III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
伊藤雅之	てんかんの病理	辻　貞俊	最新医学別冊. 新しい診断と治療のABC 74	最新医学社	大阪	201	72-82

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Arai A, Saito T, Hanai S, Otsuki T, Nakagawa E, Takahashi A, Kaneko Y, Kaido T, Saito Y, Sugai K, Sasaki M, Goto Y, Itoh M.	Abnormal maturation and differentiation of neocortical neurons in epileptogenic cortical malformation: unique distribution of layer-specific marker cells of focal cortical dysplasia and hemimegalencephaly.	Brain Res	1470	89-97	2012
Sakakibara T, Sukigara S, Otsuki T, Takahashi A, Kaneko Y, Kaido T, Yuko Saito Y, Sato N, Nakagawa E, Sugai K, Sasaki M, Goto Y, Itoh M.	Imbalance of interneuron distribution between neocortex and basal ganglia: Consideration of epileptogenesis of focal cortical dysplasia.	J Neurol Sci	323	128-133	2012
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Itoh M, Tahimic CGT, Ide S, Otsuki A, Sasaoka T, Noguchi S, Oshimura M, Goto Y, Kurimasa A.	Methyl CpG-binding protein isoform MeCP2_e2 is dispensable for phenotypes but essential for embryo viability and placenta development.	J Biol Chem	287	13859-13867	2012
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Kaido T, Otsuki T, Saito Y, Sugai K, Takahashi A, Kaneko Y, Sakakibara T, Saito Y, Takahashi H, Honda R, Nakagawa E, Sasaki M, Kakita A, Itoh M.	Novel pathological abnormalities of deep brain structures including dysplastic neurons in anterior striatum associated with focal cortical dysplasia in epilepsy.	J Neurosurg Pediatr	10	217-225	2012

岩崎裕治	NICU後の障害児の行方―重症心身障害児施設の立場から	Journal of Clinical Rehabilitation	21	278-281	2012
岩崎裕治、家室和宏、宮野前健、倉澤卓也、益山龍雄、田村正徳	療育施設における医療的ケアの必要な入所児(者)およびNICU長期入院児を含む受け入れ状況等の実態調査	日本重症心身障害学会誌	37	117-124	2012
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Castilla J, Rísquez R, Cruz D, Higaki K, Nanba E, Ohno K, Suzuki Y, Díaz Y, Ortiz Mellet C, García Fernández JM, Castillón S.	Conformationally- Locked N-Glycosides with Selective β-Glucosidase Inhibitory Activity: Identification of a New Non- Iminosugar-Type Pharmacological Chaperone for Gaucher Disease.	J Med Chem	55	6857-6865	2012

ＩＶ．研究成果の刊行物・別刷

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Therapeutic chaperone effect of *N*-Octyl 4-Epi-β-valienamine on murine G_{M1}-gangliosidosis

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ABSTRACT

Therapeutic chaperone effect of a valienamine derivative *N*-octyl 4-epi-β-valienamine (NOEV) was studied in G_{M1}-gangliosidosis model mice. Phamacokinetic analysis revealed rapid intestinal absorption and renal excretion after oral administration. Intracellular accumulation was not observed after continuous treatment. NOEV was delivered to the central nervous system through the blood–brain barrier to induce high expression of the apparently deficient β-galactosidase activity. NOEV treatment starting at the early stage of disease resulted in remarkable arrest of neurological progression within a few months. Survival time was significantly prolonged. This result suggests that NOEV chaperone therapy will be clinically effective for prevention of neuronal damage if started early in life hopefully also in human patients with G_{M1}-gangliosidosis.
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1. Introduction

G_{M1}-gangliosidosis (OMIM 230500) is one of the lysosomal diseases caused by mutations of the gene *GLB1* coding for β-galactosidase (β-gal) (EC 3.2.1.23) [1] with storage of ganglioside G_{M1}, keratan sulfate, and glycoprotein-derived oligosaccharides, presenting clinically with progressive neurological deterioration mainly in infancy (infantile form) and childhood (juvenile form), and rarely in adults (adult form) [2]. Morquio B disease (OMIM 253010) is another rare disease with skeletal manifestations without involvement of the central nervous system. These clinical forms are caused by different mutations of the same gene *GLB1* [3,4]. There is a correlation between the residual enzyme activity and severity of clinical phenotype, particularly the age of onset [5]. This finding led us to search for a molecular strategy to restore the apparently lost function of the mutant enzyme molecule. Soon a molecular instability was found in some mutant enzymes at relatively high environmental temperature and high pH [6,7].

Then a paradoxical phenomenon was found wherein a high amount of free galactose enhanced remarkably the intracellular mutant α-galactosidase A enzyme activity in cultured lymphoblasts from Fabry disease patients [8]. This observation was confirmed in a short-term human experiment [9]. A galactose analog 1-deoxygalactonojirimycin (DGJ) also was found to be effective in Fabry disease cells and tissues [10]. We concluded that low molecular weight competitive inhibitors could serve as chemical chaperones to induce expression of catalytic activities of mutant enzymes after stabilization and successful intracellular transport to the lysosome in somatic cells [11].

Subsequently we developed two derivatives of a newly synthesized organic compound valienamine, *N*-octyl 4-epi-β-valienamine (NOEV) and its epimer *N*-octyl β-valienamine as chemical chaperones for mutant β-galactosidase and β-glucosidase proteins, respectively, to restore the enzyme activities in somatic cells from patients with G_{M1}-gangliosidosis and Gaucher disease [12,13]. We focused our interest on NOEV for treatment and prevention of brain damage

Abbreviations: β-gal, β-galactosidase; NOEV, *N*-octyl 4-epi-β-valienamine; DGJ, 1-deoxygalactonojirimycin; WT, wild type; KO, knockout; Tg, transgenic; LC, liquid chromatography; MS/MS, tandem mass spectrometry; LLOQ, lower limit of quantification; GOT, glutamic-oxalacetic transaminase; GPT, glutamic-pyruvic transaminase; BUN, blood urea nitrogen; PBS, phosphate-buffered saline; BSA, bovine serum albumin.

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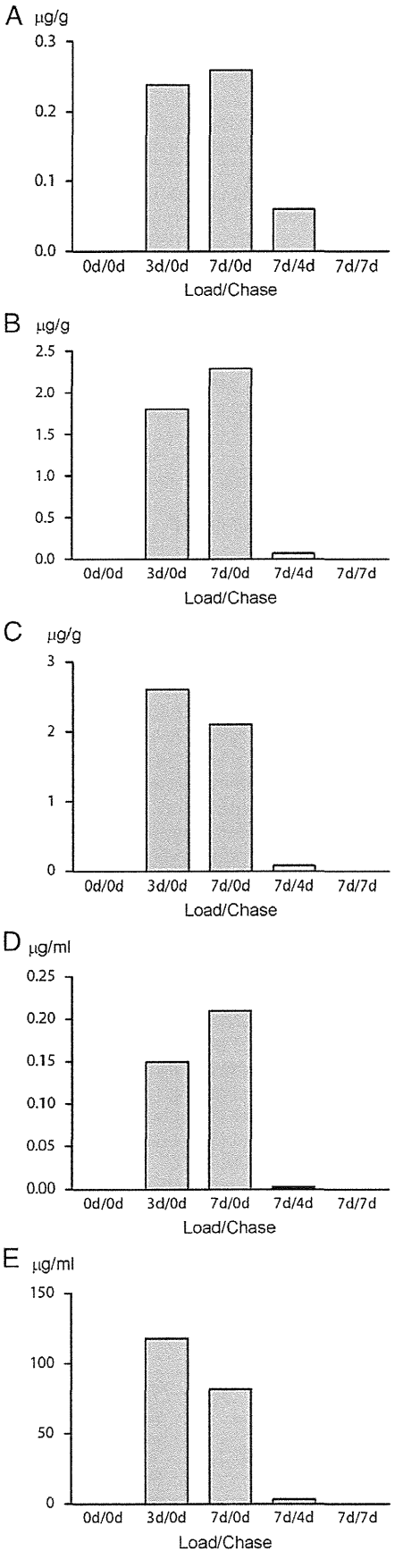

in G_{M1}-gangliosidosis, a classical neurogenetic disease in children [14]. In this article we report our experimental results of the therapeutic chaperone effect of NOEV on G_{M1}-gangliosidosis model mice. A preliminary result was published previously in a short report [15].

2. Materials and methods

2.1. NOEV synthesis and characterization

NOEV was synthesized essentially by the method described in a previous report [14]. In short, a glucocerebrosidase inhibitor [16,17] was modified by replacing the ceramide moiety with simple aliphatic chains [12,18] and multi-step epimerization at C-4 [13] to produce 4-epi-β-valienamine. In this study we used its *N*-octyl derivative, NOEV, for chaperone therapy experiments in murine G_{M1}-gangliosidosis. Its structure was assigned by a combination of COSY, TOCSY and HSQC NMR spectroscopy [14]. Then physicochemical properties were examined of molecular stability, solubility, and reactions with acids. In addition, analogous derivatives with various carbohydrate side chains were synthesized in order to evaluate relative chaperone activities.

2.2. G_{M1}-gangliosidosis model mice

We maintained a β-gal knockout (KO)-based transgenic (Tg) mouse strain overexpressing p.R201C mutant human β-gal, causing juvenile G_{M1}-gangliosidosis in humans (R201C Tg mouse; residual enzyme activity 4% of control) [14,19]. The genotype of newborn animals was confirmed by genomic analysis [14]. Wild-type (WT) mice (C57BL/6Cr) were purchased from Japan SLC (Shizuoka, Japan). The animals were kept in a temperature-controlled room (23 ± 1 °C) that was illuminated between 08:00 h. and 20:00 h. Commercial rodent chow and tap water were provided ad libitum. Body weight and fluid intake were regularly monitored.

All procedures were carried out in accordance with the Guide for Care and Use of Laboratory Animals by the National Institutes of Health, and were approved by the Animal Experiment Ethical Committees of National Institute of Biomedical Innovation, International University of Health and Welfare, Tottori University, National Institute of Neuroscience, and Seikagaku Corporation.

2.3. NOEV administration to model mice

An aqueous solution of NOEV (0.1–10 mM) was given ad libitum orally to the R201C Tg mouse. In some experiments the NOEV solution was given by gavage. The dose of daily NOEV administration was estimated by the body weight and amount of daily fluid intake. The mouse was clinically assessed regularly till the time of natural death or sacrifice followed by postmortem analysis.

2.4. NOEV determination

Tissue homogenates (20% w/v in water) were deproteinized with methanol. The supernatant was separated by centrifugation, and subjected to a combined liquid chromatography (LC) and tandem mass spectrometry (MS/MS) system (LC-MS/MS), consisting of an Agilent 1100 series quaternary pump and a thermostated column compartment at 40 °C (Agilent Technologies, Palo Alto, CA), HTS Autosampler, (Model 3133; Shiseido, Tokyo), and 4000 QTRAP mass spectrometer

Fig. 1. NOEV loading (1 mM oral, ad libitum) up to 7 days, followed by chase with water up to 7 days (WT mice, N = 2). NOEV concentrations were determined in the brain (A), liver (B), kidney (C), plasma (D), and urine (E). Each value is the mean concentration of two mouse tissues. LLOQ was 26.3 ng/ml (brain, liver, kidney), 5.25 ng/mg (plasma), or 506 ng/ml (urine). 0 d/0 d = no NOEV load, 3 d/0 d = NOEV load for 3 days without water chase, 7 d/0 d = NOEV load for 7 days without water chase, 7 d/4 d = NOEV load for 7 days followed by water chase for 4 days, 7 d/7 d = NOEV load for 7 days followed by water chase for 7 days.

(AB SCIEX, Foster City, CA). LC separation was carried out on a C18 (Atlantis dC18, particle size 5 μm; 50×2.1 mm) column (Waters, Milford, MA) with the mobile phase of methanol/10 mM ammonium formate (45/55 or 50/50, v/v). The flow rate was 0.2 ml/min, and the injection volume was 5 μl. The LC-MS/MS analyses were performed using a turbo ion spray interface and the positive ion multiple reaction monitoring mode. The lower limits of quantification (LLOQ) are indicated in Fig. 1 and Table 2.

2.5. β-Gal assay

The tissues were collected and directly frozen at −80 °C before use. β-Gal was assayed using 4-methylumbelliferyl β-galactopyranoside (Nacalai Tesque, Kyoto) [20]. Tissues were homogenized with 0.1% Triton X-100 in dH_2O. After centrifugation to remove insoluble materials, 10 μl of lysates with 20 μl of the substrate solution in 0.1 M citrate buffer (pH 4.5) was incubated at 37 °C for 30 min, and the reaction was terminated by adding 0.2 M glycine–NaOH buffer (pH 10.7). The liberated 4-methylumbelliferone was measured with a fluorescence plate reader (excitation 340 nm; emission 460 nm; Infinite F500, TECAN Japan, Kawasaki, Japan). Protein concentration was determined using a Protein Assay Rapid Kit (Wako, Tokyo, Japan).

2.6. Clinical assessment

We used three motor assessment tests in this study (Table 1): tail posture, tail suspension [21], and misstep on wire mesh to judge gripping power and strength [22]. They are easy to perform without special equipment for testing. Each test was scored into 4 grades (0–3) based on severity of abnormality. The highest total score was 9 for those with the most severe neurological abnormalities. Reliability and reproducibility of this test method were established [23]. GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA) was used for statistical analysis of two-way ANOVA (neurological course) and Gehan–Breslow–Wilcoxon Test (survival time).

2.7. Blood chemistry and urinalysis

Blood was collected by cardiac puncture in a heparinized tube, and plasma was separated by centrifugation. Urine was collected by external pressure or direct puncture of the bladder. The samples were kept frozen at −80 °C before use. Plasma was analyzed using FUJI DRI-CHEM 3000 V (Fuji Film, Tokyo) for glutamic-oxalacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactate dehydrogenase, blood urea nitrogen (BUN), creatinine, total protein, albumin, leucine aminopeptidase, alkaline phosphatase, total glyceride, total cholesterol, glucose, creatine kinase, and calcium. Urinalysis was performed using Uro-Labstix SG-L (Bayer Medical Ltd., Tokyo) for specific gravity, pH, protein, glucose, ketone bodies, urobilinogen, occult blood, and leukocytes.

2.8. General pathology and neuropathology

The animals were deeply anesthetized with diethyl ether before dissection and body fluid collection. For morphological studies, they were perfused through the heart with 4% phosphate-buffered paraformaldehyde. Then the tissues were collected for general pathology, neuropathology and immunohistochemistry [14,15].

Semi-quantitative histochemical assessment of ganglioside G_{M1} was performed as reported in a previous study [14]. Brain tissue sections were permeabilized with 0.25% Triton X-100 in phosphate-buffered saline (PBS) for 15 min at room temperature, blocked with 1% bovine serum albumin (BSA) in PBS for 1 h at room temperature, and incubated with monoclonal anti-G_{M1} antibody (clone GMB16) (Seikagaku, Tokyo, Japan) at 4 °C overnight. The sections were washed with 1% BSA in PBS 3 times for 5 min each at room temperature. They were then incubated with FITC-conjugated anti-mouse IgM, washed with PBS 3 times for 5 min each, and mounted on a slide glass [24]. Randomly selected 10 microscopic areas (500×500 μm^2) were subjected to fluorometric analysis, using Leica Confocal Software (Leica, Heidelberg) operated on the TCS SP2 confocal laser spectroscope (Leica, Wetzlar). Results of pathological examination were graded into 4 or 5 scores according to severity of findings in each tissue (Table 4).

3. Results

3.1. Physicochemical properties of NOEV

NOEV is an *N*-octyl derivative of galacto-type 4-epimer of valienamine, with N instead of O at C-1, and binding between C-1 and C-5 with C instead of O in the galactose core structure [5,13,25]. The chemical formula is $C_{15}H_{29}NO_4$ and molecular weight is 287.40.

It is an optically active unitary substance; colorless, oily, and hygroscopic; stable at dark place at room temperature and in vacuum; soluble in water, methanol, and ethanol; not soluble in chloroform. It reacts with CO_2 to form carbonate salt, and reacts with acids to form hydrochloride, sulfate, acetate, and citrate salts. The hydrochloride salt is white powder and hygroscopic. In this study we used the hydrochloride salt for all experiments. We tested compounds with carbohydrate chains of various lengths. *N*-octyl derivative showed the highest chaperone effect among them (data not shown).

3.2. Blood NOEV concentrations after single dose administration

Two different doses were given to WT mice for the time course study of blood concentrations after single gavage of 3 mg/kg (10 ml/kg) or 1.5 mg/kg (5 ml/kg) each of 1 mM free NOEV or hydrochloride salt solution (Table 2). Pharmacokinetic parameters were calculated, indicating that C_{max} and AUC were higher in the 3 mg/kg groups as compared to the 1.5 mg/kg groups. Higher water solubility of the hydrochloride salt resulted in more effective absorption as compared to free NOEV in the blood of mice in this study.

3.3. Tissue NOEV concentrations

Tissue distribution of NOEV was studied in WT mouse tissues and body fluids after short-term ad libitum oral administration of 1 mM NOEV (hydrochloride) solution (Fig. 1). NOEV was loaded for 3–7 days, followed by washout by administration of water without

Table 1
Motor assessment of G_{M1}-gangliosidosis model mice.

Test	Tail posture	Tail suspension	Misstep
Handling and observation	Rigidity and elevation	Response of hind limbs similar to parachute reflex in human infants	Stepping and walking on horizontal wire mesh for 30 s[a]
Score 0	Normal	Normal extension and abduction of hind limbs >45°,	No misstep for 30 s
Score 1	Slight elevation <20°	Hind limb abduction <45°	Misstep at 21–30 s
Score 2	Persistent elevation 20–45°	Minimal response of extension and abduction	Misstep at 11–20 s
Score 3	Persistent elevation >45°	Persistent flexion and adduction of hind limbs	Misstep at <10 s

[a] Mesh size 23.5×23.5 cm; mesh 2×2 cm.

Table 2
Pharmacokinetics of NOEV administration.

	C_{max} (ng/ml)	T_{max} (min)	$T_{½}$ (min)	$AUC_{0-\infty}$ (ng-min/ml)	AUC/D (ng-min-kg/ml/ng)	$MRT_{0-\infty}$ (min)
Free NOEV (3 mg/kg, $N=2$)	501.5	60.0	86.5	94,703	0.03	149.0
HCl salt (3 mg/kg, $N=4$)	664.0	60.0	112.3	144,037	0.05	186.5
Free NOEV (1.5 mg/kg, $N=2$)	259.2	30.0	76.0	45,996	0.03	127.1
HCl salt (1.5 mg/kg, $N=2$)	368.6	45.0	77.9	50,346	0.03	121.2

C_{max} = peak blood concentration; T_{max} = time to reach C_{max}; $T_{½}$ = elimination half-life; MRT = mean residence time; AUC = area under the blood concentration–time curve; AUC/D = AUC/dose. LLOQ = 24.6 ng/ml.

NOEV up to 7 days. NOEV was saturated in the brain, liver and kidney within 3–7 days. NOEV in these tissues and body fluids (plasma and urine) disappeared within 4–7 days after chase with water without NOEV. The level of NOEV concentration remained essentially unchanged in a small number of mice during the experimental period up to 6 months (Fig. 2). The NOEV concentration in the brain was about 10% of that in the liver and kidney. Plasma concentration remained low, and NOEV was mainly secreted in the urine after continuous NOEV administration for 6 months (data not shown).

3.4. β-Gal activity

In parallel with the NOEV concentration, β-gal activity remained stable in Tg mouse tissues during the course of NOEV treatment (1 week–6 months) (data not shown). β-Gal activity in the Tg mouse brain was enhanced to 20–25% of the WT mouse brain after treatment with NOEV for 2–5 months (Fig. 3). The enzyme activity was elevated to the normal level in the kidney, and significantly higher than normal in the liver.

3.5. Clinical effect

The NOEV treatment was started at 1–2 months after birth (Fig. 4). Dose-dependent changes of assessment scores were observed in the three Tg mouse groups in this study; 0.1 mM NOEV (low dose; $N=11$), 0.3 mM NOEV (medium dose; $N=12$) and 1 mM NOEV (high dose; $N=6$). The roughly calculated daily NOEV dose was 6.5 mg/kg/day, 20 mg/kg/day, and 65 mg/kg/day, respectively. Among the three groups, the high-dose NOEV group showed a remarkable arrest of the increase in assessment scores as compared to the water group within a few months after starting treatment. The other two groups also showed highly significant effects with less remarkable arrest of progression.

Survival time was significantly prolonged in the 0.1 mM and 0.3 mM groups as compared to the water group (Table 3). However, the 1 mM group showed no significant prolongation in spite of a remarkable clinical effect as shown in Fig. 3. Further, higher doses of NOEV administration (3 mM and 10 mM) resulted in apparently shorter survival time, but statistical analysis was not performed because of small mouse numbers.

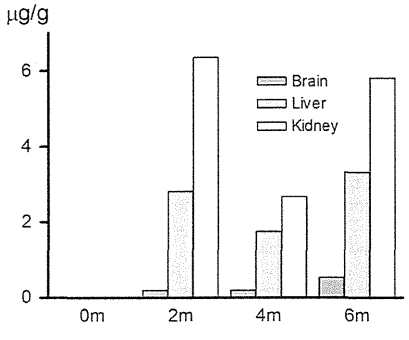

Fig. 2. Tissue concentrations during long-term NOEV treatment. R201C Tg mouse tissues (n = 2) were subjected to NOEV determination every two months as described in Section 2.4. Some variations were observed in individual samples. However, no remarkable chronological changes were noted in the brain, liver or kidney.

3.6. Blood chemistry and urinalysis

GOT and GPT were high in some WT, Tg, or KO mice with or without 1 mM NOEV treatment. They were not correlated with the genotype, clinical course, age, or NOEV treatment. BUN and creatinine,

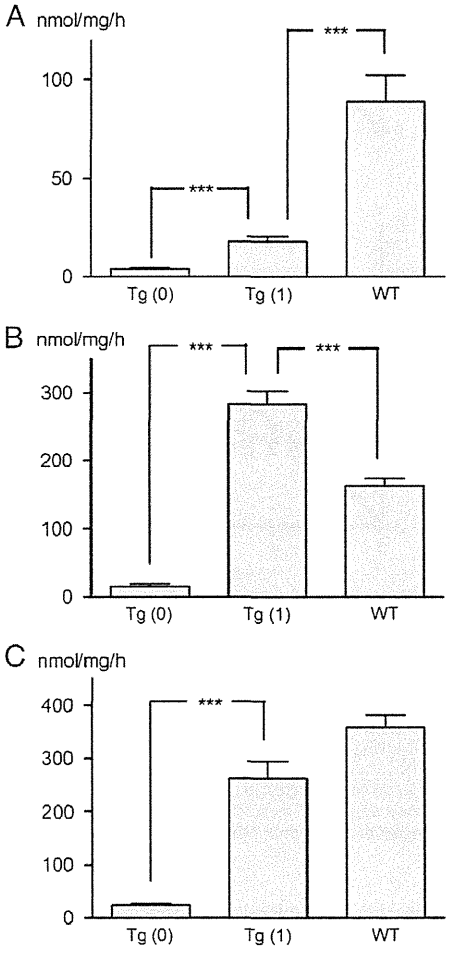

Fig. 3. β-Gal activity in the brain (A), liver (B), and kidney (C) of Tg and WT mice with or without NOEV treatment (1 mM solution orally ad libitum). Tg(0) = Tg mice without NOEV treatment (age 7–14 months, N = 8), Tg(1) = NOEV-treated Tg mice (age 7–14 months, NOEV treatment for 2–5 months, N = 8), WT = WT mice without NOEV treatment (age 7–14 months, N = 5). Each column indicates mean ± SEM. Enzyme activity is expressed as nmol of 4-methylumbelliferone/mg protein/h. Statistical analysis: p = 0.0002 for Tg(0) vs Tg(1), and p = 0.0016 for T(1) vs WT in the brain; p = 0.0009 for Tg(0) vs Tg(1), and p = 0.0043 for Tg(1) and WT in the liver; p = 0.0002 for Tg(0) vs Tg(1), and p = 0.1274 for Tg(1) vs WT in the kidney.

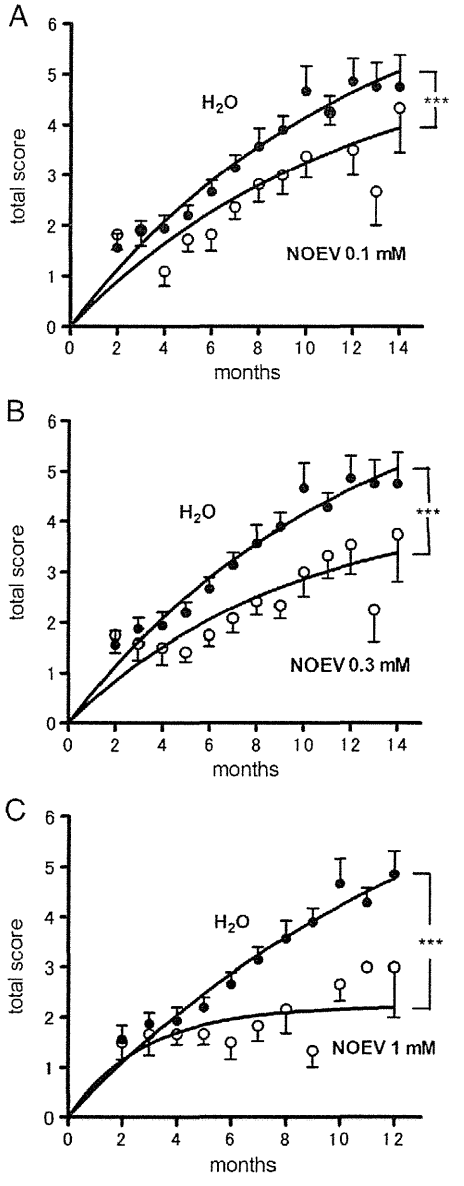

Fig. 4. Neurological assessment of NOEV-treated G_{M1}-gangliosidosis model mice (R201C Tg mice). After starting oral NOEV administration ad libitum at 1–2 months after birth, the three assessment tests were performed every month in individual mice, and total scores were recorded. The scores for each treatment group were compared with those for the non-treatment (water) group of the same age. Each value indicates mean ± SEM. Statistical analysis (two-way ANOVA) revealed $p<0.0001$ for water mice (N = 16) vs 0.1 mM (low dose) NOEV mice (N = 11) (A); $p<0.0001$ for water mice (N = 16) vs 0.3 mM (medium dose) NOEV mice (N = 12) (B); and $p<0.0001$ for water mice (N = 16) vs 1 mM NOEV (high dose) mice (N = 6) (C). NOEV dose was estimated on the basis of body weight and mean daily water intake: 6.5 mg/kg/day in 0.1 mM NOEV mice, 20 mg/kg/day in 0.3 mM NOEV mice, and 65 mg/kg/day in 1 mM NOEV mice.

urinary protein and occult blood, and other markers related to renal function were all normal (data not shown).

3.7. Pathology and immunohistochemistry

Neuronal cell degeneration was significantly improved in the mice treated with 1 mM NOEV for 2–7 months (Table 4). One case of 10 mM NOEV administration also showed a marked arrest of degeneration within 2 months of NOEV therapy. Immunohistochemical stain revealed a marked decrease in G_{M1} storage in NOEV-treated Tg mice, although the statistical analysis was not performed because of small numbers of cases (Table 4).

Table 3
NOEV effect on survival time.

NOEV	N	Survival (median)		Effect[a]
0 mM	26	5–16 m	(11 m)	–
0.1 mM	11	11–22 m	(14 m)	S(0.1) > S(0) (p = 0.0090)
0.3 mM	12	11–18 m	(14 m)	S(0.3) > S(0) (p = 0.0082)
1 mM	7	8–16 m	(10 m)	S(1) ≈ S(0) (p = 0.2102)
3 mM	3	8–10 m	(8 m)	S(3) ≤ S(0)[b]
10 mM	2	2–3 m	(2.5 m)	S(10) < S(0)[b]

R201C Tg mice on various concentrations of NOEV were compared.
S(0) = survival on water, S(0.1) = survival on 0.1 mM NOEV, S(0.3) = survival on 0.3 mM NOEV, S(1) = survival on 1 mM NOEV, S(3) = survival on 3 mM NOEV, S(10) = survival on 10 mM NOEV.
[a] Gehan–Breslow–Wilcoxon test.
[b] No statistical analysis because of small sample numbers.

General pathology showed no specific changes in NOEV-treated mouse tissues as compared to those from non-treated mice. Representative results are summarized for the liver, kidney, pancreas, and thymus (Table 4). Degeneration of hepatic cells, renal tubular cells, Langerhans cells, and thymus was observed in some mice in both treated and non-treated groups. We noticed a slight increase of tubular degeneration in the kidney of mice treated with 1 mM NOEV for 5–7 month, whereas a remarkable tubular degeneration was observed in a high-dose treatment mouse (10 mM NOEV for 2 months).

4. Discussion

G_{M1}-gangliosidosis is a relatively rare disease. The incidence was estimated to be 1:100,000–200,000 live births [26,27]. It is the 4th common sphingolipidosis in Turkey [28]. The chaperone effect is gene mutation-specific. After our report on the β-gal cDNA cloning [1], more than 160 mutations have been identified [2,27,29–31]. Mutations in G_{M1}-gangliosidosis patients are heterogeneous and complex. No ethnic prevalence has been known although some common mutations have been identified: p.R482H in Italian patients with infantile G_{M1}-gangliosidosis; p.R208C in American patients with infantile G_{M1}-gangliosidosis; p.R201C in Japanese patients with juvenile G_{M1}-gangliosidosis; and p.I51T in Japanese patients with adult G_{M1}-gangliosidosis [2]. Another mutation p.W273L is known to cause Morquio B disease [4].

Table 4
Semi-quantitative pathological scores after NOEV treatment (R201C Tg mouse).

	NOEV	0 mM	1 mM	10 mM	Score range
Neuropathology	Neuron[a]	4.80 (n = 10)	3.57 (n = 7)**	3 (n = 1)	1–5
	G_{M1}[b]	3.00 (n = 3)	1.25 (n = 4)	–	1–5
General pathology	Liver[c]	0.50 (n = 10)	0.71 (n = 7)	1 (n = 1)	0–3
	Kidney[c]	0.40 (n = 10)	0.57 (n = 7)	3 (n = 1)	0–3
	Pancreas[c]	0.20 (n = 10)	0.57 (n = 7)	1 (n = 1)	0–3
	Thymus[c]	0.30 (n = 10)	1.14 (n = 7)	2 (n = 1)	0–3

NOEV treatment (p.o., ad libitum) for 2–7 months (1 mM; age 4–11 months) or 2 months (10 mM; age 4 months). Each figure indicates the mean score in each group. **p = 0.0013 (0 mM vs 1 mM). No statistical difference or not tested in other groups.
[a] Neuronal degeneration: 0 = normal, 1 = vacuolation/degeneration <25%, 2 = vacuolation/degeneration <50%, 3 = vacuolation/degeneration <75%, 4 = vacuolation/degeneration <100%, 5 = extreme neuronal loss and gliosis/severe vacuolation and degeneration of remaining neurons.
[b] G_{M1} storage: 0 = no storage (normal), 2 = slight storage, 3 = moderate storage (TG mouse level at the end stage), 4 = high storage, 5 = extremely high storage (KO mouse level at the end stage).
[c] Liver: degeneration of hepatocytes, kidney: degeneration/dilatation of renal tubules, pancreas: degeneration of Langerhans cells, thymus: atrophy with loss of lymphocytes. Four semi-quantitative grades based on regular microscopic observations: 0 = normal, 1 = slightly abnormal, 2 = moderately abnormal, 3 = highly abnormal.

Various experimental therapeutic approaches have been reported toward G_{M1}-gangliosidosis. A thiol protease inhibitor prolonged the effect of exogenous β-gal in human G_{M1}-gangliosidosis fibroblasts [32]. The effect was enhanced when the enzyme was supplied as liposomes. Enzyme replacement of cultured cells from cats with G_{M1}-gangliosidosis was tried with the liposome-entrapped enzyme, and the storage of glycopeptides decreased [33]. Allogeneic bone marrow transplantation was performed in a Portuguese water dog affected with G_{M1}-gangliosidosis using a dog leukocyte antigen-identical sibling as donor [33]. β-Gal activity in leukocytes of the transplanted dog was similar to that in the donor. However, neither the subsequent clinical course nor the enzyme activity was modified. Beneficial effects of substrate reduction therapy were obtained in a mouse model of G_{M1}-gangliosidosis [34]. Galactose has been reported to be a potential chemical chaperone in some G_{M1}-gangliosidosis mutations as well as in Fabry disease [35].

At present no clinical therapeutic trial has been reported for G_{M1}-gangliosidosis. We have tried to develop a molecular therapeutic technology based on a new concept (chaperone therapy) toward a few lysosomal diseases as first examples [8,10,14,36]. An exogenous competitive inhibitor of a lysosomal enzyme binds to the mutant enzyme protein to form a stable complex at neutral pH of the rough endoplasmic reticulum–Golgi compartment. The enzyme-chaperone complex is safely transported to the lysosome, and dissociated under the acidic condition and in the presence of excessive storage of the substrate. The mutant enzyme remains stabilized, expressing catalytic function [5].

First we used cultured cells from Fabry patients with generalized vasculopathy [6,8,10], and then turned our attention to G_{M1}-gangliosidosis, a classic neurogenetic disease mainly occurring in infancy and childhood [14]. We started an extensive survey of chaperones for β-gal, but no commercially available compound was found to be sufficiently effective to β-gal. DGJ was effective to some extent, but we needed a much higher dose for G_{M1}-gangliosidosis than for Fabry disease [37]. Then we found a new galacto-type valienamine derivative produced by organic synthesis as a β-gal inhibitor [13]. It exhibited potent inhibitory and chaperone activities toward the human enzyme [14]. The octyl derivative NOEV showed the highest chaperone activity, and its hydrochloride salt was found to be easily soluble in water. We used the water solution of NOEV hydrochloride for subsequent experiments.

Molecular modeling of human β-gal protein was reported on the basis of *Penicillium* sp. enzyme structure with some theoretical insight on mutant proteins and enzyme–chaperone interactions [30,38,39]. Our preliminary computational calculation indicated that the binding free energy between NOEV and enzyme is higher at acidic pH in the lysosome than that at neutral pH in the endoplasmic reticulum-Golgi apparatus [5,23,38], thus suggesting that the enzyme protein is more easily dissociated from the enzyme-chaperone complex in the lysosome, stays stable, and exhibits catalytic activity. Recently three-dimensional crystal structure of the human enzyme was reported [40]. We expect that this information will further promote our understanding of chaperone biology in the near future.

After preliminary studies on culture cells, we chose 1 mM NOEV solution for chaperone therapy experiments on G_{M1}-gangliosidosis model mice [14]. Oral administration of NOEV demonstrated delivery to the central nervous system through the blood–brain barrier to enhance the β-gal activity and to reduce the substrate storage in this study as well as in previous preliminary studies [14,15] within a few days after starting oral administration. NOEV disappeared within a few days after cessation of oral administration. There was no tendency of intracellular accumulation. The data in this report suggests that NOEV is largely excreted in the urine through the kidney possibly without structural modification of the compound molecule, although its metabolites were not specifically searched for in this study.

In parallel with an increase of NOEV in neural and non-neural tissues, β-gal activity increased remarkably to normal or even higher level, particularly in the liver. The enzyme activity reached 20–25% of normal level in the brain. We have no data on the molecular mechanism of delivery of this galactose analog compound to the brain. The molecule is small in size, with both hydrophilic and hydrophobic structures, and any of the galactose transporters may well be involved in delivery through the blood–brain barrier.

For clinical assessment of the chaperone effect on experimental model mice on NOEV treatment, we developed simple motor and reflex testing methods that can be used manually without any special instruments. At first we took 11–16 different tests [23], then selected the three more specified tests avoiding overlaps of the test results in this study. Tail posture is a very sensitive sign of early brain damage (data not shown). Tail hanging demonstrated hind limb extension equivalent to a well-documented parachute reflex in normal human infants and children [21]. Further we examined missteps (formerly horizontal wire netting [15]) on a horizontally placed wire mesh. It was a sensitive method to detect abnormality in equilibrium and reflex grasping strength after the mid-stage of the disease. This is a test similar to that described by Papaioannou [22]. We calculated total scores of these three tests, which were reliable and reproducible to estimate progression of the reflex-motor aspect of the brain damage in G_{M1}-gangliosidosis mice. We did not try to evaluate the higher cortical function. In this assessment system, a relatively high dose of 1 mM NOEV treatment showed a remarkable effect for arrest of the disease progression within a few months after starting NOEV administration. Treatment of lower doses (0.1 mM and 0.3 mM) resulted in less impressive results, although all these three doses gave highly significant differences statistically as compared to non-treated mice. Neuropathology and immunohistochemistry supported these clinical findings, indicating less severe neuronal degeneration and decrease of G_{M1} storage. Early treatment was absolutely necessary to achieve such a dramatic result. Treatment at the late stage of the disease was clinically not effective. We did not start the treatment in the neonatal period immediately after birth for technical reasons to feed the water solution before weaning.

In spite of these neurological findings, effects on survival time were less remarkable particularly in the high-dose group (1 mM NOEV = 75 mg/kg/day) as compared to the medium-dose group (0.3 mM NOEV = 20 mg/kg/day) or low-dose group (0.1 mM NOEV = 6.5 mg/kg/day). In order to investigate the reason of this apparent discrepancy between the neurological effect and survival time, we analyzed carefully pathological and clinical laboratory data. Renal tubular changes were the only noticeable abnormality we could detect in general pathology in one case of very high dose NOEV treatment (10 mM NOEV = 650 mg/kg/day). This may have affected the life survival in large dose mouse groups.

In conclusion NOEV is definitely effective to prevent the progression of brain pathology at low doses, although we need to evaluate the possible subclinical adverse effect(s) on extraneural tissues in more detail, particularly on the renal tissue at high-dose treatment. Still, low-dose NOEV treatment will be sufficient to prevent disease progression of the central nervous system in G_{M1}-gangliosidosis if started early in life. Judging from the data in this study we suggest that the daily dose of 30–50 mg/kg or less will be appropriate in mice. Also intermittent administration, such as alternate day therapy, will be practically more feasible for reduction of the treatment dose, as the chaperone effect of NOEV lasts at least 2 days without supplementation. Prenatal chaperone therapy may be possible to supply the intrauterine fetus with NOEV through the placenta by its administration to the pregnant mother. There is no experimental data on this therapeutic possibility at present. We hope that chaperone therapy will be a new molecular therapy for prevention of progressive brain disease among a large number of human genetic diseases, as no effective therapy has been documented at present for any primary

neurogenetic disease. This is the first scientific approach to a rare but theoretically significant neurogenetic disease in children.

Conflict of interest

There is no conflict of interest in this work.

Acknowledgments

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原著

療育施設における医療的ケアの必要な入所児(者)および NICU 長期入院児を含む受け入れ状況等の実態調査

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要約

近年人工呼吸管理等のため NICU に長期入院児が増加している。一方療育施設でも、超・準超重症児が増加し課題も多い。そこで各療育施設での NICU 長期入院児を含む入所の受け入れ状況、人工呼吸器管理の必要な児(者)の長期・短期入所の状況等を調査し、現状と課題を明らかにした。重症心身障害児病棟を持つ国立病院機構病院 74 カ所、公法人立重症心身障害児施設 120 カ所へのアンケート調査を実施した。何らかの呼吸管理を受けている入所児(者)は、全体の 5.9% で、人工呼吸器管理を要する入所児(者) 10 名以上の施設が 33% であった。各療育施設で把握している長期入所の待機人数は、総数 971 名(小児 457 名、成人 514 名)であった。平成 19-20 年度長期入所の受け入れは 678 名で NICU 長期入院児は 74 名、小児科長期入院児 128 名であった。療育施設では待機児(者)も多く、受け入れには医療環境の差などを懸念する声も多い。さらなる受け入れには職員の確保、ハード面の整備、中間施設の検討などが必要と思われる。また具体的な地域連携の検討も重要である。

キーワード：重症心身障害児(者)、NICU 長期入院児、地域連携

Ⅰ．はじめに

近年、周産期医療の進歩に伴い乳児死亡率は著明に低下がみられたが、人工呼吸器管理などが必要なために長期に NICU に入院を余儀なくされる児が増加し、患者の QOL の低下を招いている[1)]。そういった中、新生児医療関係者の間で、NICU 長期入院時の受け入れ機関として療育施設（公法人立重症児施設ならびに指定医療機関である国立病院機構重症児病棟）への移行を希望する声も多い。しかし重症心身障害児(者)を受け入れている療育施設では、NICU 長期入院児のみならず、超重症児といった濃厚な医療的ケアが必要な入所児(者)が増加し課題も多い。そこで今回、各療育施設での NICU 長期入院児を含む入所の受け入れ状況、人工呼吸器管理の必要な児(者)の長期・短期入所の状況等を調査し、療育施設の現状と課題を明らかにした。

Ⅱ．対象と方法

重症心身障害児病棟を持つ国立病院機構病院 74 カ所(以下、国立病院機構病院)、公法人立の重症心身障害児施設 120 カ所(以下、公法人立施設)を対象に、2009 年 12 月にアンケート調査を実施した。調査項目は、1)各施設の病床数(長期入所、短期入所、医療入院)、呼吸器管理等の現状および入所待機児(者)、短期入所の実態等、2)平成 19-20 年度の NICU 長期入院児を含む重症心身障害児(者)の受け入れ状況や課題、3) NICU 長期入院児の受け入れ、中間施設の

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必要性に関する意見等。4）地域連携の状況および意見等。

なお長期入院児とは、NICU または小児科に 3 カ月以上入院していた児とした。

Ⅲ．結果

1．アンケート回答率

国立病院機構病院 35 カ所、公法人立施設 76 カ所から回答があった（それぞれ回答率 47.3%、63.3%）。

2．各療育施設の病床数

回答をいただいた施設の病床数は全体で 11,910 床。その内、国立病院機構病院では医療入院の割合が多く（8.8%）、短期入所の病床が少ない（1.2%）。逆に公法人立施設では、短期入所が多く（4.3%）、医療入院の病床が少ない（1.3%）という結果であった。

3．呼吸管理等が必要な入所児（者）の状況

図 1 のように、なんらかの呼吸管理を受けている入所児（者）は、全体の 5.9% で、SpO_2 や心拍モニターなどが必要なケースまで入れると 17.7% となる。呼吸器が 10 台以上稼動している施設は、国立病院機構病院で 7 施設（20%）、公法人立施設で 17 施設（22%）、20 台以上の施設は、国立病院機構病院 2 施設（5.7%）、公法人立施設 4 施設（5.3%）であった。一方 33 施設では呼吸器管理の必要な患者が入所していなかった。

4．長期入所児（者）待機状況

各療育施設で把握している、長期入所を希望して申請中の待機人数は、総数 971 名（小児 457 名、成人 514 名）で、その内超・準超重症児（者）は小児で 37.4%、成人で 11.3% であった。待機場所は半数以上が自宅で、NICU が 74 名、病院が 162 名だった（図 2）。

5．平成 19-20 年度 NICU 長期入院児受け入れ状況（図 3）

療育施設への長期入所の受け入れは、全体で 678 名で、このうち詳細なデータが得られた 646 名を分母とすると、NICU 長期入院児は 11.6%（74 名）、小児科長期入院児が 20.6%（128 名）であった。超・準超重症児の割合は、NICU 長期入院児で 76.0%、小児科長期入院児で 71.4%、その他が 21.6% となり、NICU 長期入院児および、小児科長期入院児は、その他の入所児に比べ超・準超重症児が多かった。

6．NICU 長期入院児受け入れに何が必要か

新規に呼吸器管理の患者を受け入れることが可能かという問いに対し、111 施設中 53 施設が呼吸器を使用していても受け入れ可能と回答があった（国立病院機構病院 19 施設 52.8%、公法人立施設 34 施設 44.7%）。しかし逆にいうと 58 施設では人工呼吸器管理を要する患者の受け入れは現時点では難しいということである。また NICU 長期入院児の受け入れを進めていくうえで、療育施設側として何が必要かを聞いたところ、図 4 のように全体では、医師看護師不足の改善が、54 施設と最も多かった。また医療機器不足の改善 36 施設、診療報酬改善 31 施設など

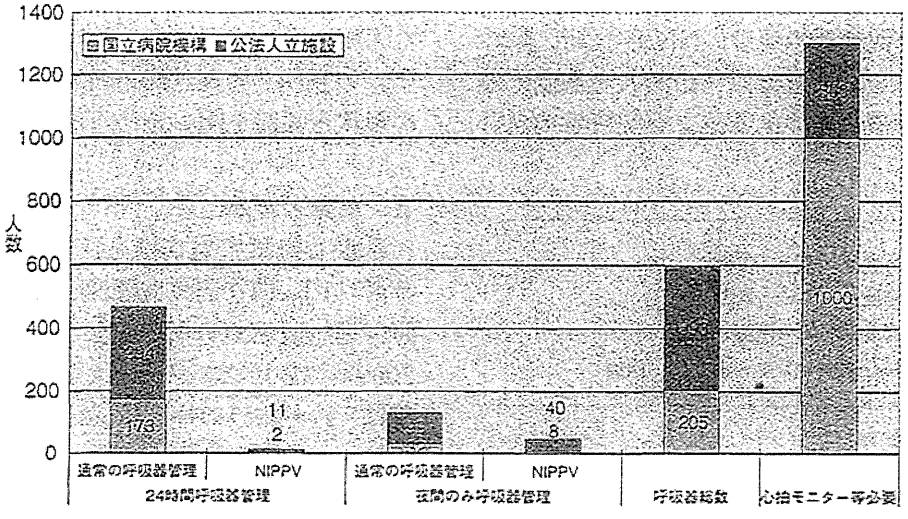

図 1　療育施設入所中の呼吸器管理の必要な入所児（者）

療育施設に入所中で、何らかの呼吸管理を受けているケースは、全体の 5.9% で、パルスオキシメーターや心拍モニターなどが必要なケースまで含めると 17.7% となる。

も多かった。連携関連では、急変事の後方施設を求める意見が51施設と最も多く、ついでNICU等との連携・情報交換40施設、中間施設後の受け入れ33施設となっている。また在宅・地域移行関連では、家族の理解・協力が42施設と多かった。施設への移行前に病院(NICU)側に何を望むかという問いには、移行のメリット・デメリットにつき十分に説明をお願いしたい、急変事の受け入れ、将来の見通しを説明して欲しい、十分な情報交換、施設の現状を理解して欲しい、病院(NICU)での同席しての面接や回診など、連携に関連する項目が多かった(図5)。

7. 短期入所の現状

平成19-20年度の療育施設での人工呼吸器管理が必要な患者の短期入所受け入れ状況をみてみると、図6のように、約半数の施設が受け入れをしている。延べ50名以上受け入れている施設は、平成19年度

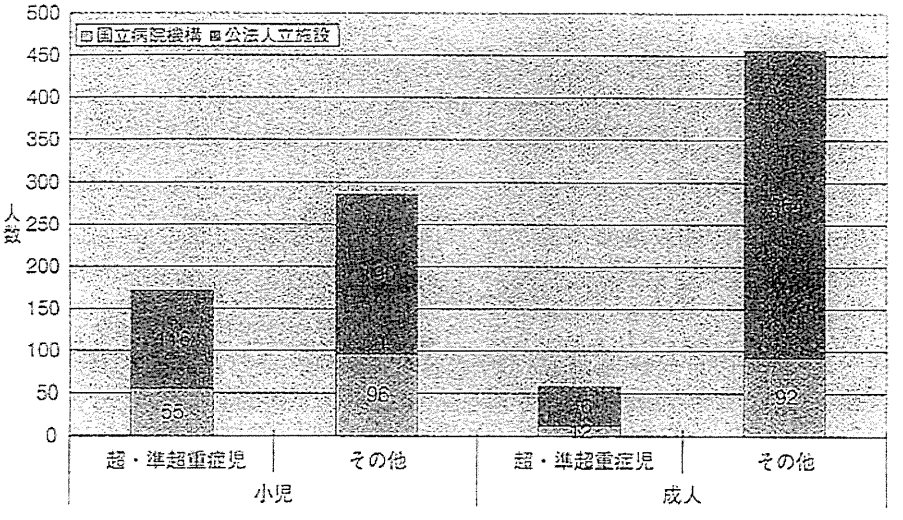

図2 入所待機児(者)人数

療育施設で把握している、長期入所の待機人数は、総数971名(小児457名、成人514名)で、その内、超・準超重症児(者)は小児で37.4%、成人で11.3%であった。待機場所は半数以上が自宅で、NICUが74名、病院が162名だった。

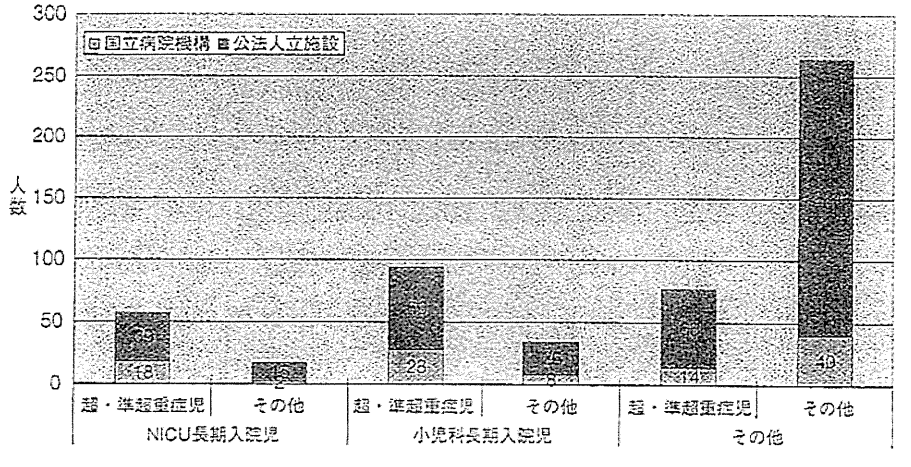

図3 平成19-20年度長期入所受け入れ実績(療育施設)

療育施設への長期入所の受け入れは、全体で678名で、このうち詳細なデータが得られた646名を分母とすると、NICU長期入院児は11.6%(74名)、小児科長期入院児が20.6%(128名)であった。超・準超重症児(者)の割合は、NICU長期入院児で76.0%、小児科長期入院児で71.4%、その他が21.6%となり、NICU長期入院児および、小児科長期入院児は、その他の入所児に比べ超・準超重症児が多かった。

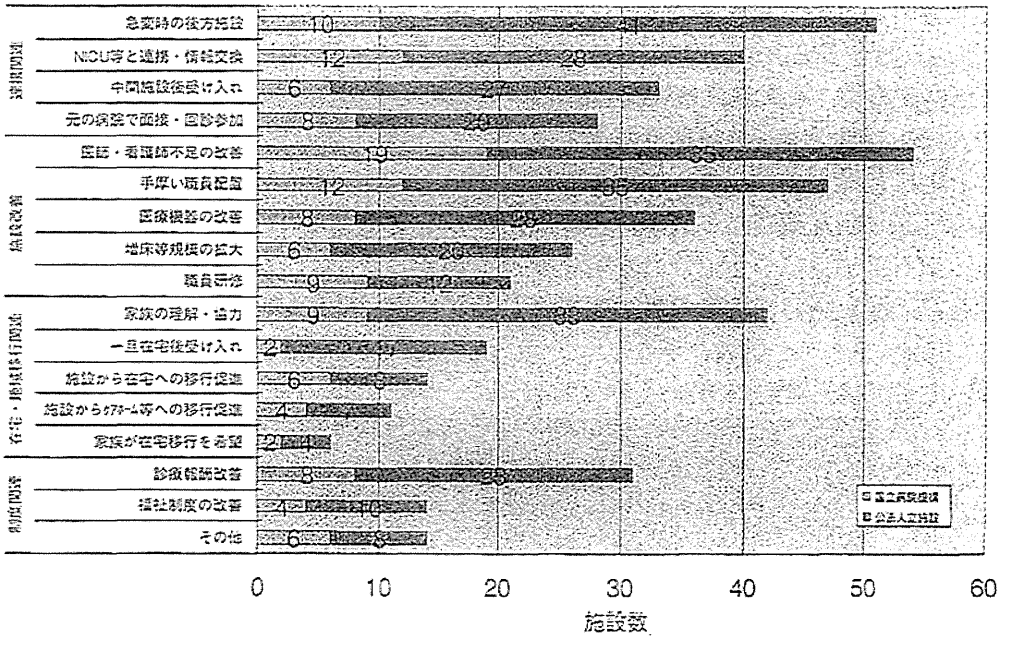

図4　NICU長期入院児受け入れに何が必要か

NICU長期入院児の受け入れを進めていくうえで、療育施設側として何が必要なのかを聞いたところ、全体では、医師・看護師不足の改善が一番であった。また医療器機不足の改善、家族の協力理解、診療報酬改善などを望む声も多かった。地域連携関連では、急変事の後方施設、NICU等との連携・情報交換、中間施設で受け入れ後に移行等が多かった。

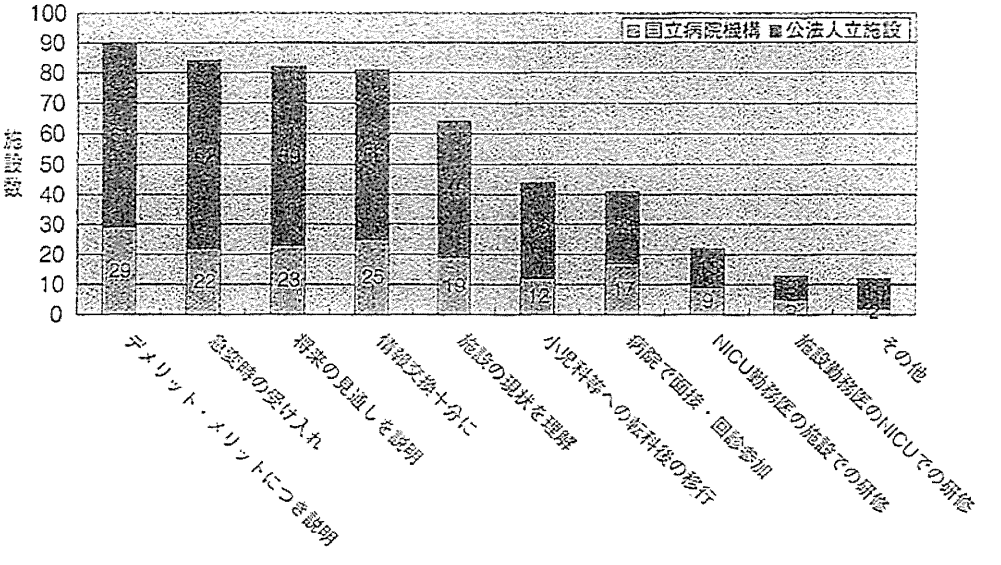

図5　療育施設への移行前に望むこと

施設への移行前に病院（NICU）側に何を望むかという問いには、移行のメリット・デメリットにつき十分に説明をお願いしたい、急変事の受け入れ、将来の見通しを説明して欲しい、十分な情報交換、施設の現状を理解して欲しい、病院（NICU）での同席しての面接や回診など、連携に関連する項目が多かった。

は7施設であったが、20年度は12施設と増加してきている。しかし受け入れがないという施設も半数近くあった。受け入れが困難な理由としては、長期入所の受け入れ困難な理由と同様、看護師・医師不足が一番で、2番目には、ベッドが足りない、また医療器材が不十分などであった。短期入所の給付費が不十分という意見も19施設からあった。人工呼吸器管理を受けている患者の短期入所利用の動向としては、徐々に増加していると答えた施設が多く、希望通りの受け入れは難しいと答えている。

8. NICU長期入院児の受け入れ先として療育施設が期待されていることについて

役割の重要性やニーズは理解している、その児にあった療育の場の提供と考えているという肯定的な意見があった。しかし環境や医療レベル(ハードやソフト面)の違いを認識しないと危険、急変事の後方支援が必要、ご家族の理解、ご家族との連携が必要などの意見も多かった。一部では、空床がないので困難、在宅を目指すなら中間施設を考えた方が良いという意見もあった。また重症度に応じた対応を考えるべきという意見もあった。

9. 中間施設に対する意見

NICUと療育施設では医療レベルや環境が違いすぎるので、小児科病棟などの中間施設で状態を安定させ、またご家族にも状況を理解していただき、その後療育施設に移行するのが良いという意見が多数であった。また中間施設の役割の検討が必要という意見もあった。

10. 地域連携

地域連携については、何らかの地域連携をしていると答えた施設が、国立病院機構病院で54%、公法人立施設で56%であった。また地域連携をすることで在宅移行が進むかという問いには2/3の施設で「はい」と答えている。

Ⅳ. 考察

平成20年度厚労省科研費補助「重症新生児に対する療養・療育環境の拡充に関する総合研究」の報告書で植田は、NICU長期入院児(1年以上NICU、GCUに入院)年間の発生数は、全国で約220例と推定している。長期入院児の基礎疾患の内訳をみると、先天異常、新生児仮死、染色体異常、神経・筋疾患などが多く、早産児は長期入院になっても在宅に帰れる可能性が高いとしている[2)]。長期入院児は基礎疾患でわかるようにほとんどが重症心身障害児であり、そこで新生児施設側からは在宅に帰れないケースについて地域の療育施設への入所を期待する声もある。また前田らは、新生児病床長期入院児と重症心身障害児施設入所している就学前の児でQOL評価を行い比較し、いずれの項目も重症心身障害児施設で

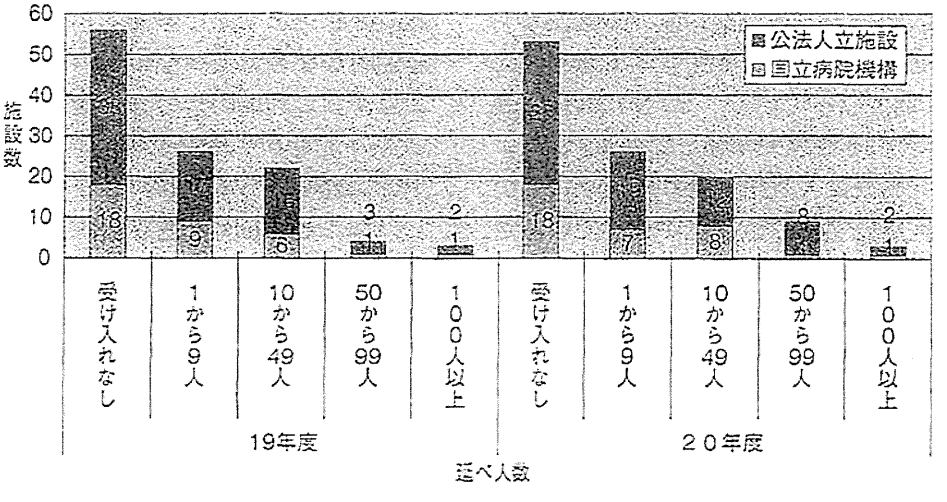

図6 呼吸管理の短期入所受け入れ

平成19-20年度療育施設での人工呼吸器管理が必要な患者の短期入所受け入れ状況をみてみると約半数の施設が受け入れをしている。延べ50名以上受け入れている施設は、平成19年度は7施設であったが、20年度は12施設と増加してきている。

QOL 評価点が有意に高値だったという調査結果を報告し、重症心身障害児施設には、施設内にとどまらず新生児医療施設や在宅の QOL 向上に専門的な見地から指導的役割を果たすことが期待されると述べている[1]。それでは、療育施設の状況はどうであろうか。今回の調査では療育施設において把握している長期入所の待機児(者)数は 971 名であった。東京、大阪市、横浜市などでは待機児は児童相談所が管理していてこの数には含まれていないことや、回答率を考えると、全国では最低でも 3,000 名はいるのではないかと推測される[3]。このように待機児(者)が多く、経験上 NICU や小児科長期入所児よりも在宅にいて困っている方たちを優先せざるを得ない場合も多々ある。さらに療育施設の入所児(者)や、在宅での重症心身障害児(者)の問題の一つとして、高齢化がある。加齢とともに機能が低下してくることが報告されており、嚥下機能の低下により、経管栄養になったり、呼吸機能の悪化のため気管切開を要し、さらに人工呼吸管理となることもある[4]。このように加齢とともに医療的な重症度が増加することが入所児(者)の重症度の増加につながり、またこの高齢化により入所となるケースも多いことが推測される。

平成 19-20 年度に新たに療育施設へ長期入所となったのは 678 名で、その内、NICU 長期入院児は 74 名で、小児科長期入院児が 128 名である。この 2 つを合わせると全体の新規入所児(者)の 32% となる。また NICU や病院からの入所受け入れが進むにつれ、療育施設内に人工呼吸器管理・酸素投与や、モニター管理が必要なケースが増えてきており、入所児(者)の 20% 弱となっている。また約 20% の施設では人工呼吸器が 10 台以上稼動している。このように NICU、小児科長期入院児を受けていくことで多くの施設では入所児(者)の重度化が進んでいるが、一方 33 施設では人工呼吸器管理の必要なケースの入所はなく施設間での差がある。また約半数の施設では、新たな人工呼吸器管理の必要な患者の受け入れは困難としており、現在呼吸器管理をしている施設でも、手一杯になっていることがうかがえる。

NICU 長期入院児の受け入れが困難な理由で最も多かったのは、看護師不足、医師不足である。この問題は療育施設では大きな課題となっており、看護基準でも 7：1 がとれる施設は数少なく、10：1、13：1 がほとんどである。医師は絶対数も少ないが、小児科の常勤医師がいない施設さえある[5]。このような状況は療育施設に携わっていなければ医療関係者の間でもなかなか理解されていないだろう。人工呼吸器を行っている患児を受け入れるには十分な看護師・医師の配置、モニター・検査機器などの医療器材、重度の患者のケアに適した病棟の構造などが必要で、どの施設でも受け入れが可能ということではない。また家族の理解が必要という意見も 42 施設と多かったが、NICU と療育施設の違いや患者の状況を、家族が十分に理解されていないまま施設へ移行になりトラブルになるというケースが少なくない。家族とのトラブルについて家室は、NICU から直接入所してきた群の死亡率は間接的に入所してきた群に比べ高く(11/16=69%)、その医療的重症度は想像以上であり保護者対応は困難をきわめた、また保護者とのトラブルは NICU と同等の医療を望み、リハビリを始め療育に過大の期待をしていたことにある、と述べている[6]。今回のアンケートで家族の理解・協力の項目の自由記載としては、呼吸器管理重症児のリスクや予後について NICU 側からもご家族に十分理解してもらえる説明があって、療育施設との役割に違いを理解した上での受け入れが必要、医療レベルの違いや、死亡リスクなどについても説明が必要などの意見があった。また家族の障害受容や、医療的に重度であるという認識があることという意見もあった。家族とのトラブルが発生する原因は、家族に施設への移行を説明する NICU 関係の医療者側も施設の状況を十分に理解できていない、または十分な説明がなされていないということも原因であろうと思う。これは図 5 の療育施設への移行前に望むこととという問いで、移行のメリット・デメリットにつき十分に説明をして欲しいという施設が一番多かったということからも、施設側が家族の理解や協力がとても重要であると認識していることがうかがわれる。このような事実を NICU 関係者などとの連携の中でうまく伝えていくことも今後重要となってくる。連携に関連しては、急変事の後方施設を求める意見が最も多く、ついで NICU 等との連携・情報交換、中間施設後の受け入れという順番であった。急変時にすぐに転院できるということは ICU 的な機能を持たない療育施設で NICU 退院後の濃厚な医療を必要とする患者をみていく上でとても重要な条件である。これらの項目は、地域の中で、NICU や地域中核病

院などとの連携や相互理解、情報交換などを進めていく重要性を示唆している。

在宅で人工呼吸器管理などの濃厚な医療的ケアを受けている患者数は増加してきている[7]。そのような子を抱える家族には短期入所などの在宅支援が必要である。しかし人工呼吸器管理が必要な患者の短期入所での受け入れは約1/4の施設が難しく、これも施設間で大きく差がある。短期入所は自立支援法下の制度で費用は給付費のみとなるが、人工呼吸器管理などが短期入所中に必要となると、現在の給付費の点数では見合っていない[3]。短期入所の費用を福祉部分と医療の部分で請求できるように見直しが必要と考える。

さらに短期入所で気をつけておかなければいけないのは、短期入所の際には、在宅から施設という、大きな環境の変化が起こるため、体調を崩すことも少なくないということである[8)9]。短期入所にはこのようなリスクも含まれていることを、家族も含め関係者はよく認識しておく必要がある。

NICU長期入院児の受け入れ先として期待されていることにつき療育施設としては、そのニーズは理解しており、QOLを考えると施設の方が適しているという意見もあるが、NICUとは医療環境（ハード、ソフト面ともに）の違いがあり、NICUから療育施設への直接の移行は難しいと考えている施設も多い。そのため、病院と福祉施設の中間の性格を持つ中間施設の必要性には、肯定的な意見が多い。たとえばNICUから同じ病院の小児科に一度移り、環境の違いにも慣れた頃に施設への移行を考える方がリスクも少ない。一旦療育施設に移行した後に、急変した際の後方支援を考えると小児科の協力も必要になる。また重度の障害を持っている児は、いろいろな合併症を併せ持つことが多い。療育施設では小児科、内科、精神科の医師がほとんどであり、他科の合併症の治療は難しいことも多い。これらの合併症への対応も療育施設に移行する前に、総合病院などである程度治療が済み、また何かあればそこで診てもらえる体制を確保しておきたい。地域中核病院へのアンケートでは、在宅移行後の急性増悪時の一時的な呼吸管理が可能かという問いに約1/3の病院が可能と答えている。条件付も含めると2/3が可能ということでありこれらの病院は中間施設となりうるかもしれない[10)11]。しかし中間施設という言葉は、これまで具体的にどういう施設を指すのか中身が十分に検討されておらず、定義もはっきりしない。今後、議論を進めていく上でさらに検討が必要である。

地域連携については、半数以上の施設で行っており、また在宅移行には有用と考えている施設が多い。地域の中でネットワークを構築したり、また訪問看護や相談支援専門員の相談支援・コーディネート機能を中心にした地域のネットワーク作りを行っている地域もみられる[12～14]。今後このような地域での取り組みを全国に拡げていくことも必要かと考える。

NICUや小児科から療育施設への入所は、医療的ケアの状況や、ご家族の事情により、必要となるであろうが、家族の絆の形成を考えると、在宅に帰れる可能性のある児は、一度は家族の下に帰り、家族と一緒に暮らす機会を持てると良いと思う。その児の状態や家族の状況に合わせ、在宅、中間施設、療育施設など、その児に最も適した環境や生活を、地域の中で支援していくシステムを、NICU、療育施設、地域の病院・診療所や訪問看護ステーションなどの関連機関、行政などの機関が連携し、役割分担を図り作り上げていくことが、その患者や家族にとり、療養環境の拡充や、充実につながると考える。

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Research on admission of the persons with severe motor and intellectual disabilities (SMID) depending on medical cares, including the children with prolonged hospitalization in NICU wards to residential hospitals for persons with SMID.

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The number of children admitted to NICUs for long-term hospitalization to receive artificial respiration and other treatments is on the rise. More and more children with severe or profound disabilities are being admitted to residential hospitals for SMID, bringing greater challenges. We investigated the acceptance circumstances for admission to each residential hospital for SMID including of children admitted to NICUs for long-term hospitalization and long- and short-term admission of patients who are dependent on artificial respiration, in order to clarify the actual situation and challenges. Questionnaires were administered to 74 hospitals run by the National Hospital Organization that had a ward for children (people) with SMID and 120 public and private residential hospitals for patients with SMID. A total of 5.9% of all patients admitted required some types of respiratory assistance, and 33% of facilities had 10 or more children (people) admitted who were dependent on artificial respiration. A total of 971 people (457 children and 514 adults) were on the waiting list for long-term admittance to a facility according to residential hospitals. A total of 678 patients were admitted to residential hospitals for long-term hospitalization during FY2007-2008, including 74 long-term hospitalized children in NICUs, and 128 children in pediatrics wards. There are many patients on the waiting list for admittance to residential hospitals, and many people expressed concern about differences in the quality of the healthcare environment even if admitted. To increase the acceptance rate, there is a need to procure more staff and consider equipment and facilities as well as transitional facilities. Concrete plans for regional cooperation must also be considered.