid (CSF) examination. (**A**) Percentage of $CD4^+$ T cells in CSF; (**B**) percentage of $CD8^+$ T cells; (**C**) percentage of $CD3^+$ T cells; (**D**) interferon γ (IFNγ) level; (**E**) tumor necrosis factor α (TNFα) level; (**F**) interleukin 4 (IL-4) level; (**G**) Granzyme B level; (**H**) IL-12 level. Rasmussen: data from RS patients. Horizontal bars show mean levels. Mean interval between disease onset and first examination of Granzyme B was 37.8 ± 42.0 months (mean ± SD).
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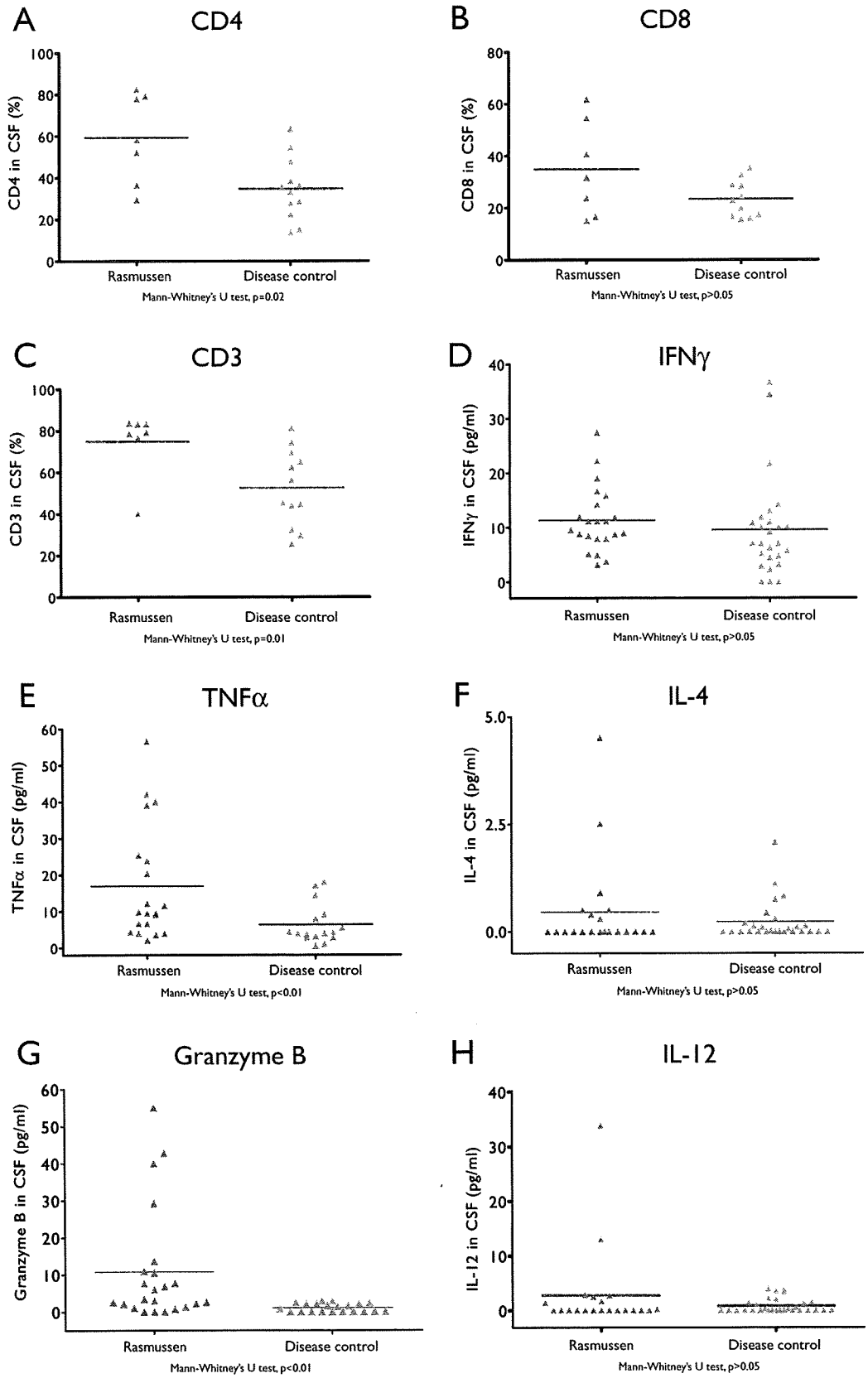

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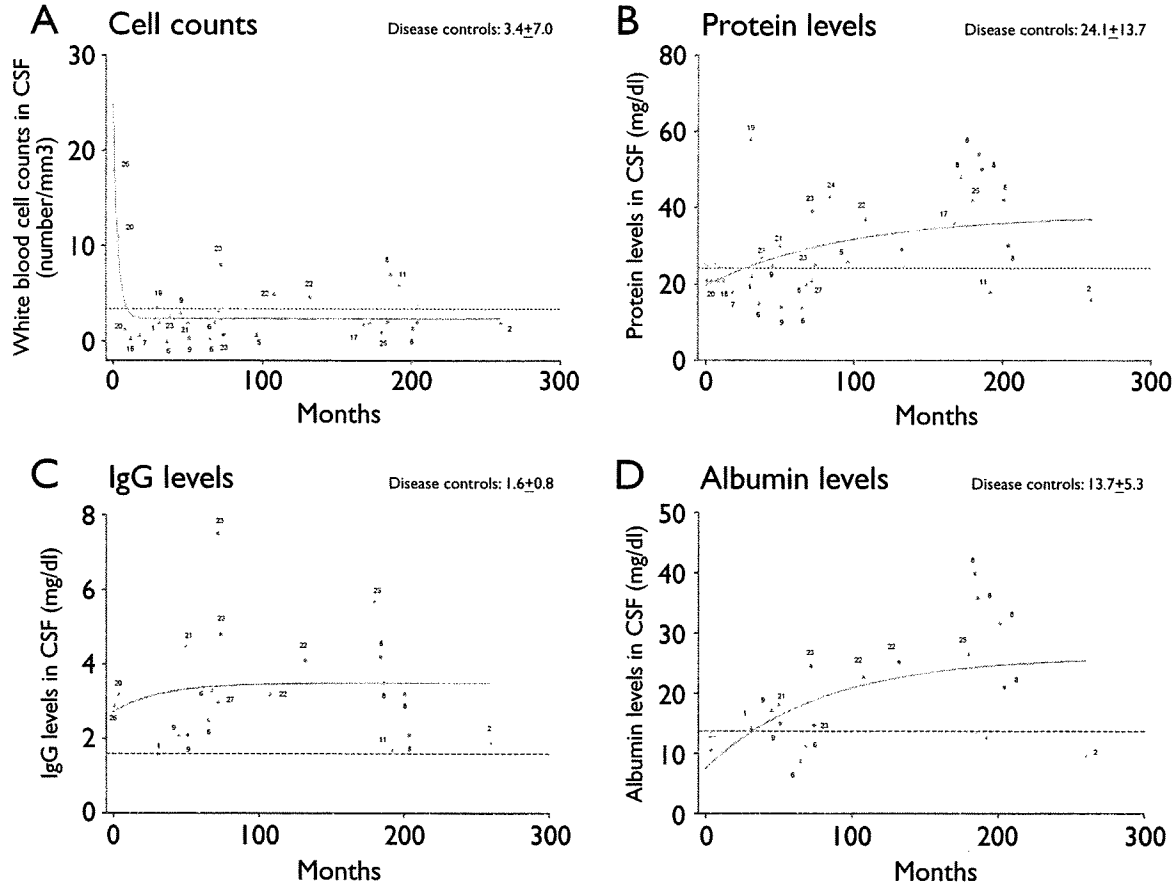

Figure 3.
Conventional and immunologic molecules in cerebrospinal fluid (CSF). (**A**) White blood cell count in CSF; (**B**) protein level; (**C**) immunoglobulin G (IgG) level; (**D**) albumin level. Horizontal axis in each panel shows time (months) from onset of epilepsy. Value (mean ± SD) for disease controls is shown above each panel. Numbers indicate patients' numbers in Table 1. Blue triangle symbols show data of patients without immunologic treatment; orange circle symbols show data of patients after introduction of immunologic treatment. Dotted lines show mean levels of disease controls. Green solid lines show nonlinear regression curves produced by computer software, GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, U.S.A.). In (**A**), nonlinear regression was done by equation of one phase exponential decay [95% confidence interval (CI) of plateau, 1.472–3.278]. In (**B**), nonlinear regression was done by equation of one phase association (95% CI of plateau, 16.49–59.78). In (**C**), nonlinear regression was done by equation of one phase association (95% CI of plateau, 2.328–4.659). In (**D**), nonlinear regression was done by equation of one phase association (95% CI of plateau, 12.33–39.91).

(Fig. 6C, D). As the clinical course evolved, the proportions of patients positive for autoantibodies against GluR ε2 (NR2B) (IgG) decreased. In five of eight patients (patients 1, 6, 8, 18, and 20), autoantibodies against GluR ε2 (NR2B) (IgG or IgM) disappeared evolutionally (Table 1). In two of five patients (patients 8 and 20), the autoantibodies disappeared after the initiation of tacrolimus treatment. In all three patients without immunologic treatment (patients 1, 6, and 18), the autoantibodies disappeared in ordinary epilepsy treatment.

Discussion

We studied 27 patients who were diagnosed with RS based on clinical criteria including (1) intractable partial seizures and (2) interictal symptoms and EEG, suggesting progressive involvement of unilateral hemisphere, independent of histologic characteristics. These criteria may exclude patients with RS at an early stage before deterioration, who may be included by European consensus criteria (Bien et al., 2005).

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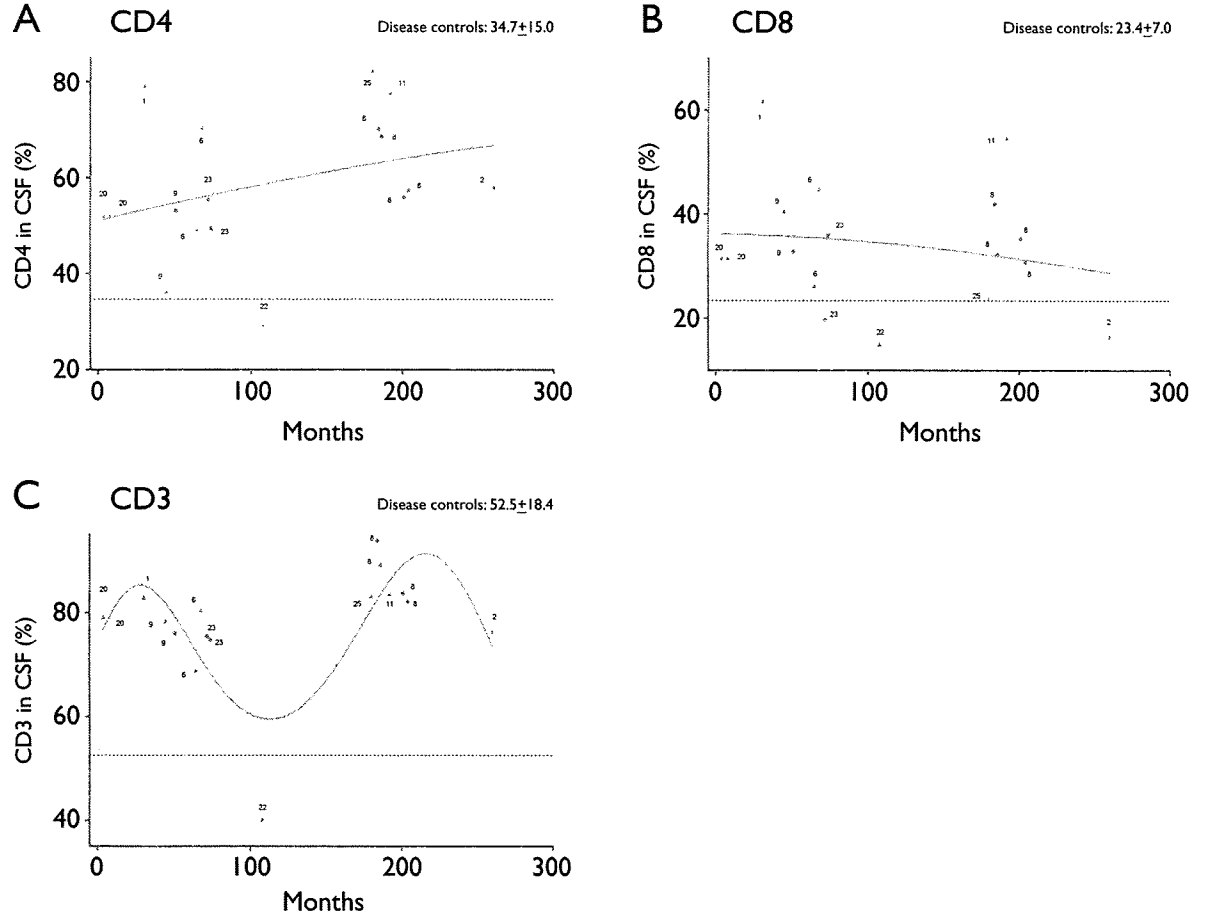

Figure 4.
Cell surface markers of lymphocytes in CSF. (**A**) Percentage of $CD4^+$ T cells; (**B**) percentage of $CD8^+$ T cells; (**C**) percentage of $CD3^+$ T cells. Horizontal axis in each panel shows time (months) from onset of epilepsy. Value (mean ± SD) for disease controls is shown above each panel. Numbers indicate patients' numbers in Table 1. Blue triangle symbols show data of patients without immunologic treatment; orange circle symbols show data of patients after introduction of immunological treatment. Dotted lines show mean levels of disease controls. Green solid lines show nonlinear regression curves produced by computer software, GraphPad Prism 5 (GraphPad Software Inc.). In (**A**), nonlinear regression was done by equation of Gaussian distribution (95% CI of amplitude, −124.8 to 266.5). In (**B**), nonlinear regression was done by equation of Gaussian distribution (95% CI of amplitude, 8.908 to 63.63). In (**C**), nonlinear regression was done by equation of sum of two Lorentzian (95% CI of amplitude 1, 52.04–90.62).

Although an early diagnosis of RS is important to improve outcome, patients with RS are usually diagnosed with partial epilepsy at the onset of epilepsy. The possibility of RS is suspected only after epileptic seizures aggravate and brain function is impaired. We analyzed the conventional and immunologic test data of the first CSF examination, and found that IgG level, $CD4^+$ T cells, TNFα level, and Granzyme B level may contribute to a diagnosis of immune-mediated epilepsy including RS (Figs. 1 and 2). In patients with frequent partial seizures, these immune molecules should be measured for an early diagnosis of RS and the evolutional changes of these molecules should be followed to confirm the diagnosis of RS (Figs. 3–6). Clinical symptoms, MRI findings, and EEG findings are also essential for the diagnosis (Oguni et al., 1991; Bien et al., 2005).

Our cross-sectional data and nonlinear regression curves of immunologic molecules in CSF from early to progressed stages imply that white cell count and Granzyme B level are elevated in the early stage of RS around the onset of epilepsy, and decline within a few months to more or less constant levels (Figs. 3–6). $CD8^+$ T cells are

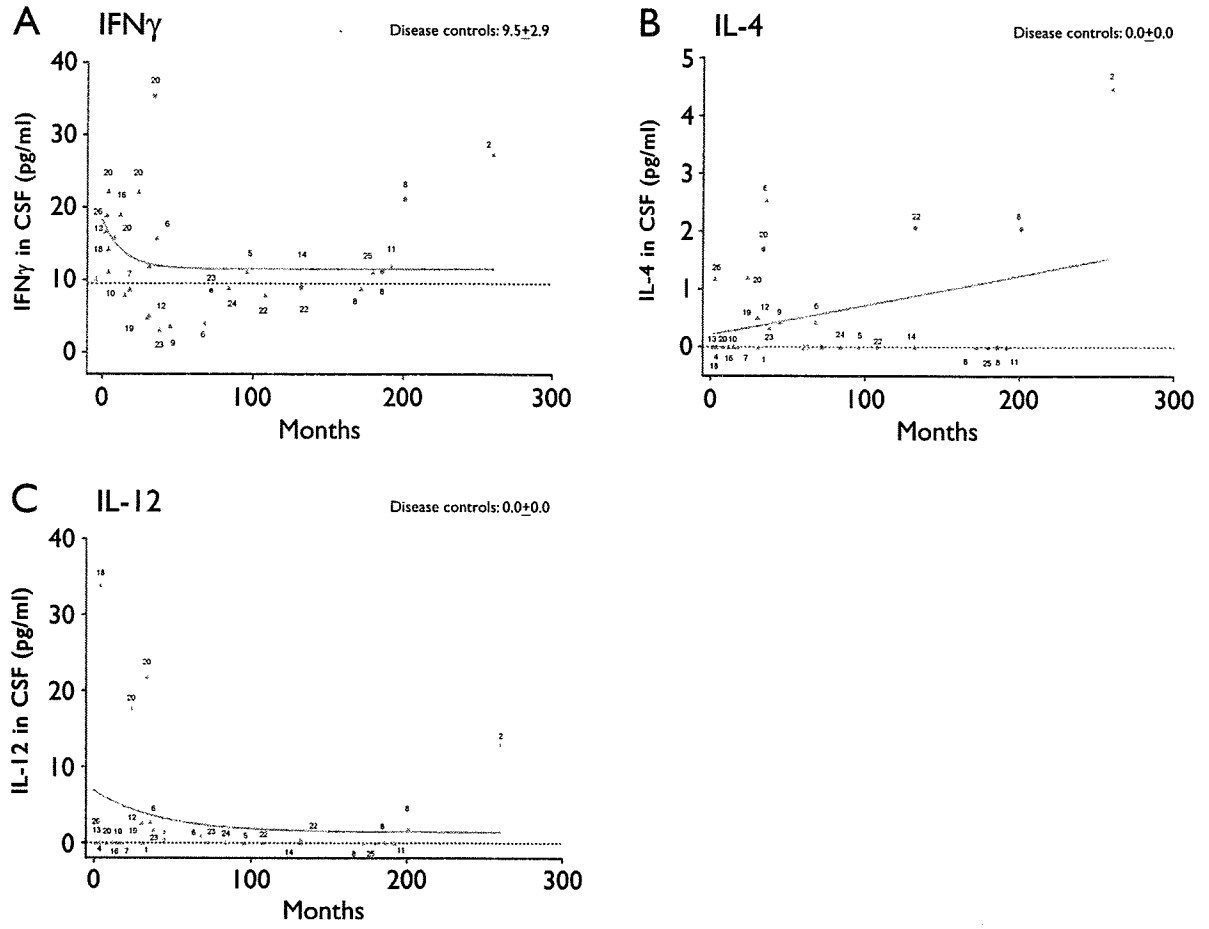

Figure 5.
Interferon γ 1 (IFNγ 1), interleukin 4 (IL-4), and IL-12 in cerebrospinal fluid (CSF). (**A**) IFNγ level in CSF; (**B**) IL-4 level; (**C**) IL-12 level. Horizontal axis in each panel (**A–C**) shows time (months) from onset of epilepsy. Value (mean ± SD) for disease control is shown above each panel. Numbers indicate patients' numbers in Table 1. Blue triangle symbols show data of patients without immunologic treatment; orange circle symbols show data of patients after introduction of immunologic treatment. Dotted lines show mean levels of disease controls. Green solid lines show nonlinear or linear regression curves produced by computer software, GraphPad Prism 5 (GraphPad Software Inc.). In (**A**), nonlinear regression was done by equation of one phase association (95% CI of plateau, 7.382–15.60). In (**B**), linear regression was done (95% CI of slope, −0.0001157 to 0.01034). In (**C**), nonlinear regression was done by equation of one phase association (95% CI of plateau, −5.106 to 7.900).

also elevated in the early stage and decline gradually toward the progressed stage. Granzyme B is usually secreted from CTLs, and sometimes from NK cells. Because the previous study of resected brain tissues has demonstrated that Granzyme B–secreting cells are not NK cells, but $CD8^+$ T cells (CTLs) in RS (Bien et al., 2002), we estimate that production of Granzyme B from $CD8^+$ T cells is activated more strongly in the early stage around onset, and continues even in the progressed stages (Figs. 4B and 6B). The cytotoxic mechanisms by Granzyme B may be very important, especially in the early stage around onset. Our data suggest that a crucial cytotoxic process contributes to the pathophysiologic mechanisms during the first few months of the disease, and declines in the progressed stage.

Our cross-sectional data and their nonlinear regression curves imply that IFNγ and IL-12 are produced especially in the early stage around onset, and $CD4^+$ T cells and TNFα level are elevated from the early stage to the progressed stage. IFNγ activates macrophage to secrete IL-12 and TNFα, and IL-12 facilitates the proliferation of Th1 cells in $CD4^+$ T cells. Therefore, differentiation and proliferation of autoreactive Th1 cells induced by cytokines in the early stage increase the ratio of $CD4^+$ T cells in CSF,

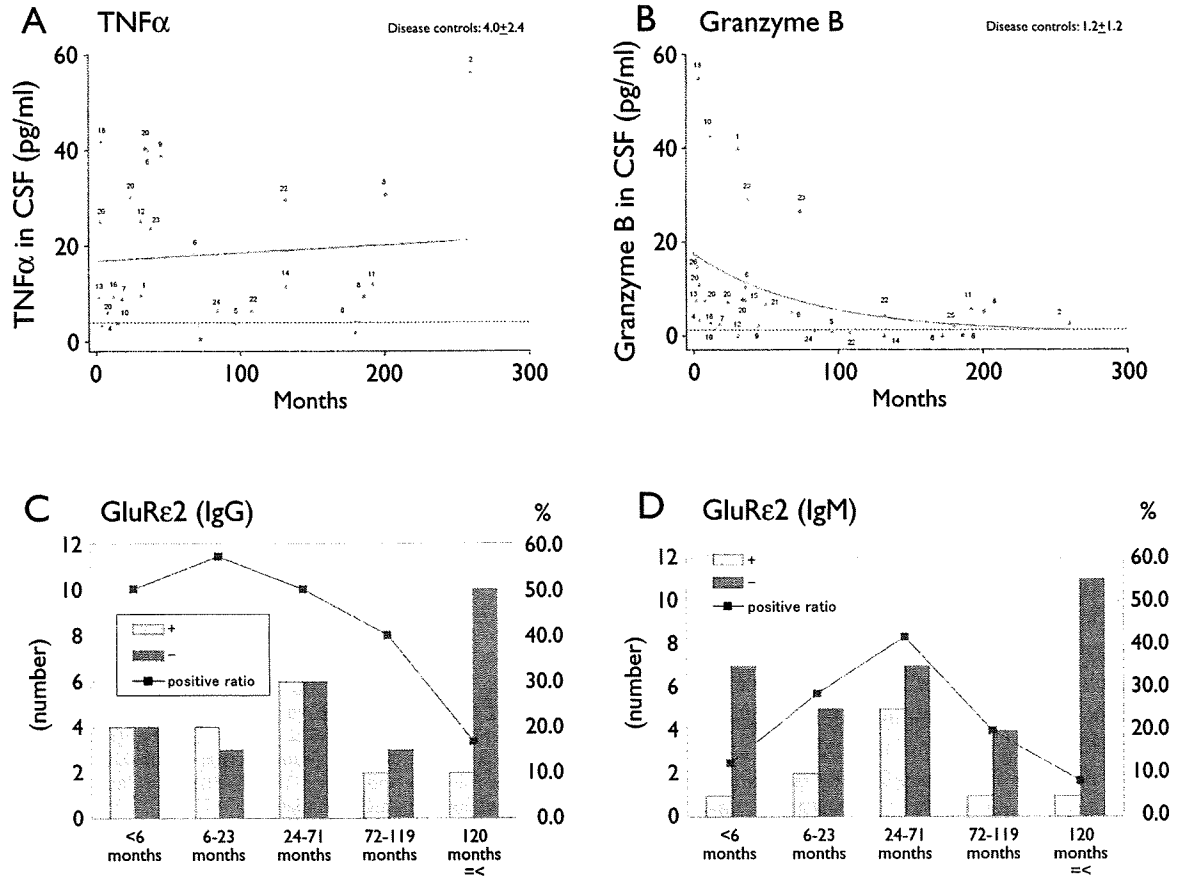

Figure 6.
Tumor necrosis factor α (TNFα), Granzyme B, and autoantibodies against GluR ε2 (NR2B) in cerebrospinal fluid (CSF). (**A**) TNFα level in CSF; (**B**) Granzyme B level; (**C**) immunoglobulin G (IgG) autoantibodies against GluR ε2 (NR2B); (**D**) IgM autoantibodies against GluR ε2 (NR2B). In panels **C** and **D**, yellow columns show the number of samples with antibodies against GluR ε2 (NR2B), and blue-green columns show the number of samples without autoantibodies against GluR ε2 (NR2B). Horizontal axis in each panel (**A–B**) shows time (months) from onset of epilepsy. Value (mean ± SD) for disease control is shown above each panel. Numbers indicate patients' numbers in Table 1. Blue triangle symbols show data of patients without immunological treatment; orange circle symbols show data of patients after introduction of immunological treatment. Dotted lines show mean levels of disease controls. Green solid lines show linear or nonlinear regression curves produced by computer software, GraphPad Prism 5 (GraphPad Software Inc.). In (**A**), linear regression was done (95% CI of slope, −0.06487 to 0.09824). In (**B**), nonlinear regression was done by equation of one phase association (95% CI of plateau, −20.17 to 21.29).

and initiate the subsequent autoimmune mechanisms. Prolonged production of TNFα from the early stage to the progressed stage leads to elevation of IL-6 in CNS. IL-6 may contribute to the inflammatory process and inhibition of regulatory T cells, resulting in augmentation of the autoimmune process. TNFα is reported to modulate AMPA-induced excitotoxicity (Bernardino et al., 2005), and to reduce GABA receptor (Stellwagen et al., 2005). Furthermore, transgenic mice of TNFα came to show epileptic seizures (Probert et al., 1995). These findings suggest that TNFα may contribute directly to epileptogenesis. Adding to the cytotoxic T-cell–mediated immune mechanisms, the autoimmune process mediated by Th1 cells and the epileptogenic effect of TNFα seem to be important also in RS. On the other hand, IFNγ induces the expression of major histocompatibility complex (MHC) (class I+ II) and Inter-Cellular Adhesion Molecule 1 (ICAM-1), and production of TNFα in microglia. These effects of IFNγ lead to the enhancement of the autoimmune cytotoxic process in CNS by $CD8^+$ T cells. TNFα induces the expression of MHC class I on astrocytes, and loosens capillary endothelial junctions. These effects of TNFα may also lead to

apoptosis of astrocytes by $CD8^+$ T cell and inflammation. Brain tissues of patients with RS are reported to show characteristic astrocytic apoptosis (Bauer et al., 2007).

Tacrolimus, an inhibitor of cytokine production, is effective in preserving neurologic function and delaying the progression of cerebral hemiatrophy in RS (Bien et al., 2004). Because IFNγ and Granzyme B are elevated, especially in the early stage, early initiation of tacrolimus may improve the outcome of RS. In patients 8, 20, and 22, development or progression of mental retardation was not observed after introduction of tacrolimus. However, in patient 23, progression of mental retardation was observed and higher levels of Granzyme B were sustained. Although our study showed no significant difference of CD4, CD8, CD3, Granzyme B, IL-4, IL-12, TNFα, or IFNγ between patients without immunologic treatment and patients after introduction of immunologic treatment, this may be attributed to the variety of clinical stage at the introduction of immunologic treatment and the variety of immunologic treatment. Further investigation is required to examine the effects of early initiation of tacrolimus in RS patients, which will depend on a correct early diagnosis using immunologic data in CSF and other methods.

Detrimental effects of autoantibodies against GluR mimicking excess of glutamate are reviewed in epilepsy, encephalitis, and other diseases (Levite & Ganor, 2008). Autoantibodies against GluR ε2 (NR2B) (IgG) were detected in half of patients within 6 months of epilepsy onset, and the autoantibody positive rate was lower in the progressed stage (Figure 6), and in all three patients without immunologic treatment, the autoantibodies disappeared evolutionally (Table 1). These data suggest that autoantibodies against GluR ε2 (NR2B) may be involved in the pathologic mechanisms from the early stage up to several years after onset of epilepsy. In a previous study in which we examined the effect of IgG antibodies against GluR ε2 (NR2B) in CSF from RS patients on excitatory postsynaptic current (EPSC) using patch clamp methods, both IgG in CSF from RS patients and rabbit IgG antibodies against mouse GluR ε2 (NR2B) had no effect on EPSC (Takahashi et al., 2006). However, anti-dsDNA antibodies in CSF from patients with systemic lupus erythematosus have been shown to cross-react with the N terminus of GluR ε2 (NR2B) and cause neuronal apoptosis in the rat hippocampus (DeGiorgio et al., 2001). It is possible that autoantibodies against GluR ε2 (NR2B) may also cause apoptosis in the rat hippocampus. Furthermore, autoantibodies against the N terminus of GluR ε2 (NR2B) have been reported to cause hippocampal neuron damage with ensuing memory impairment (Kowal et al., 2006), and amygdala neuron damage with emotional behavior impairment (Huerta et al., 2006). Therefore, autoantibodies against GluR ε2 (NR2B) may contribute to the cognitive and behavioral changes in RS through inducing apoptosis. A recent study has reported a causal relationship between autoantibodies against the N terminus of NMDA-type GluR hetero complexes and paraneoplastic encephalitis in patients with ovarian teratoma (Dalmau et al., 2007; Takahashi, 2008). Further investigations and a more suitable assay for the quantitative measurement of antibodies to NMDA receptors are required to elucidate the involvement of autoantibodies against GluR ε2 (NR2B) in the pathophysiologic mechanisms of RS.

In the later stages of RS, nonlinear regression curves of albumin levels in CSF imply that the CSF albumin level (protein level) increases evolutionally (Fig. 3). Direct brain exposure to serum albumin results in albumin uptake into astrocytes through transforming growth factor-beta receptors (TGF-β R), and induces NMDA-receptor–mediated neuronal hyperexcitability and subsequently epileptiform activity (Ivens et al., 2007). Therefore, elevated albumin levels in CNS may contribute to the pathologic mechanisms of intractable epilepsy, and TGF-β R may be a candidate therapeutic target for epilepsy in RS also.

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We have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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those lesions. However, AQP4 and GFAP were strongly stained as reactive astrogliosis surrounding the lesions. In contrast in those lesions, myelin basic protein (MBP)-stained myelinated fibers were relatively preserved in the lesions where AQP4 was lost. In contrast to NMO lesions, AQP4 was preserved in demyelinating MS lesions and controls. In vitro, there are growing evidences of the effect of AQP4 antibody on primary astrocytes, suggesting its pathogenic implications of astrocytic damage in NMO. Furthermore, the lesions lacking AQP4 was appeared by passive-transferred Lewis rats with human purified IgG from NMO patients, which strongly suggested its autoimmune mechanisms in NMO pathomechanisms. Recent growing evidences suggest that astrocytic impairment associated with humoral autoimmunity against AQP4 may be primarily involved in the pathogenesis of NMO, which is probably distinct from those of MS, primarily demyelinating disorder.

IN24-TU-03
Repair strategies in multiple sclerosis

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Current treatments for multiple sclerosis assume that the immune system destroys oligodendrocytes and axons. Some lead to a partial clinical response, but many patients progress to severe, permanent disability. To induce a sustained response, we propose targeting oligodendrocytes, neurons and axons, CNS cells that play a critical role in the disease process. Our current experimental therapies target these cells to activate oligodendrocytes to produce new myelin or activate neurons to extend their processes. We discovered that natural autoantibodies in the serum of healthy individuals contain immunoglobulins directed against surface molecules on oligodendrocytes. One antibody, HIgM22, produced dramatic remyelination in various animal models of multiple sclerosis apparently by acting against integrins on the cell surface of oligodendrocytes. The antibody binds to lipid rafts on oligodendrocytes to induce a calcium influx through an AMPA-mediated channel, resulting in phosphorylation of specific remyelination-inducing molecules. HIgM12 and HIgM42, also discovered in our laboratory, apparently target sialidase-containing compounds on gangliocytes. These antibodies induce neuron outgrowth. Recent experiments in mice chronically infected with Theiler's murine encephalomyelitis virus (TMEV), a model for human multiple sclerosis, demonstrate that the remyelinating antibody (HIgM22) and the neurite-binding antibodies (HIgM12 and HIgM42) enter the CNS of animals to reverse dramatically persistent neurological deficits. Recombinant HIgM22, generated in large quantities in a GMP facility, targets injured areas of CNS and promotes maximal remyelination within 5 weeks after a single low dose (25 microg/kg). Unlike current MS therapies for MS aimed at treating inflammation, remyelination-promoting antibodies induce tissue repair within the CNS at sites of damage on the myelin-synthesizing cells. Our goal is to initiate a long-term reparative effect on the central nervous system.

IN25 – Neuro-oncology 2

IN25-TU-01
Primary CNS lymphoma

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IN25-TU-02
Limbic encephalitis associated with ovarian teratoma

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Purpose: From 1960s to 1980s, limbic encephalitis had been recognized as paraneoplastic subacute encephalitis with various autoantibodies, for example, anti-Hu antibodies, etc. These autoantibodies recognize intracellular antigens. On the other hand, in 2007, Dalmau et al., reported antibodies to cell surface structures of N-methyl-D-aspartate-type glutamate receptor (NR) complex composed of NR1 and NR2B/2A, in patients of acute limbic encephalitis with ovarian teratoma (ALE-OT). We studied characteristics of antibodies to NR in ALE-OT.

Method: We examined clinical characteristics and antibodies to NR in 53 patients with ALE-OT. Antibodies to whole molecules of GluRε2 (NR2B) were detected by immunoblot with antigens produced by Tet-system. Antibodies to n-terminal (NT2) and c-terminal (CT1) of GluRε2 were detected by ELISA with synthetic peptide-antigens. Antibodies to n-terminal (NT) and c-terminal (CT) of GluRζ1 (NR1) were detected by ELISA. Antibodies to NR-complex composed of NR1 and NR2B/2A were detected by immunocytochemistry developed by Dalmau et al..

Results: IgG- & IgM-antibodies to whole molecules of GluRε2 (NR2B) were detected in 41.7% & 25.0% of patients' sera, and in 57.7% & 27.5% of patients' CSF. The levels of antibodies to GluRε2-NT2 & CT1 in sera of patients were significantly higher than those of healthy controls ($p = 0.031$ & $p = 0.008$). The levels of antibodies to GluRε2-NT2 & CT1 in CSF of patients were significantly higher than those of disease controls ($p < 0.001$ & $p < 0.001$). The levels of antibodies to GluRζ1-NT & CT in sera of patients were significantly higher than those of healthy controls ($p < 0.001$ & $p < 0.001$). The levels of antibodies to GluRζ1-NT & CT in CSF of patients were significantly higher than those of disease controls ($p < 0.001$ & $p < 0.001$). Antibodies to NR-complex (Dalmau's method) were detected in 78.3% of patients' CSF.

Conclusion: Antibodies to NR2B and or NR1 may contribute to the pathogenesis in ALE-OT.

IN25-TU-03
Paraneoplastic neurologic disorders

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Paraneoplastic neurologic disorders (PND) are rare syndromes that are associated with cancer. PND are heterogeneous and may affect any part of the nervous system from cerebral cortex to neuromuscular junction and muscle. Among the classical syndromes are encephalomyelitis, limbic encephalitis, cerebellar degeneration, opsoclonus-myoclonus, sensory neuronopathy, Lambert-Eaton myasthenic syndrome and dermatomyositis. The onset of neurological symptoms often precedes the cancer diagnosis, and the recognition of PND should lead to immediate search for cancer. Various tumours are associated with PNS, in particular small cell lung cancer, cancer of the breast and ovary, and thymoma. The pathogenesis of PND is probably autoimmune, involving both antibodies and T cells that are directed against shared antigens that are expressed by cancer cells and neurons. Onconeural antibodies that are often recognized in serum and cerebrospinal fluid are very useful diagnostic markers for PND, and in many cases can narrow the search for an occult tumour to a few organs. When conventional imaging fails to identify the cancer, fluorodeoxyglucose positron emission tomography (FDG-PET) is useful. The most important therapy of PND is the treatment of the underlying cancer. In some of the PND, immunosuppressive therapy is of additional benefit. The prognosis of the different PND varies depending on the level of affection and the degree of neuronal death.

IN26 – Neurology of extreme conditions 2

IN26-TU-01
Heat stroke

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FULL-LENGTH ORIGINAL RESEARCH

Stiripentol open study in Japanese patients with Dravet syndrome

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SUMMARY

Purpose: To survey the treatment situation of Dravet syndrome in Japan and to compare this result with effectiveness of stiripentol (STP) add-on therapy in an open-label multicenter study.

Methods: Medical records of patients with Dravet syndrome who visited the study institutions during 2006 were surveyed to examine the effect of antiepileptic drugs (AEDs) on clonic or tonic–clonic seizures (GTCS). Patients older than 1 year of age treated with at least one conventional AED and more than four GTCS per month were invited to participate in the STP study. Seizure status and adverse effects during the first 4 weeks of STP (50 or 1,000 mg/day) add-on therapy (early period) and during long-term treatment were compared with baseline.

Results: Only 15% of the treatment trials with 15 conventional AEDs in 112 patients succeeded in reducing seizures by more than 50%. With STP, GTCS were reduced more than 50% in 14 of 23 patients (61%), including 2 who became seizure-free, in the early period. Moreover, duration of seizures was shortened in 10 patients and status epilepticus decreased in 6. These effects continued in the long-term although to a lesser degree. Adverse effects (loss of appetite, sleep disturbance, ataxia, hyperactivity/irritability) disappeared after dose modification in most cases. STP was effective at a lower than initial dose in five patients. Some patients benefited from STP added on clobazam despite mutation in *CYP2C19*.

Conclusion: Our data suggest that an early introduction of STP into Japan will result in substantial patient benefit.

KEY WORDS: Severe myoclonic epilepsy in infancy, Dravet syndrome, Stiripentol, Clobazam, Cytochrome P450.

Severe myoclonic epilepsy in infancy, or Dravet syndrome, is one of the most severe forms of epileptic encephalopathy, having onset within the first year of life with fever-induced hemi- or generalized clonic or tonic–clonic seizures (GTCS), which in due course increase in frequency and not rarely prolong or result in convulsive status epilepticus. In addition, myoclonus, absence, or complex partial seizures may appear. The psychomotor development, which was normal before the appearance of seizures, may show stagnation after the second year of life. Ataxia or some other neurologic signs may also develop. The frequency of Dravet syndrome is estimated at one in 40,000 children (Hurst, 1990). De novo mutation in the neuronal sodium channel alpha subunit *SCN1A* is a major cause of this syndrome (Fujiwara et al., 2003).

The seizures of Dravet syndrome are known to be very resistant to therapy (Dravet et al., 2005). In general, conventional treatment is disappointing, and introduction of newer antiepileptic drugs (AEDs), including topiramate (TPM) and stiripentol (STP), has been recommended

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(Chiron et al., 2000; Ceulemans et al., 2004; Chiron, 2005; Kröll-Seger et al., 2007).

Stiripentol, a novel AED developed in France, was approved recently by the European Medicines Agency (EMEA) for the treatment of Dravet syndrome, as an adjunct to valproate (VPA) and clobazam (CLB). Double-blind studies and long-term follow-up studies demonstrated a promising effect of STP on Dravet syndrome, although the interaction with concomitant AEDs through cytochrome P450 enzymes (CYP) may complicate the dose adjustment (Chiron et al., 2000; Chiron, 2005). STP has been shown to inhibit the metabolism of CLB, especially norclobazam (NCLB) hydroxylation by CYP2C19 (Giraud et al., 2006). The efficacy of STP could be related not only to its ability to increase the effective concentration of other drugs, but also to positive modulation of γ-aminobutyric acid (GABA)ergic inhibitory neurotransmission (Quilichini et al., 2006) and enhancement of the action of benzodiazepines (Fisher, 2009).

In Japan, where most of the newer AEDs were not available, the treatment of Dravet syndrome posed a challenge to the pediatrician. Although some reports indicate the efficacy of bromide (Br) (Oguni et al., 1994), zonisamide (ZNS) (Tanabe et al., 2008), or the ketogenic diet, the results are far from satisfactory.

We, therefore, performed a study to survey the effects of conventional AEDs on Dravet syndrome in Japan. We then started compassionate use of STP as add-on therapy in an open-label multicenter study to examine whether STP contributes to the treatment of this syndrome in Japan.

Methods

Six institutions participated in a retrospective survey of the treatment situation of Dravet syndrome. All medical records of the patients with Dravet syndrome who visited these institutions in 2006 (the majority had been visiting the institutions regularly) were reviewed for the following items: present age, age of seizure onset, family history, seizure types, presence of status epilepticus, neuropsychological status, electroencephalography (EEG) and radiologic findings, mutation analysis, AEDs previously used, and efficacy of these AEDs and adverse effects. AED efficacy was classified into seizure-free, >50% reduction, >25% reduction, no effect, or aggravation (>25% increase) during a period of at least 3 months, compared to the seizure frequency before initiation of the drug. AEDs used for <3 months were excluded from the analysis except in the case of aggravation. Only the effect on GTCS was analyzed.

Patients with Dravet syndrome who were older than 1 year of age, treated with at least one AED, and who had more than four GTCS per month were invited to participate in the STP open-label study. After a baseline period of 4 weeks, STP (administered twice daily) was initiated at a dose of 50 mg/kg/day, or 1,000 mg/day in patients weighing more than 20 kg. The doses of the concomitant drugs could be decreased if necessary. Then all drug doses were fixed for 4 weeks. Seizures were monitored during the subsequent 4 weeks (early period) and compared to those in the initial 4-week baseline period (Fig. 1). Thereafter the doses of STP (maximum 100 mg/kg/day or 4,000 mg/day) as well as the concomitant drugs were adjusted according to the clinical conditions. After the doses were stabilized for some time, all drug doses were then fixed for 4 weeks. Seizures were monitored during the subsequent 4 weeks (late period) and again compared with the initial 4-week baseline period. Other seizure-related symptoms (status epilepticus or clustering, duration, awake/sleep distribution) and behaviors as well as adverse effects were also assessed. When consent was obtained, mutation of *CYP2C19* and *SCN1A* was examined. Mutation of *CYP2C19* was examined using the *CYP2C19*-mutation detection kit (Roche Diagnostics, Mannheim, Germany). In patients taking CLB, steady-state serum concentrations of CLB and NCLB were measured using high-performance liquid chromatography (HPLC), when possible. We measured serum concentration of STP, but not systematically, so that the results were

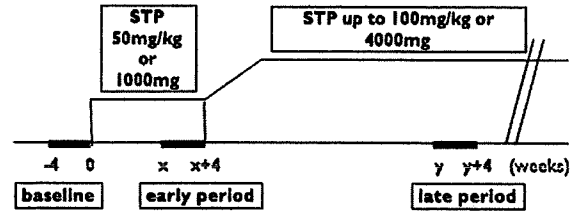


Figure 1.
Study design. Following a 4-week baseline period, stiripentol (STP) was introduced at a dose of 50 mg/kg/day (or 1,000 mg/day for patients weighing >20 kg). After dose adjustments of concomitant antiepileptic drugs (AEDs) as necessary, all drug doses were fixed for 4 weeks (point x). Seizures and adverse effects were monitored during the subsequent 4 weeks (x + 4) and compared to that of the baseline period. Patients subsequently entered a long-term treatment phase where STP and concomitant AEDs doses were adjusted according to clinical need (STP maximum dose was 100 mg/kg/day or 4,000 mg/day). Upon completion of dose adjustments all drug doses were kept constant for a further 4 weeks (point y). Seizures and adverse effects were again monitored during the subsequent 4 weeks (y + 4) and compared to that of the baseline period.

withdrawn from the analysis. The ethical committees of the individual institutions approved all these procedures.

All the patients fulfilled the following diagnostic criteria of Dravet syndrome: onset of the epilepsy in the first year of life with clonic or tonic–clonic generalized (or hemibody and alternant) seizures, but normal psychomotor development and normal EEG, progressive appearance of mental delay after 1 year of age, and usually with other types of seizures (myoclonia, atypical absence, partial seizures) (Dravet et al., 2005).

Results

Treatment situation in Japan

There were 112 patients (47 males and 65 females) from whom the effect of AED treatment was successfully extracted from the medical records. Median age at examination was 15 years (range 1–46 years) and age at epilepsy onset 6 months (range 2–12 months). AEDs were used almost continuously during this period. Family history of epilepsy/seizure was noted in 48%, mental retardation in 90%, and spike or spike-waves were found in the previous EEGs in 66% and normal radiography in 84%. Myoclonic seizure was found in 81 patients, absence in 20, partial seizures in 93, and convulsive status in 99. *SCN1A* mutation (direct sequencing) was found in 51 of 67 patients studied.

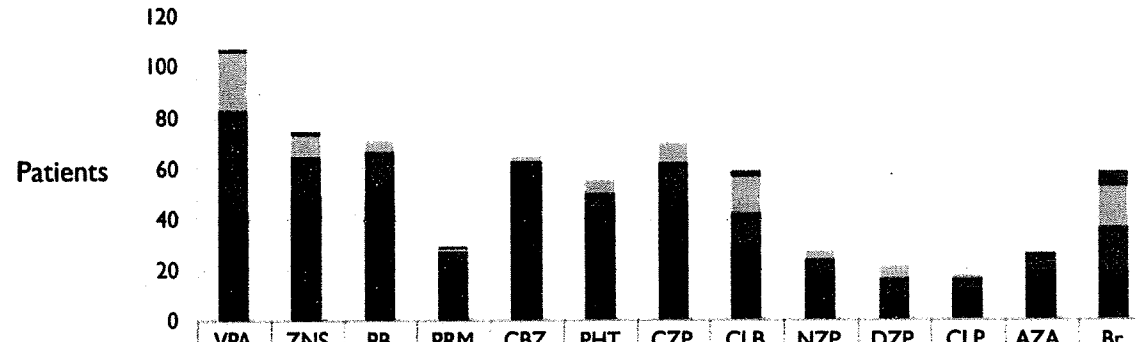
Fifteen conventional drugs were evaluated. The effectiveness of various AEDs in individual patients was evaluated for a mean period of 14 years (range 1–44 years). The efficacy of each drug was shown in Fig. 2. VPA was most often used (108 patients), followed by zonisamide (ZNS) (74), phenobarbital (PB) (71), and clonazepam (CZP) (71), carbamazepine (CBZ) (64), CLB (58), and Br (57). Ketogenic diet was tried in 12 patients.

The introduction of VPA decreased seizures in 24 patients (22.2%) by more than 50% (including one patient who became seizure-free), Br in 21 patients (36.8%) (5 patients became seizure-free), CLB in 16 patients (27.6%) (2 patients became seizure-free), and ZNS in 10 patients (13.5%) (1 patient became seizure-free). Other drugs were less successful to reduce seizures by more than 50%: phenytoin (PHT) 9.1%, PB 7%, and CBZ 3.1%. Aggravation was found in CBZ, PHT, CLB, Br, and others. More than 90% of 12 patients responded to the ketogenic therapy to various degrees. In total, only 15% (106 of 698) of the treatment trials with 15 conventional AEDs succeeded in reducing seizures by more than 50%.

Severe adverse effects that led to the discontinuation of the drug were observed in 22 occasions (supplementary Table S1): ZNS in four patients, CBZ in three, Br in two, PB in two, primidone (PRM) in two, PHT in two, CLB in two, VPA in one, CZP in one, nitrazepam (NZP) in one, ethosuximide (ESM) in one, and acetazolamide (AZA) in one.

STP add-on therapy

Twenty-five patients participated in the open study. There were seven males and 18 females. Median age at



	VPA	ZNS	PB	PRM	CBZ	PHT	CZP	CLB	NZP	DZP	CLP	AZA	Br
free	1	1		1				2					5
>50% reduction	23	9	5	1	2	5	8	14	3	5	1	0	16
25% reduction	40	15	16	4	2	5	15	12	6	6	4	7	19
no effect	43	49	50	23	57	42	46	28	18	10	10	19	15
aggravated					3	3	1	2			1		2

Figure 2.
Effects of conventional antiepileptic drugs (AEDs) on clonic or tonic–clonic seizures in the retrospective study. VPA, valproate; ZNS, zonisamide; PB, phenobarbital; PRM, primidon; CBZ, carbamazepine; PHT, phenytoin; CZP, clonazepam; CLB, clobazam; NZP, nitrazepam; DZP, diazepam; CLP, Clorazepate; AZA, acetazolamide; Br, bromide.

epilepsy onset was 6 months (range 2–10 months). The age at study ranged from 1 to 22 years: 17 patients were between 1 and 8 years (median 3 years) (younger group: group Y) and eight patients were between 13 and 22 years (median 19 years) (elder group: group E). There was one boy aged 1 year 11 months who discontinued STP at 42 days because of loss of appetite. A 5-year-old girl showed irritability soon after introduction of STP, so that the dose had to be reduced. The concomitant drug was VPA in both cases. These two patients were excluded from the analysis. All the other patients (23 patients: 15 in group Y and 8 in group E) were entered into the assessments in the early and late periods. The study period lasted 6–34 months (mean 14.1 months). The time before entering the early period was 4–8 weeks (mean 5.9) and the time from the early period to the late period was 3–14 months (mean 6.1 months). Mutation of *SCN1A* was found in 17 of 18 patients tested.

Concomitant drugs were VPA in 22 patients, CLB in 11, Br in 5, PB in 5, ZNS in 3, CZP in 3, ESM in 1, PHT in 1, CBZ in 1, and diazepam (DZP) in 1. The combination was VPA in five patients, VPA + CLB in eight, VPA + PB in one, and other combinations with more than three drugs in nine. In the late period, STP daily dose ranged from 30 to 100 mg/kg (mean 59.0 mg/kg) in group Y and 500–3,000 mg (mean 1,469 mg) in group E. In five patients, the STP dose in the late period was less than the initial dose.

In the early period, GTCS of 14 patients (61%) were reduced by more than 50%, including two patients who became seizure-free. In the late period, 11 patients (48%) remained having >50% seizure reduction (Table 1 and supplementary Table S2). Groups Y and E behaved similarly.

Status epilepticus or seizure clustering disappeared in one patient and decreased in frequency in five patients (Table 2). Duration of seizures was shortened in 10 patients, although partly not quantitatively measured. Awake seizures were reduced in three patients. These effects continued in the late period, although to a lesser degree, without any age effects. The parents reported improvement of behavior or cognitive function in four patients in the early period and in five patients in the late period.

Table 1. Effect of stiripentol on clonic or tonic–clonic seizures

Seizure reduction	Early period (Y15, E8)	Late period (Y15, E8)
100%	2 (Y1, E1)	1 (E)
>50%	12 (Y9, E3)	10 (Y6, E4)
>25%	3 (Y2, E1)	3 (Y2, E1)
No change	6 (Y3, E3)	7 (Y5, E2)
Worse	0	2 (Y)

Y, younger group; E, elder group.

Table 2. Effect of stiripentol on seizure status and behavior

	Early period	Late period
Status/cluster		
Less	6 (Y5, E1)	6 (Y5, E1)
More	0	0
Seizure duration		
Shorter	10 (Y6, E4)	5 (Y3, E2),
Longer	0	1 (Y)
Awake seizure		
Less	3 (Y)	3 (Y),
More	0	1 (E)
Behavior		
Improved	4 (Y3, E1),	5 (Y4, E1)
Worse	1 (E)	0

Y, younger group; E, elder group.

The most often encountered adverse effects were loss of appetite, sleep disturbance, hyperactivity or irritability, and ataxia during the early period and dose adjusting (intermediate) period. In most cases, these effects disappeared after dose modification of other AEDs/STP or in the late period (Table 3). Concomitant drugs were reduced in 16 patients. STP was reduced in five patients, and the dose in the late period was 32.5 mg/kg (30–37.5 mg/kg) in three group Y patients, and 500 and 750 mg in two group E patients.

Six patients discontinued STP in the later phase because of no effect on seizure or adverse effects (Table 4). The mean highest dose of STP in these patients was 80 mg/kg (54–100 mg/kg) in group Y and 2,500 mg (2,000–3,000 mg) in group E. The concomitant drugs were VPA in one patient, VPA + CLB in two, VPA + CBZ + CZP in two, VPA + ZNS + CZP in one, and VPA + PB + Br in one.

CYP2C19 polymorphism was examined in 21 patients: there were nine with *1/*1, six with *1/*2 or *1/*3, and

Table 3. Adverse effects observed during stiripentol add-on therapy

	Early period	Intermediate period	Late period
Loss of appetite	8 (Y7, E1)	16 (Y12, E4)	3 (Y1, E2)
Drowsiness	10 (Y6, E4)	15 (Y10, E5)	0
Nausea	0	3 (Y1, E2)	0
Hyperactivity/irritability	6 (Y3, E3)	7 (Y4, E3)	0
Ataxia	5 (Y4, E1)	7 (Y5, E2)	1 (E)
Insomnia	2 (E)	2 (E)	0
None	5 (Y2, E3)	1 (E1)	19 (Y14, E5)

Y, younger group; E, elder group.

six with *2/*2, *3/*3 or *2/*3. Eight patients (seven in group Y and one in group E) were taking CLB, and three patients in the early period and two patients in the late period benefited from VPA + CLB therapy without significant adverse effects despite mutation in *2C19* (Table 5), although two patients stopped taking STP (reason: seizure aggravation in one, unknown in one). NCLB concentration could be measured off and on STP in only three patients, and NCLB level–dose-ratio calculated as NCLB (ng/ml) divided by CLB (mg/kg) did not increase in one poor metabolizer (Table 6).

Table 4. Reasons for stiripentol discontinuation (n = 6)

Time from stiripentol introduction to discontinuation	Y4: 11–22 months, mean 16 months E2: 8–9 months, mean 8.5 months
Aggravation of seizure	2 (Y)
No change of seizure frequency	2 (E)
Adverse effects	1 (Y): loss of appetite
Unknown	1 (Y)

Y, younger group; E, elder group.

Table 5. Effectiveness of stiripentol in patients with or without *CYP2C19* mutation taking clobazam

	CYP2C19		
	*1/*1	*1/*2	*2/*2, *2/*3
Patients with CLB (N)	4 (Y3, E1)	2 (Y)	2 (Y)
>50% reduction (Early/late period)	3/1	2/1	1/1
STP discontinuation	0	1	1

Y, younger group; E, elder group; CLB, clobazam; STP, stiripentol.

Table 6. Norclobazam level–dose ratio before and after introduction of stiripentol in patients with or without *CYP2C19* mutation

Patient	Off STP	On STP
*CYP2C19*1/*1*	2,423	4,356
*CYP2C19*1/*2*	861	3,908
*CYP2C19*2/*2*	14,973	9,114

NCLB level–dose-ratio = NCLB (ng/ml)/CLB (mg/kg).
STP, stiripentol.

Discussion

According to Oka et al. (2006), Dravet syndrome was found in 9 of 2,220 patients with epilepsy, or 9 of 250,997 population younger than age 13 years living in Okayama prefecture of Japan on December 31, 1999, that is, 0.4% of children with epilepsy and one in 27,888 children younger than 13 years had Dravet syndrome, which was slightly higher than the figure indicated by Hurst (1990). One of our study institutions, the National Epilepsy Center Shizuoka, where mainly patients with intractable epilepsy are treated, found 34 patients with Dravet syndrome among 7,310 patients of all ages visited during 2006, a figure of 0.47%.

Our results of the treatment survey in Japan confirmed the intractability of this syndrome. Only 15% of the treatment trials successfully reduced GTCS by more than 50%. There were only 10 patients (8.9%) who became seizure-free. The successful drugs were Br, CLB, VPA, and ZNS in order of frequency. PB, PHT, and especially CBZ failed to show effectiveness. Br is an old and often forgotten drug, but its efficacy on Dravet syndrome should be reappraised (Oguni et al., 1994). At the time of the survey no patients received TPM, as it was not yet approved in Japan.

Tanabe et al. (2008) investigated the efficacy of the conventional drugs used daily against status epilepticus in 99 patients with Dravet syndrome and found efficacy with Br, followed by ZNS, CLB, VPA, and others. This result was similar to our result.

According to an expert consensus survey conducted in Japan in which 69 epileptologists responded (Inoue & Nishida, 2004), VPA was considered as the treatment of choice for convulsive seizures of Dravet syndrome by 73% of epileptologists, followed by CZP, ZNS, CLB, and others. These reports thus indicate that VPA, Br, ZNS, CLB, and CZP are the more successful and recommended conventional AEDs.

Beyond the conventional drugs, newer drugs are increasingly being used for Dravet syndrome. TPM in combination therapy with VPA was reported to achieve a >50% reduction of seizure frequency in 55–72% of patients and freedom from seizure in 10–16%, and was thus recommended as an optimal treatment (Ceulemans et al., 2004), although all the TPM studies in Dravet syndrome were open labeled and not controlled with placebo.

Stiripentol is another recommended drug. Chiron et al. (2000) conducted a randomized, double blind, parallel-group adjunctive trial in which STP or placebo was evaluated over a 2-month period in a total of 41 patients with Dravet syndrome. All the patients were on a combination of VPA and CLB. They found 71% responders (>50% seizure reduction) including nine seizure-free patients in the STP group, compared to 5% responders in placebo group. Twenty-one of the 37 patients who entered subsequent open-label long-term treatment with STP showed a favorable response in a median follow-up period

of 24 months. A broader assessment of long-term outcome data including additional 46 patients from another trial concluded that STP added to VPA and CLB maintained long-term efficacy (Thanh et al., 2002).

Kröll-Seger et al. (2006) examined the benefit of TPM in 34 patients, two-thirds of whom were on STP in addition to other drugs, and found 78% showing more than 50% reduction of GTCS and 17% seizure-free for at least 4 months. Therefore, in patients not satisfactory controlled by STP, TPM seems to offer a substantial additional benefit.

Our result of STP add-on therapy indicated a more than 50% seizure reduction in 61% and seizure freedom in 8.7%. The effect continued, although slightly less (48%), in the long-term. This result was almost comparable to those of previous reports (Chiron et al., 2000; Thanh et al., 2002). Although past studies suggested that the efficacy of STP is better in younger children and tolerability poorer in elder children (Thanh et al., 2002; Chiron, 2007), we could not confirm these data. Our results indicated apparently much higher efficacy with STP than that seen with the conventional AEDs in Japan.

Significant benefits of STP were also reported to reduce the duration of GTCS (Thanh et al., 2002) and the frequency of status epilepticus (Chiron, 2005). These effects were also confirmed by our study: seizures were shortened in 43% (early period) or 22% (late period) of the patients, and status epilepticus or clustering reduced in 26%. Furthermore, awake seizures became less frequent in 13% and caregivers reported improvement of behavior in 17% (early period) or 22% (late period) of the patients. These beneficial effects contributed to the improvement of quality of life of the patients and caregivers.

The most common adverse effects included drowsiness, tremor, ataxia, hyperexcitability, insomnia, nausea, weight loss, and occasional vomiting (Trojnar et al., 2005), most of which can be ascribed to toxicity from other AEDs, because many adverse events were resolved after a reduction in dosage of comedication. Our patients also showed drowsiness, loss of appetite, hyperactivity or irritability, and ataxia, in descending order of frequency, in the early period; many of these disappeared in the late period. Adverse effects were usually manageable by adjusting the dose of concomitant drugs, except in one patient who discontinued STP.

Stiripentol is known to be associated with several drug interactions. The metabolism of STP is significantly accelerated by enzyme-inducing AEDs, whereas STP strongly inhibits the metabolism of other AEDs. Therefore, dose reduction of concomitant drugs including CBZ, PHT, CLB, PB, and PRM is recommended. STP was also reported to decrease the metabolism of VPA (Levy et al., 1990), but other reports indicated a lack of interaction between STP and VPA (Farwell et al., 1993). In our study, the dose of comedication was reduced in 16 patients.

In five patients, the STP dose in the late period was lower than the initial dose. All patients had adverse effects in the early period. Four of them showed more than 50% seizure reduction in both the early and late periods. Therefore, STP should have been effective at a lower dose. Considering the two patients who dropped out of study at the initial stage because of adverse effects, the initial dose of STP 50 mg/kg or 1,000 mg (body weight > 20 kg) may be too high for some patients. Actually, the clinical course of the 5-year-old girl, in whom irritability appeared soon after introduction of STP resulting in STP reduction, may be of interest. Although she dropped out of the study, the parents strongly wished to continue STP and we gradually re-increased STP from 7.4 to 30 mg/kg. Although seizure reduction was between 25% and 50%, status epilepticus disappeared completely and seizures were shortened and occurred only during sleep. She became active and development was advanced during the 11 months of follow-up. These facts indicate that STP may be effective even at a lower dose. Considering also that 18 of our 23 patients showed adverse effects in the early period, it may be practical to set a lower starting dose of STP such as 30 mg/kg/day, with subsequent upward titration.

Stiripentol inhibits CLB demethylation and more strongly NCLB hydroxylation (Giraud et al., 2006). Therefore, plasma concentrations of CLB and NCLB increase significantly when STP is used together with CLB. Giraud et al. (2004) found that 3A4 and 2C19 are the main CYP involved in CLB demethylation, whereas 2C19 is mainly involved in NCLB hydroxylation. Clinical safety and efficacy of CLB treatment are, therefore, altered by CYP2C19 polymorphism, and NCLB is known to contribute to the therapeutic and adverse effects more than CLB on long-term treatment (Giraud et al., 2006). Giraud et al. (2006) hypothesized that in patients carrying defective *2C19* alleles, the addition of STP to an initial CLB treatment would have almost no effect on the CLB and NCLB concentrations. The most common deficient alleles *2C19*2* and *2C19*3* correspond to lack of enzyme activity (Ozawa et al., 2004), and the combined frequency of *2 and *3 alleles is known to be higher in the Japanese population (Kosaki et al., 2004). We assessed blood concentrations of CLB and NCLB in only one patient who carried *2C19*2/*2*, and found no increase but rather a decrease in NCLB. One patient with *2/*3 had a favorable result (75% seizure reduction both in the early and late periods) with STP addition, which might indicate a proper antiepileptic effect of STP, although another patient with *2/*2 did not benefit from STP add-on therapy. An extensive study is needed to clarify the correlation between *CYP* mutation and effectiveness/safety of STP–CLB combination therapy.

In summary, STP was effective as an add-on therapy in Japanese patients with Dravet syndrome. Our data would

suggest that an early introduction of STP into Japan will result in substantial patient benefit.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Severe drug-related adverse effects identified in the retrospective study.

Table S2. Demographics of patients with significant (>50%) seizure reduction when prescribed stiripentol.

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DEVELOPMENT OF WEARABLE AIRBAGS FOR FALLS ON THE LEVEL FLOORS

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A wearable air-bag system for falls on the floor is being developed. This system consists of fall detection sensors, calculating process unit and one or two more airbags, which protect heads, buttocks, and backs against the hit on the level floor. The airbag system is especially designed to protect against backward falls, because backward falls are comparatively more risky than forward falls, which means pedestrians can soften hit force by themselves and protect their heads with upper limbs.

Various experiments using a dummy with fixed or non-fixed joints are conducted to evaluate the shock absorption performance of wearable airbags against hit on the level floor. The wearable airbags can considerably reduce hit by falls, but the present capacity of the shock absorption and location and size of wearable airbags should be improved for actual use.

Introduction

A wearable air-bag system for falls on the floor is being developed. Because, there are many fall down accidents, especially among elder persons, and measures for the accidents are needed. There are two types of measures; one is prevention of accidents, and another is reduction of damages by accidents. We adopted the latter, because we have developed airbag-type protective devices for fall from height (Fukaya, 2003) and for rollover of wheelchair (Fukaya, 2006), and we have experience and technology to reduce the shock of hit on the ground.

The wearable air-bag system consists of fall detection sensors, calculating process unit and one or two more airbags, which protect heads (Figure 1), buttocks (Figure 2) and backs against the hit on the level floor. The airbag system is especially designed to protect against backward falls, because backward falls are comparatively more risky than forward falls, which means pedestrians can soften hit force by themselves and protect their heads with upper limbs.

There are two major problems concerning the air-bag system; one is the air-bag itself including the shock absorption performance, and another is fall detection sensor and inflator. In this paper, we discuss mainly on the former problem.

About the latter we use both an accelerometer and a rotation sensor to detect falls. Both sensors are necessary to distinguish sudden falls from daily non-risky movements, such as sitting, standing, etc. The sensor system detected fall in case of attaching it to a dummy. And the sensor could distinguish intentional fall and some type of daily non-risky movements, such as sitting, in case of attaching it to a human. There are too many kinds of daily non-risky movements, and we continue the tests of the sensor in actual life. The detail of the sensor will be discussed in another report.

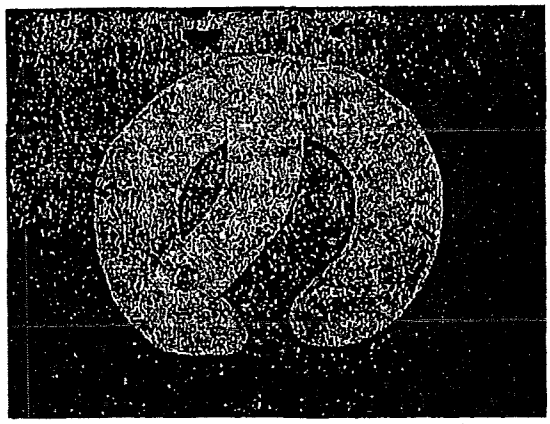

Figure 1. Airbag for head protection

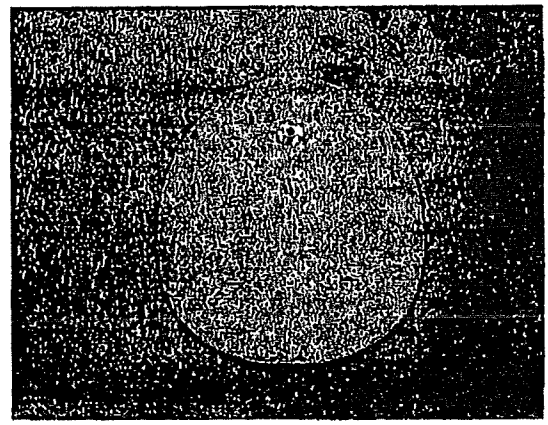

Figure 2. Airbag for buttocks protection

Method of experiment

To evaluate the shock absorption performance, turn over tests were conducted. We turned over a dummy, which was equipped with two 3-axis accelerometers, to the floor and measured the accelerations.

The experiment system was divided into two major parts; the measurement system (Figures 3 & 4) and the turnover generation system (Figure 5).

The measurement system consisted of a dummy, two 3-axis accelerometers, 6-channel amplifier and a memory recorder (50kHz sampling on each channel). 3-axis accelerometers were attached to the dummy; one was in the back of the head (Figure 3) and another was on the buttock (Figure 4). This dummy has joints in shoulders, elbows, hip, knees and so on. The friction of the joints could be adjusted, and the condition of the joints could be changed from fixed to non-fixed. In case of fixed joints the falling situation was falling like rigid bodies (rigid body type fall), and in case of non-fixed joints the falling situation was falling on his buttocks (buttock type fall).

The turnover generation system consisted of a frame, moving platform, and its controller, and hit the floor. This system simulated a falling created by slip. The dummy was hanged from the frame through a release device. After the start of the moving platform the dummy was released, and the dummy was turned over.

Using this experiment system, experiments of backward fall-down with/without airbag system were conducted. In this experiment, the airbag was expanded by using compressor before turnover. Experiments of forward turnover were also conducted, because elder persons sometimes could not protect their head. In forward fall-down two types of airbag were tested; that is, airbag for backward fall-down protection and airbag for forward fall-down protection. They were same one except the way of wear (Figure 8).

In pilot study, backward turnovers of dummy were conducted, and the shocks were greater in rigid body type fall than in buttocks type fall. Therefore in these experiments we turned over the dummy mainly in rigid body type fall.

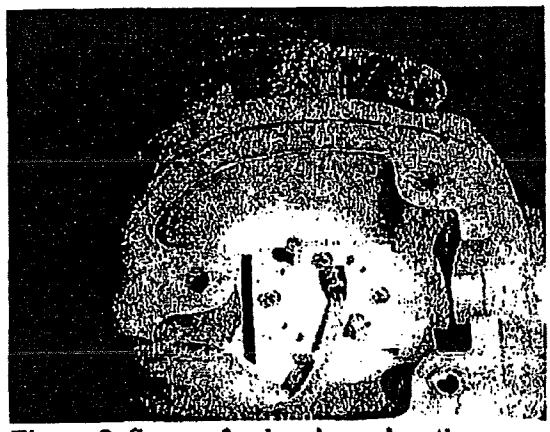

Figure 3. Sensor for head acceleration

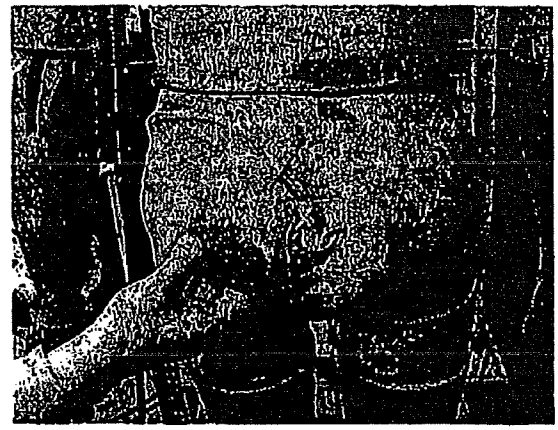

Figure 4. Sensor for buttocks acceleration

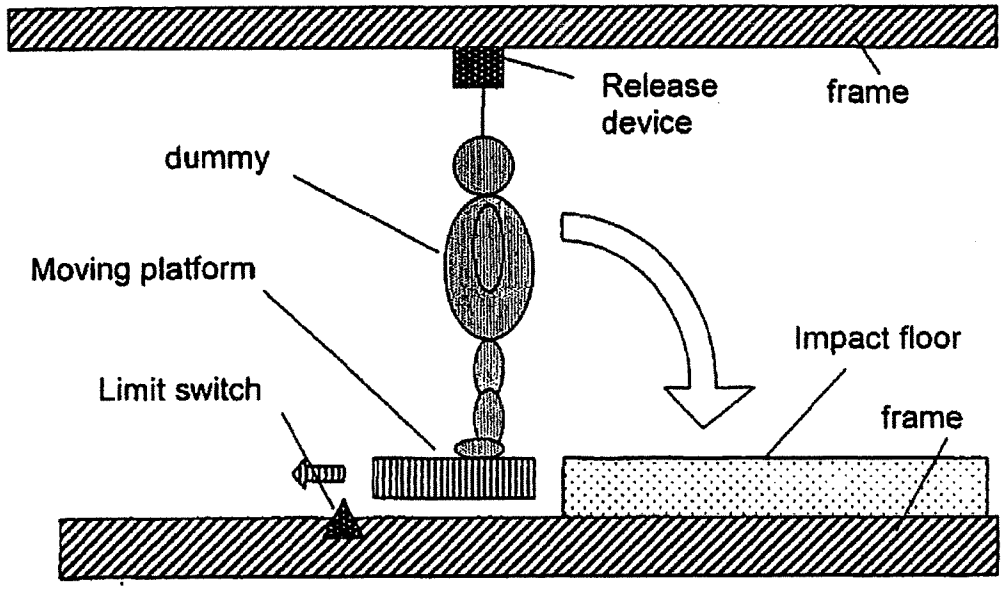

Figure 5. Turnover generation system

Result of experiment

Figure 6 and figure 7 show example of fall down situations. Figure 7 shows that left side of the dummy hit on the ground before right side of the dummy. This generated buffering effect. In my previous research (Fukaya, 2003), when a turn over process is divided into two or more steps, such as hit on left shoulder and right shoulder, or hit on buttocks and head, the maximum acceleration is smaller compared to the case when the whole dummy hit on the ground simultaneously.

Figure 8 shows the maximum accelerations in case of both with airbag and without airbag. The maximum acceleration was calculated. These data were combined from 3-axis acceleration and averaged of 10 data in order to get off noise.

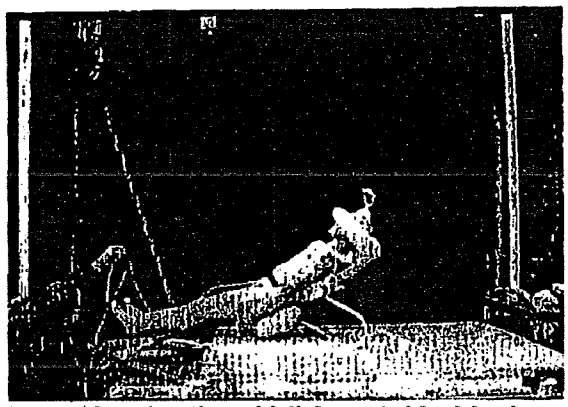

Figure 6. A situation of fall down (with airbag)

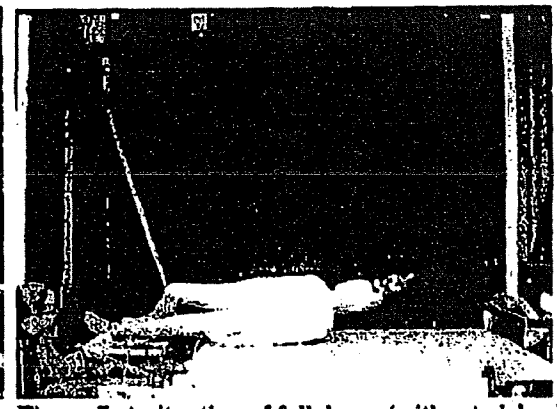

Figure 7. A situation of fall down (without airbag)

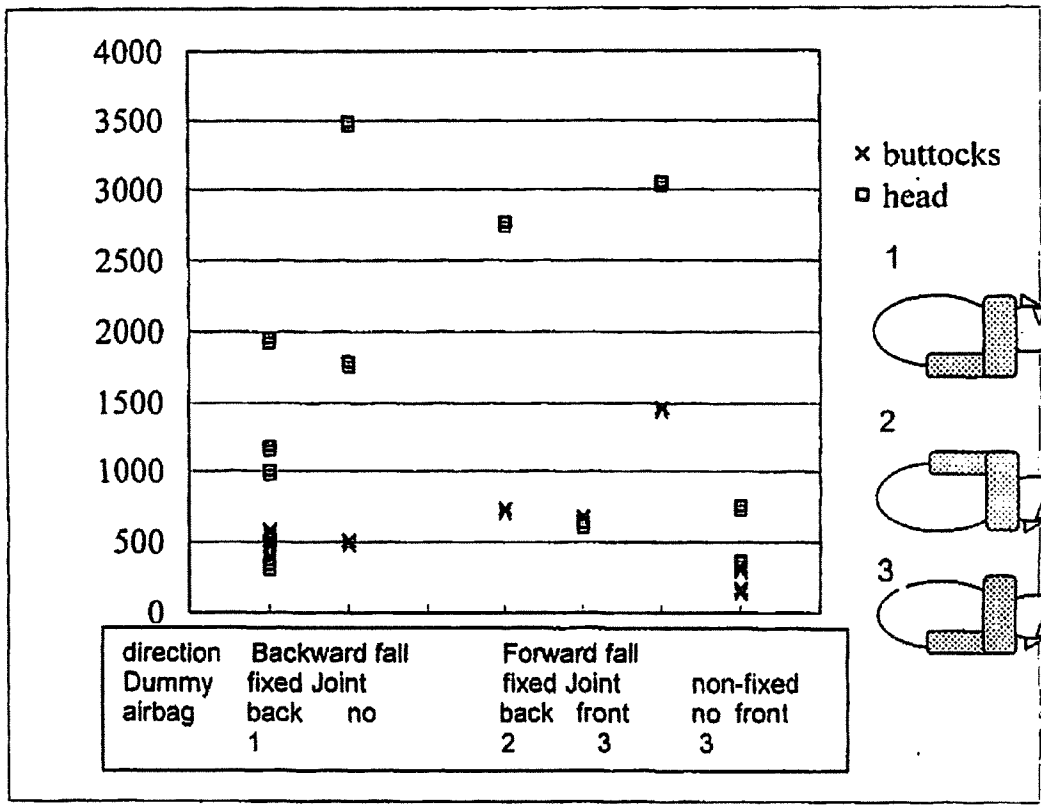

Figure 8. Maximum accelerations of each fall down condition

Discussion

Fall-down experiments were conducted. By comparing the maximum acceleration with wearable airbag and the maximum acceleration without wearable airbag, the effect of wearable airbag system was efficient.

As described earlier, minor difference of falling figure makes the difference of hit process and maximum acceleration. This is one reason of dispersion. Despite dispersion, the effect of airbag was evident.