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Intractable itch relieved by 4-phenylbutyrate therapy in patients with progressive familial intrahepatic cholestasis type 1

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Abstract

Background: Progressive familial intrahepatic cholestasis type 1 (PFIC1), an inherited liver disease caused by mutations in *ATP8B1*, progresses to severe cholestasis with a sustained intractable itch. Currently, no effective therapy has been established for PFIC1. Decreased function of the bile salt export pump (BSEP) in hepatocytes is suggested to be responsible for the severe cholestasis observed in PFIC1. We found a previously unidentified pharmacological effect of 4-phenylbutyrate (4PB) that increases the expression and function of BSEP. Here, we tested 4PB therapy in three patients with PFIC1.

Methods: The therapeutic potency of 4PB in these patients was tested by oral administration of this drug with gradually increasing dosage (200, 350, and 500 mg/kg/day) for 6 months. Biochemical, histological, and clinical data were collected.

Results: 4PB therapy had no beneficial effect on the patients' liver functions, as assessed by biochemical and histological analyses, despite an increase in hepatic BSEP expression. However, therapy with 4PB at a dosage of 350 or 500 mg/kg/day significantly relieved the intractable itch. Serum levels of potential pruritogens in cholestasis were much higher than the reference ranges during the 4PB therapy.

Conclusions: 4PB therapy may be a new medication for patients with intractable cholestatic pruritus and may improve quality of life for patients and their families.

Keywords: Pediatric liver disease, Cholestasis, PFIC1, Pruritus, 4PB

Background

Progressive familial intrahepatic cholestasis type 1 (PFIC1), a rare inherited autosomal recessive liver disease caused by mutations in *ATP8B1*, is characterized primarily by normal serum gamma-glutamyl transferase (GGT), intrahepatic cholestasis and jaundice in the first year of life [1]. This disease progresses to severe cholestasis with sustained intractable itching, jaundice, watery diarrhea, failure to thrive, pancreatitis, and deafness, resulting in liver failure and death before adulthood [2]. The main complaint in the clinical course of patients with PFIC1 is often intractable itching, which significantly disrupts the patients' ability to sleep and thus decreases the quality of life of patients and their families [3]. No effective medical therapy for this disease is currently available [3]. Even liver transplantation is insufficient to improve the clinical course and outcomes of patients with PFIC1 because of steatosis and fibrosis [4].

ATP8B1 is a member of the P4 subfamily of P-type adenosine triphosphatases and is expressed on the apical membrane of many epithelial cells including hepatocytes. ATP8B1 translocates phosphatidylserine (PS) from the outer leaflet to the inner leaflet and thereby contributes to

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making the hepatocanalicular membrane (CM) a rigid, liquid-ordered membrane [5,6]. In patients with PFIC1, the well-organized aminophospholipid asymmetry of the CM is disrupted by the impaired function of ATP8B1, leading to a decrease in the transport activity of the bile salt export pump (BSEP), an ABC transporter that is localized on the CM and that predominantly mediates biliary excretion of bile salts [7-10], and subsequently to the onset of severe intrahepatic cholestasis [11]. Alternatively, in patients with PFIC1, nuclear translocation of the farnesoid X receptor (FXR), a transcription factor that controls bile acid homeostasis, is disrupted and causes a decrease in BSEP expression at the CM because of mass action related to the decreased expression of BSEP mRNA [12]. Therefore, in either cause of PFIC1, an increase in BSEP function is expected to compensate for the reduced capacity for bile salt excretion into bile in patients with PFIC1, and may improve their liver function.

We have published experimental evidence that 4-phenylbutyrate (4PB), a drug used to treat ornithine transcarbamylase deficiency (OTCD), has another newly identified pharmacological effect that increases the hepatocanalicular expression of BSEP and the hepatocyte capacity for biliary excretion of bile salts when given at a clinically relevant concentration in OTCD patients [13]. The higher BSEP expression level in liver specimens from patients with OTCD after 4PB therapy compared with that before 4PB therapy suggests that 4PB treatment increases BSEP expression in humans [14]. Furthermore, our group and Gonzales *et al.* reported recently that 4PB therapy restored decreased BSEP expression, improved liver functions in histological and biochemical analysis, and relieved intractable pruritus in patients with PFIC type 2 (PFIC2), an inherited autosomal recessive liver disease caused by mutations in *BSEP* [15,16]. PFIC2 patients present with similar clinical symptoms and biological parameters as PFIC1 patients [17,18]. Together, these results suggest the possibility that 4PB may be a potential therapeutic compound for PFIC1 patients that could act to restore the reduced capacity of biliary excretion of bile salt through increasing BSEP expression on the CM.

To test this hypothesis, our current study investigated the effects of 4PB therapy in three PFIC1 patients. 4PB was administered orally with gradually increasing dosage (200, 350, and 500 mg/kg/day) for 6 months. We collected data on serum liver tests, histological analyses, pruritus score, and the clinical course for these patients.

Methods

We obtained approval for the study from the institutional ethics review boards. Informed consent was obtained from the patients' parents before assessment because the patients were younger than 18 years of age. A detailed description of the materials and methods is presented in the Additional file 1. All materials and methods used standard techniques and commercially available reagents.

Patients

The patients enrolled in our study were three Japanese boys (Patient 1, 2, and 3) who were seen at Osaka University Hospital in 2012 and aged 2-, 6-, and 16-years old, respectively. All three patients developed hepatocellular cholestasis with mild elevation of serum aspartate aminotransaminase (AST) and alanine amino transaminase (ALT) levels and normal GGT levels as infants and experienced sleep disturbance because of intractable itch at around 4, 6, and 4 months of age, respectively. Patient 3 had difficulty in getting to sleep by the end of elementary school. Despite treatment with drugs including ursodeoxycholic acid, topical steroids, and antihistamine agents for 1.5, 5, and 15 years in patient 1, 2, and 3, respectively, these patients continued to experience severe cholestasis with sustained intractable itch, jaundice, diarrhea, and failure to thrive, which are typical clinical symptoms of PFIC1. The patients and/or their families preferred medical treatment to surgical procedure like partial external biliary diversion. Therefore, the patients were enrolled in this clinical study. The administration of original drugs was maintained during and after the course of 4PB treatment. The drugs given to the patients before, during, and after the course of this study are listed in the Additional file 1: Table S1.

Sequence analysis of *ATP8B1* and *ABCB11*

Genomic DNA was isolated from peripheral blood leukocytes using a Wizard Genomic DNA Purification Kit (Promega, Madison, WI), and all exons of *ATP8B1* and *ABCB11* and flanking intron–exon boundaries were analyzed as described previously [16,19,20].

Treatment of PFIC1 patients with 4PB

Oral administration of 4PB (Ammonaps; Swedish Orphan Inter AB., Stockholm, Sweden) was started at a daily dosage of 200 mg/kg/day divided into four doses a day. After 1 month, the dosage was increased to 350 mg/kg/day and this was maintained for an additional month. Because neither a therapeutic effect nor any side effects were observed, the dosage was increased to 500 mg/kg/day, which is the clinically relevant dosage for OTCD, and this dosage was maintained for the next 4 months. A liver biopsy sample was collected 1 day before and after the course of 4PB treatment. A part of the sample was preserved in RNAlater (Qiagen, Hilden, Germany) for RNA preparation and stored at −20°C. Another portion was fixed in 10% formaldehyde at room temperature for

histological analysis, and the remaining portion was snap-frozen in liquid nitrogen for preparation of membrane fractions and stored at −70°C in a deep freezer. Serum was collected before, during, and after the course of 4PB treatment. Liver function tests were performed using standard methods immediately after collection, and the remaining specimens were preserved at −70°C for further analysis.

Pruritus evaluation

Pruritus severity was scored as reported previously [21]: 0, none; 1, mild scratching when undistracted; 2, active scratching without abrasion; 3, abrasions; or 4, cutaneous mutilation, with bleeding and scarring.

Quantitative determination of pruritogen levels in serum

The concentration and activity of autotaxin (ATX) in serum were assessed using a specific two-site enzyme immunoassay and the measurement of choline liberated from the substrate lysophosphatidylcholine as described previously [16,22].

Histological analysis of the patients' liver specimens

Liver biopsy specimens were fixed in 10% formalin and embedded in paraffin. Four-micrometer-thick sections were prepared from the liver specimens and subjected to hematoxylin-eosin (HE) staining and immunohistochemistry followed by microscopic analysis with an Olympus CX41 or Olympus BX40 microscope (Olympus, Tokyo, Japan) to evaluate the degree of cholestasis, fibrosis, and inflammation in the liver tissues.

Preparation of crude membrane, nuclear, and cytosolic fractions from the patients' liver specimens

Liver specimens from the patients were homogenized in hypotonic buffer (1 mM EDTA, 5 mM sodium phosphate, pH 7.0) supplemented with protease inhibitor cocktails (Sigma-Aldrich, St. Louis, MO) using a QIAshredder (Qiagen), and then centrifuged at 800 × g for 10 min at 4°C. The supernatant was ultracentrifuged at 100,000 × g for 1 h at 4°C and the pellet and supernatant were used as the crude membrane and cytosolic fractions, respectively. After centrifugation at 800 × g, the pellet was suspended with high salt buffer (20 mM Tris–HCl pH 7.9, 400 mM NaCl, 0.1 mM EDTA, 0.1 mM EGTA Na, 0.1% NP-40, 1 mM DTT, 10% glycerol, 0.1% protease inhibitor cocktail), incubated on ice for 50 min with vortex mixing every 10 min, and centrifuged at 3000 × g for 10 min at 4°C, and the supernatant was used as the nuclear extract.

Immunoblotting

Specimens were loaded into each well of a 7% SDS-PAGE plate with a 3.75% stacking gel, and subjected to immunoblotting as described previously [13,14,23]. Immunoreactivity was detected with an ECL Advance™ Western Blotting Detection Kit (Amersham Biosciences, Piscataway, NJ). The intensity of the band was quantified by MultiGauge software (version 2.0; Fujifilm, Tokyo, Japan). Expression levels of ATP8B1, BSEP, and CDC50A were normalized by the expression of Na^+, K^+-ATPase α1 subunit (NaKα1), which was not affected by the treatment with 4PB (data not shown).

Results

Diagnosis of PFIC1 in the patients

Sequencing analysis of all encoding exons and flanking intron–exon boundaries of *ATP8B1* identified a heterozygous mutation c.3033–34del (frame shift or splicing defect) in patient 1 and a heterozygous mutation c.1587–89del (p.F529del) in patient 2 (Table 1). The c.1587–89del (p.F529del) mutation has been reported previously in European PFIC1 patients of Caucasian descent [19]. Although no other mutations were found in *ATP8B1* on the other allele, as was the case for several PFIC1 patients reported in a previous study [19], both patients were diagnosed with PFIC1 because they exhibited the typical clinical symptoms of PFIC1 and because of the low mRNA expression and no detectable protein expression of ATP8B1 in their liver biopsy specimens (Figure 1A, B). The near absence and marked decrease of hepatic ATP8B1 mRNA in patients 1 and 2 may be explained by other mutations in the promoter region and/or untranslated region (UTR) of *ATP8B1* on the other allele that affect transcription of *ATP8B1* and/or stabilization of ATP8B1 mRNA. Patient 3 was diagnosed with PFIC1 because of lower mRNA and protein expression of ATP8B1 in his liver specimen (Figure 1A, B) and because of his clinical symptoms including intrahepatic cholestasis with normal GGT, intractable itching, failure to thrive, and deafness. The sequencing analysis of *ATP8B1* in patient 3 identified c.234C > G (p.H78Q) (rs3745079) and c.2021 T > C (p.M674T) (rs35470719) mutations on one allele and a mutation c.1729A > G (p.I577V) (rs3745078) on the other allele. However, given that these mutations had no significant effect on mRNA and protein expression, trafficking to the plasma membrane, and PS flippase activity of ATP8B1 in *in vitro* studies (Additional file 2: Figure S1 A–D), it is likely that the decreased mRNA and protein expression of ATP8B1 in this patient is caused by mutations in the promoter region and/or UTR of *ATP8B1* that affect transcription of *ATP8B1* and stabilization of ATP8B1 mRNA, but not by the mutations analyzed in this study.

Therapeutic effect of 4PB in PFIC1 patients

During the period of 4PB treatment, no improvement was observed in liver function tests for any of the patients (Figure 2). However, their itching started to attenuate in patient 1 three weeks after the dosage of 4PB

Table 1 ATP8B1 mutation and biochemical parameters in patients enrolled in this study

	Sex	Age	*ATP8B1* mutation in allele 1	*ATP8B1* mutation in allele 2	AST/ALT/GGT (U/L)	T-Bil/D-Bil/BA (μM)	Pruritus score
Patient 1	M	2	c. 3033-3034del (Frame shift)	Not found	83/60/36	4.8/4.6/301.3	4
Patient 2	M	6	c.1585-1587TTCdel (p.F529del)	Not found	81/15/27	3.4/3.2/214.1	4
Patient 3	M	16	c.234C > G (p.H78Q) c.202IT > C (p.M674T)	c.1729A > G (p.I577V)	63/51/19	0.6/0.3/54.6	4

was increased to 350 mg/kg/day, in patient 2 one week after the dosage was increased to 500 mg/kg/day, and in patient 3 four weeks after the dosage of 4PB was increased to 350 mg/kg/day. The itching score declined from 4 to 2 in all patients (Figure 3A, B). Although there were multiple dark erosions in the skin of all patients and elephantiasis in patient 3 due to intense and continual scratching, after the onset of 4PB treatment at the dosage of 350 or 500 mg/kg/day, the frequency and intensity of skin scratching was markedly decreased, leading to diminished skin erosion and hemorrhage and improved skin appearance (Figure 3C). At the end of the therapy, hemorrhage and eschar on the patients' skin were diminished and areas of fresh normal skin were evident. The parents of the patients noted an improvement in sleep disturbance during the night and in their child's skin condition. In contrast to the relief of the itching, the serum levels of bile acids and ATX and of ATX activity, all of which have been proposed as potential pruritogens in cholestasis [24], were not decreased by 4PB therapy in any of the patients (Figures 2B, 3A, B). The itch remained unchanged for 6, 4, and 6 weeks after cessation of 4PB therapy in patients 1, 2, and 3, respectively, but then gradually exacerbated, resulting in

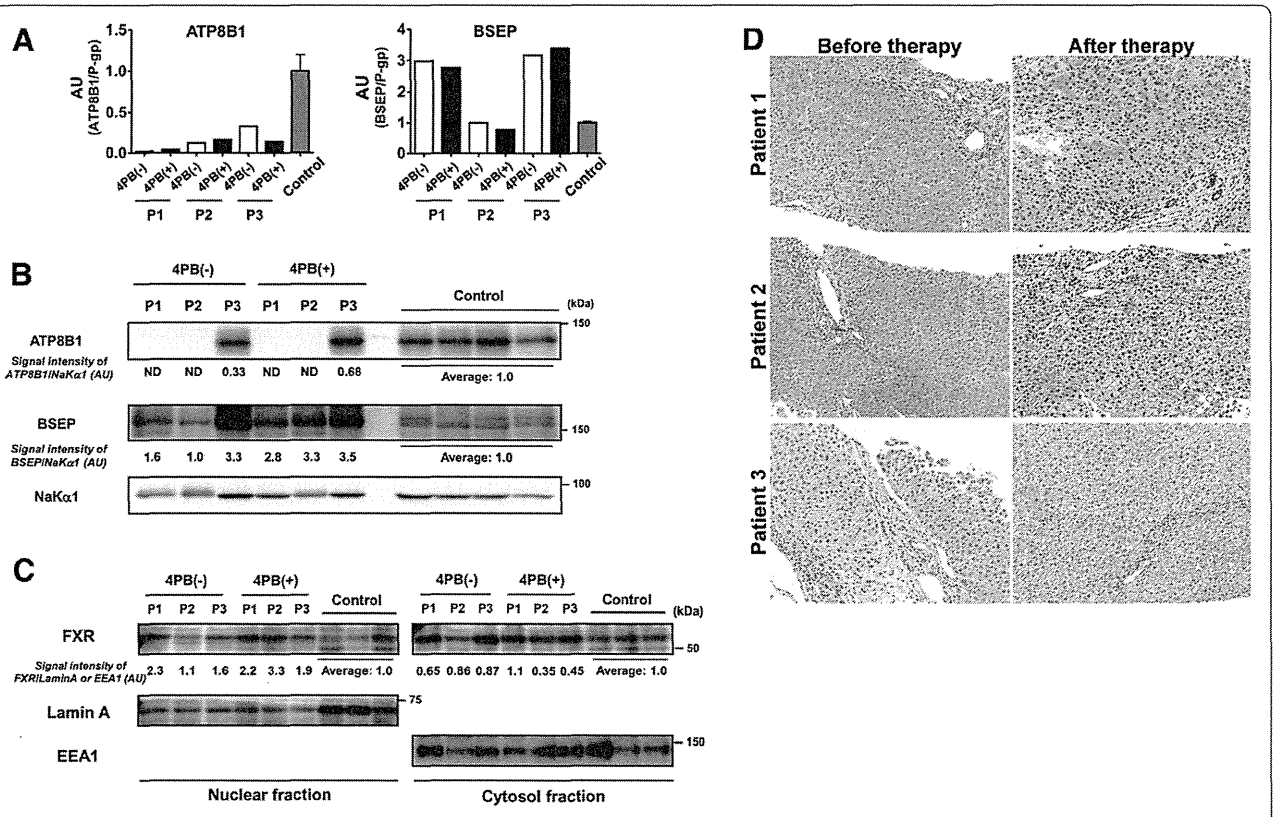

Figure 1 Studies of liver biopsy specimens obtained from the patients before and after 4PB therapy. (D) Histological characteristics of liver sections. Liver sections prepared from the liver biopsy specimens of the patients before and after the 4PB therapy were subjected to HE staining as described in Patients and Methods. A typical image under each condition is shown. Original magnification; 200×. **(A-C)** Analysis of mRNA and protein expression levels. cDNA **(A)**, crude membrane fractions **(B)**, and nuclear and cytosolic fractions **(C)** were prepared from liver biopsy specimens from the patients and then analyzed by qPCR **(A)** and immunoblotting **(B and C)** as described in Materials and Methods. In **(A)**, the data were obtained from triplicate determination. Each bar represents the mean ± SE of individual specimens. In **(B and C)**, the signal intensity of ATP8B1, BSEP, and FXR relative to that of NaKα1, LaminA, and EEA1 is presented below each panel. AU, arbitrary unit; P-gp, P-glycoprotein; P1, patient 1; P2, patient 2; P3, patient 3; 4PB(−), before 4PB treatment; 4PB(+), after 4PB treatment.

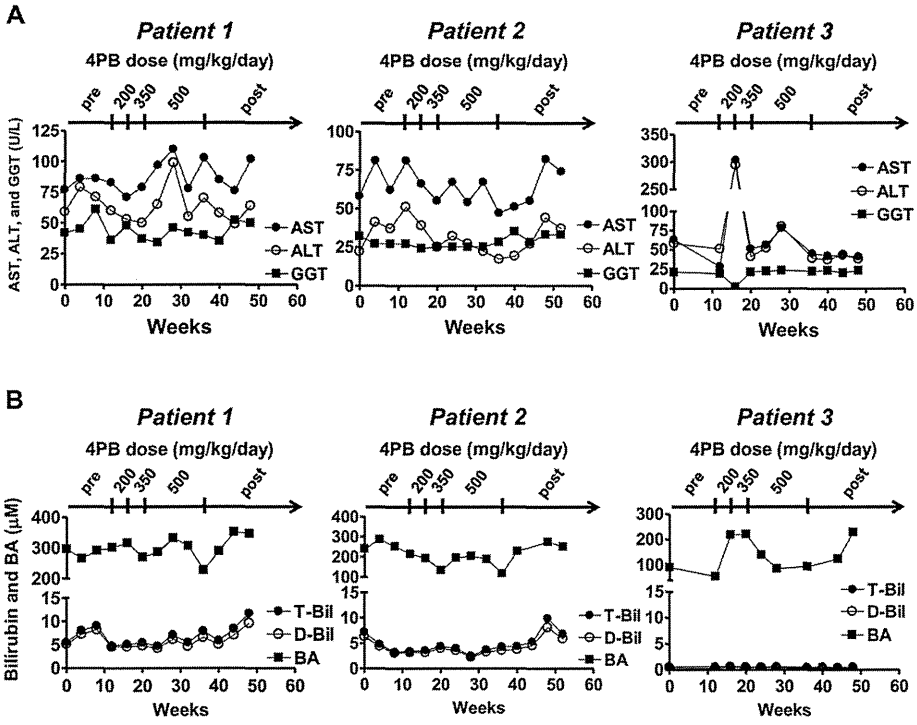

Figure 2 Liver function testing before, during and after the course of 4PB therapy in the patients. Serum AST, ALT, GGT **(A)**, total bilirubin, direct bilirubin, and bile acids **(B)** levels were monitored before, during and after the 4PB therapy. T-Bil, total bilirubin; D-Bil, direct bilirubin; BA, bile acids.

regeneration of erosion and hemorrhage again because of intense scratching. In all the patients, 8 weeks after the end of 4PB therapy, the itching score returned to values equal to those before the treatment (Figure 3A, B). Because of the bad taste of 4PB, all patients had difficulty taking the doses at the beginning of the therapy. However, their parents noted the improvement in their child's sleep during the night and in the skin conditions, and encouraged their child to continue the therapy. No patients dropped out of this study. No severe side effects were observed during and after the 4PB therapy. The temporary elevation of AST and ALT concentrations after patient 3 began 4PB treatment at 200 mg/kg/day was thought to be caused by adenovirus infection and not by any adverse effect of the 4PB therapy, because both markers increased promptly after the adenovirus infection appeared and decreased to the basal levels concurrently with recovery from the infection (Figure 2A).

Effect of 4PB therapy on liver histology and BSEP expression in PFIC1 patients

A liver biopsy was performed 6 months after the initiation of 4PB therapy and compared with the specimens obtained 1 day before onset of 4PB therapy. The specimens of the age-matched control subjects were obtained from OTCD patients without administration of 4PB when they underwent liver transplantation. qPCR and immunoblot analysis demonstrated that even in the specimens taken after the 4PB therapy, the mRNA expression of ATP8B1 was still much lower in all the patients than that of age-matched control subjects, and ATP8B1 protein expression in the membrane fraction was undetectable in patients 1 and 2. In patient 3, ATP8B1 expression was increased about 2-fold by 4PB therapy, but still lower than that in age-matched control subjects (Figure 1B, C). This result was consistent with the lack of change in ATP8B1–FLAG ^{F529del} and a 2.1- and 1.3-fold increase in ATP8B1$^{H78Q+M674T}$–FLAG and ATP8B1^{I577V}–FLAG in UPS-1 cells after treatment with 4PB at a clinically relevant concentration (1 mM) (Additional file 3: Figure S2). BSEP protein expression was increased after 4PB therapy without affecting its mRNA expression as is the case in patients with PFIC2 and OTCD (Figure 1A, B) [14,16]. The amount of FXR in the nuclear fraction of cells from the PFIC1 patients was nearly equal to or a little higher than that of age-matched control subjects, and was not significantly affected by 4PB therapy except for patient 2 (Figure 1C). In this patient, the amount of FXR was increased 3-fold after 4PB therapy. Histological analysis showed that in the specimens obtained from the PFIC1 patients before this study, the portal area was enlarged and had progressed to fibrosis with mild inflammation and partly bridging fibrosis and

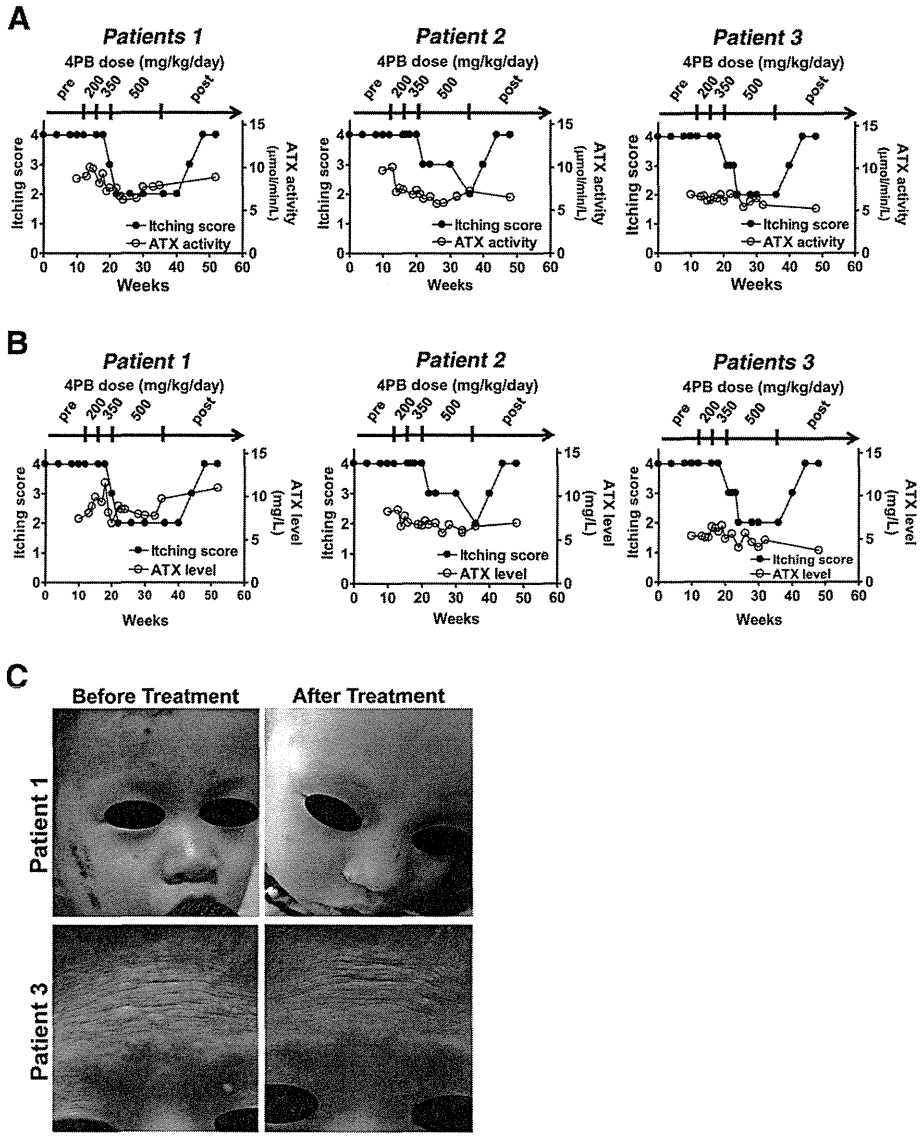

Figure 3 Itching intensity in the patients before, during, and after the course of 4PB therapy. (A, B) Correlation diagram of itching scores for the PFIC1 patients with serum ATX activity **(A)** and ATX level **(B)** in the patients before, during, and after 4PB therapy. Pruritus severity was scored ranging from 0 (no pruritus) to 4 (cutaneous mutilation, with bleeding and scarring) as described in Patients and Methods. **(C)** Skin of the patients before and after the 4PB therapy.

that 4PB therapy caused no remarkable change in these features (Figure 1D).

Discussion

The main complaint in the clinical course of PFIC1 is often the intractable itching, which significantly disrupts the patients' activities of daily living, work productivity, and ability to sleep, and thereby decreases the quality of life for them and their families [2]. Topical steroids, antihistamine agents, and rifampicin are the only prescribed drugs currently available for the cholestatic pruritus in PFIC1 patients, but these medications are often ineffective, as was the case for the patients enrolled in this study [3]. The principal finding of our current study is that 4PB therapy at a clinically relevant dosage used in OTCD patients markedly relieved intractable cholestatic pruritus in PFIC1 patients. At the end of the therapy, hemorrhage and eschar on the patients' skin were diminished, and areas of fresh normal skin appeared as the frequency and intensity of skin scratching decreased. Parents of the patients noted that 4PB therapy made it easier for their child to get to sleep and markedly reduced their child's sleep disturbance during the night. Thus, favorable outcomes of 4PB therapy were observed, and these were dose-dependent, although the patients and their families in this clinical study were not

informed of the detailed protocol. The facts that the patients and their families were not informed of this aspect and that the drugs prescribed for 1.5, 5, and 15 years in patient 1, 2, and 3, respectively, before this study were ineffective in improving the sustained intractable itch suggest that the relief of refractory cholestatic itching in these PFIC1 patients occurred because of the 4PB therapy and not because of a placebo effect or an effect of other medications.

The visual analog scale (VAS) is the most general method for assessing pruritus, but is not easily applied to younger children because VAS is a graphic method based on the patients' subjective rating of symptoms [25]. Therefore, in this study, the patients' itching was evaluated on the basis of cutaneous findings and scored according to the method used in a previous report [21]. A potential concern when using this method is that the improvement in itch may be underestimated. The severity of skin erosion, thickness, and cicatrices depends on the duration of the itch and can vary in the patients scored as 4. Therefore, there may have been a time lag in the improvements in skin appearance even if the frequency and intensity of scratching decreased to the same degree in all patients. In this study, the improvement of pruritus in patient 3, who experienced intractable pruritus for a longer period than patients 1 and 2, might have been underestimated compared with that in patients 1 and 2. To overcome this limitation, it might be better to apply the 5-D itch scale, a recently developed method that assesses the subjective symptoms of itching in patients from five dimensions: degree, duration, direction, disability and distribution [25]. In the 5-D itch scale, but not in the VAS, the subjective symptoms reported by the patient can be supported by his/her family. Therefore, in future clinical studies, the change in chronic pruritus in younger patients should be explored using the 5-D itch scale as well as the method used in this study. This should allow a more accurate determination of the clinical outcomes and the beneficial effects of 4PB therapy on cholestatic pruritus in PFIC1 patients.

In contrast to the relief of intractable cholestatic itching, beneficial effects of 4PB therapy were not observed in liver function tests and liver histology despite an increase in BSEP expression in liver membrane fractions as reported previously (Figure 1B, D and 2) [14,16]. This could be because a two- to three-fold increase in BSEP expression may be insufficient to improve intrahepatic cholestasis in PFIC1 patients. The other possible reason is that the transport activity of BSEP is lost completely in PFIC1 patients because of the disrupted lipid asymmetry of the CM [6,11] and, consequently, the increase in BSEP expression by 4PB therapy cannot compensate for the reduced capacity of bile salt excretion into bile. Although no remarkable improvement in liver function was observed in the patients in our study, 4PB therapy might have therapeutic potency for specific PFIC1 patients with mutations in *ATP8B1* that attenuate ATP8B1 expression, but do not affect its protein activity. An *in vitro* analysis has shown that treatment with 4PB partially restored the decreased expression of ATP8B1 caused by p.G308V, p.D454G, and p.D544N, all of which are naturally occurring mutations [26]. Future clinical studies should validate the therapeutic effect of 4PB and its safety for use in PFIC1 patients who carry mutations that attenuate ATP8B1 expression but do not affect its protein activity.

At present, the mechanism underlying the relief of cholestatic pruritus by 4PB therapy remains to be elucidated. No decrease in the factors suspected to be causally associated with cholestatic pruritus (Figures 2, 3A, B) are consistent with the observation in PFIC2 patient during 4PB therapy [16]. 4PB and/or its metabolites may modulate the local concentrations of these pruritogens, which may not have been detected by systemic measurements. The physiological function of ATX, an enzyme secreted extracellularly that generates lysophosphatidic acid, is thought to be mediated predominantly by activation of G protein-coupled receptors (GPCRs) [27]. TGR5, a GPCR activated by bile salts, in sensory nerves could contribute to bile salt-induced itching [28]; if so, 4PB and/or its metabolites might antagonize the GPCRs responsible for itch signaling and therefore attenuate the activation of sensory neurons. Alternatively, 4PB therapy may disrupt pruriceptive projections to the brain through distribution of 4PB and/or its metabolites into the brain [29] or may affect pruritogens or antipruritogens that have not been identified yet. Further studies to test these possibilities will provide a better understanding of the mechanisms responsible for the effects of 4PB therapy on cholestatic pruritus and thereby the molecular mechanism of cholestatic pruritus itself. Information obtained from these studies will contribute to the development of new molecular target drugs for cholestatic pruritus, which will hopefully be more effective than 4PB and consequently, improve the clinical application of 4PB.

Conclusions

Our study has provided clinical evidence that 4PB therapy can relieve the refractory itching in PFIC1 patients, and thereby improved the quality of life of the patients and their families. Future clinical studies with more patients and longer time periods than were possible in this study should be undertaken to confirm the favorable effects of 4PB therapy using the 5-D itch scale and the other method used in this study. If confirmed, 4PB therapy could become the preferred choice, instead of topical steroids, antihistamine agents, and surgical procedures,

for attenuating cholestatic pruritus in patients with PFIC1 and benign intrahepatic cholestasis type 1 (BRIC1), a hereditary disorder characterized by mutations in *ATP8B1* and by recurrent and intermittent episodes of cholestasis with refractory cholestatic pruritus [30]. 4PB therapy might also be effective for intractable pruritus caused by other cholestatic disorders such as Alagille syndrome. Clinical trials will be required to determine the utility and safety of 4PB as a therapy for these diseases.

Additional files

Additional file 1: Supplemental information.

Additional file 2: Effects of mutations in *ATP8B1* on mRNA and protein expression levels, cellular localization, and function of ATP8B1.

Additional file 3: Effect of 4PB on the expression levels of ATP8B1 mutants.

Abbreviations

ALT: Alanine amino transaminase; AST: Aspartate aminotransaminase; ATX: Autotaxin; AU: Arbitrary units; BA: Bile acids; BRIC: Benign intrahepatic cholestasis; BSEP: Bile salt export pump; CM: Canalicular membrane; D-Bil: Direct bilirubin; ER: Endoplasmic reticulum; EV: Empty vector; FITC: Fluorescein isothiocyanate; FXR: Farnesoid X receptor; GGT: Gamma-glutamyl transferase; GPCR: G protein-coupled receptor; HA: Hemagglutinin antigen; HE: Hematoxylin-eosin; Na^+: K^+-ATPase α1 subunit, NaKα1; ND: Not detected because of low expression; OTCD: Ornithine transcarbamylase deficiency; PFIC: Progressive familial intrahepatic cholestasis; PS: Phosphatidylserine; qPCR: Quantitative polymerase chain reaction; SE: Standard error; T-Bil: Total bilirubin; VAS: Visual analog scale; WT: Wild type; 4PB: 4-phenylbutyrate.

Competing interests

H.H. has applied a patent on the effect of 4-phenylbutyrate on bile salt export pump (US serial No.13/299,989).

Author contribution

YH recruited and enrolled the patients, collected specimens from the patients, performed the clinical assessment and follow-up, contributed to data interpretation, and drafted the manuscript together with HH. HH directed and supervised all of the research and took a lead role in writing the manuscript. SN performed most of the *in vitro* experiments, contributed to data interpretation, and drafted the manuscript together with HH. HK and KB recruited and enrolled the patients, collected specimens from the patients, carried out clinical assessment and follow-up, contributed to data interpretation, and revised the manuscript for intellectual content. KI measured ATX concentration. KH provided UPS-1 cells. KN, TK, and AK collected specimens from the patients and carried out clinical assessment and follow-up. HN helped to make a diagnosis of the patients, and contributed to data interpretation. YM, KO, and HK contributed to data interpretation and revised the manuscript for intellectual content. All authors approved the manuscript before submission.

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9 代謝

Wilson病

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Wilson病の治療は，銅キレート薬（D-ペニシラミンまたは塩酸トリエンチン）あるいは亜鉛薬（酢酸亜鉛）の内服と低銅食療法である．銅キレート薬と酢酸亜鉛は併用も可能である．薬剤の選択は症例の臨床症状と重症度による．

診断のポイント

1. 臨床症状・所見 肝硬変，錐体外路症状ならびにKayser-Fleischer角膜輪が本症の三主徴である．幼児期以降の肝障害ならびに学童期以降に発症した神経症状をみたときには，本症を鑑別する必要がある．神経症状としては，構音障害，振戦ならびに歩行障害などが高い頻度でみられる．その他，精神症状（とくに思春期以降）や血尿などがみられることもある．

2. 臨床検査所見 特徴的生化学検査所見は，血清セルロプラスミン値の低下と尿中銅排泄量の増加である．しかし，血清セルロプラスミン値正常例が約5%の頻度で存在する点，4歳以下の年少例における尿中銅排泄量は正常対照群と比し有意差が認められない点に注意が必要である．多くの場合，血清銅値は低値であるが，溶血を伴う症例では高値となる．

3. 診 断 血清セルロプラスミン値の低下と尿中銅排泄量の増加（100 μg/日，1.5 μg/kg/日または0.2 μg/mg creatinine）を認めれば本症と診断できる[1]．確定診断法としては，肝銅含量の測定がもっとも信頼性が高い．肝組織中の銅含量が200 μg/g wet tissueあるいは250 μg/g dry tissue以上であればWilson病と診断できる．

重症度評価

重症度判定には，肝障害の程度と神経障害の程度をそれぞれ評価する．肝障害は，肝酵素の上昇のみ，急性・慢性肝炎，代償性肝硬変，非代償性肝硬変，そして肝不全と重症化していく．これらのうちのどの状態であるかを評価する．最重症型は，意識障害と溶血を伴い急速に肝不全が進行する劇症肝炎型であり，全症例の4～7%にみられる．死亡する危険が高く，肝移植の適応となる．神経症状を呈する症例の場合は，症状の進行速度と治療への反応に注意が必要である．重症例では症状が急速かつ治療抵抗性に進行し，発症後1～3か月程度で寝たきり状態になることもある．とくに，神経症状としてジストニアが強い症例にその傾向がある．

基本病態

病態の中心は，肝臓から胆汁中への銅の排泄障害による肝細胞内への銅の蓄積である．また，肝細胞内における活性型（ホロ型）セルロプラスミン合成も障害される．蓄積した銅は，当初メタロチオネインと結合し（MT-Cu），無毒化されて貯蔵される．しかし貯蔵閾値を超えたとき，銅イオンとヒドロキシラジカルなどのフリーラジカルが出現し，スーパーオキシドジスムターゼ(super oxide dismustase：SOD)などの活性酸素消去能を超えると細胞障害を生じ，肝細胞壊死がもたらされる．さらに，血中に放出された銅（非セルロプラスミン銅）は全身諸臓器，とくに大脳基底部，角膜および腎臓などに蓄積し，それらの臓器障害をひきおこす．

治療の実際

薬物治療には，銅キレート薬による銅排泄促進あるいは亜鉛薬による銅吸収阻害の2種類の方法がある．これらは単独あるいは併用にて用いられる．また，銅の摂取を制限する低銅食療法も必要となる．銅キレート薬にはD-ペニシラミン（メタルカプターゼ®）と塩酸トリエンチン（メタライト®250）の2種類があり，亜鉛薬は酢酸亜鉛(ノベルジン®)がある．

1. D-ペニシラミン わが国におけるWilson病治療の第一選択薬である．投与方法は，15～25 mg/kg/日（最大量：1,400 mg/日）を食間空腹時に2～3回に分けて内服する．服薬時のポイントは，必ず空腹時（食前1時間もしくは食後2時間以上あけて）に内服させることである．本薬剤の最大の問題点は，副作用の出現頻度が20～25%と高いことである[2]．アレルギー反応などの場合はD-ペニシラミン使用を継続できることが多いが，自己免疫疾患の出現や骨髄抑制などの重篤な副作用が出現した場合には使

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用を断念せざるをえない．また，神経症状を有する症例に対しては，一過性にその神経症状を増悪させる可能性があるため注意が必要である．

2．塩酸トリエンチン D-ペニシラミンが副作用などにより使用できない例に用いられる．また，神経症状に対する治療効果が高いとの報告があるため，神経症状がみられる症例に対してははじめから使用することもある．投与方法は，40～50 mg/kg/日（最大量：2,500 mg/日）をD-ペニシラミンと同様，食間空腹時に分2～3にて内服する．本薬剤は副作用がほとんどないことが利点である．

3．酢酸亜鉛 わが国では2008年4月に販売が開始された，最新のWilson病治療薬である．投与方法は，成人（16歳以上）では75～150 mg/日 分3，6～15歳は75 mg/日 分3，そして5歳以下は50 mg/日分2を食前1時間もしくは食後2時間に内服する（投与量はいずれも亜鉛として）．単剤での治療のみならず，銅キレート薬との併用も可能である．なお，銅キレート薬と亜鉛薬を併用する場合は，銅キレート薬と亜鉛が消化管内にて結合するのを防ぐため，服薬時間を最低でも1時間以上ずらす必要がある．

4．低銅食療法 薬物療法とともに，食事からの銅の摂取を制限する「低銅食療法」を行う．銅の摂取量は，治療開始時には1.0 mg/日（乳幼児は0.5 mg/日）以下に制限する．治療により症状や検査値が改善し安定すれば，やや制限をゆるめて1.5 mg/日まで摂取可能とする．なお，亜鉛製剤を内服しているときは，銅キレート薬のみにて治療を行っているときほど厳密な銅の摂取制限は必要ないと考えられている．

最新ガイドライン/エビデンス

日本先天代謝異常学会のホームページ（URL：http://square.umin.ac.jp/JSIMD/）に，「先天代謝異常症の診療指針」が掲載されている．Wilson病に関しても，主要症状および臨床所見，検査所見，診断基準ならびに鑑別診断が示されている．

近年のトピックス

現在のWilson病治療のkey drugは酢酸亜鉛（ノベルジン®）である．本薬剤は，発症前の症例と治療によってすでに症状と検査所見が安定している症例に対する治療効果が確認されている[3]．しかし，米国などでは亜鉛薬が第一次選択薬として幅広く用いられている[4]．**私の治療方針**で述べたように，明らかな肝障害があったとしても，本薬剤単剤で治療可能な症例が多く存在すると考えられる．

私の治療方針

Wilson病と診断された時点での臨床症状と重症度によって，初期治療に用いる薬剤を選択する．肝障害のみの場合は，代償性肝硬変までであれば酢酸亜鉛単剤にて治療を行う．非代償性肝硬変あるいはそれ以上の重症例は，塩酸トリエンチンと酢酸亜鉛の併用にて治療を開始する．神経症状がみられる場合は，（神経症状が）軽～中等度であれば塩酸トリエンチン単剤で治療を行い，重度の場合は塩酸トリエンチンと酢酸亜鉛の併用を行う．発症前の症例に対しては，酢酸亜鉛を用いる．

ピットフォールと対策

銅キレート薬，亜鉛薬ともに，その内服時間と食事との関係には十分注意する．とくに，銅キレート薬を使用する場合は「食間空腹時内服」を厳守する必要がある．せっかく早期に診断され治療が開始されたにもかかわらず，銅キレート薬を食後に内服していたため，症状が悪化して不可逆的な障害を残してしまった症例が時折みられる．また，D-ペニシラミンの服用により神経症状の悪化をみたときには，D-ペニシラミンを減量するか，塩酸トリエンチンもしくは塩酸トリエンチンと酢酸亜鉛の併用に切り替えることが望ましい．

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REVIEW ARTICLE

Challenges and prospects of a clinical database linked to the board certification system

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Abstract In Japan, the National Clinical Database (NCD) was founded in April 2010 as the parent body of the database system linked to the board certification system. Registration began in 2011, and to date, more than 3,300 facilities have enrolled and more than one million cases are expected to enroll each year. Given the broad impact of this database initiative, considering the social implications of their activities is important. In this study, we identified and addressed issues arising from data collection and analysis, with a primary focus on providing high-quality healthcare to patients and the general public. Improvements resulting from NCD initiatives have been implemented in clinical settings throughout Japan. Clinical research using such database as well as evidence-based policy recommendations can impact businesses, the government and insurance companies. The NCD project is realistic in terms of effort and cost, and its activities are conducted lawfully and ethically with due consideration of its effects on society. Continuous evaluation on the whole system is essential. Such evaluation provides the validity of the framework of healthcare standards as well as ensures the reliability of collected data to guarantee the scientific quality in clinical databases.

Keywords Quality improvement · Database · General surgery · Cancer registry · Certification board for expert surgeons

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Introduction

When evaluating healthcare quality, it is important to consider the structure, process and outcome [1, 2]. However, Japan's healthcare policies have so far been evaluated mainly from the structural viewpoint of offering a system that provides plentiful medical care, i.e., on the number of institutions, physicians, specialists and nurses, on making sure that even a sparsely populated area has a medical facility and on ensuring that patients have access to specialists. This viewpoint of providing widespread medical care has a historical background [3]. In Japan, the fair distribution of medical resources has been politically emphasized in the context of universal health insurance. The equity of healthcare services in Japan is of international value, but when the service quality is referenced, it is important to systematically evaluate not only the structures of the services, but also their processes and outcomes.

To facilitate such evaluations, all surgical societies related to general surgery cooperated to establish the National Clinical Database (NCD), which systematically collects verified data in cooperation with various clinical fields so as to achieve the social responsibility of providing the highest quality healthcare possible in Japan [4, 5]. In order to evaluate the practices and performance of specialists, a committee for each specialty has been set up, and each of them identifies its framework for benchmarking.

As the surgical societies pay for all of the development and operating costs for the database, participating institutions can use the database system for free. Thus, it is mandatory for the institutions to participate in the benchmarking project when applying for the board certification system. Over 3,500 institutions were participating in the NCD in September 2012, and over 1,200,000 cases' data had been registered in 2011. The NCD, in cooperation with the specialist system, will provide important knowledge for future clinical database design and usage [6].

Without a systematic evaluation based on objective information, it is difficult for professionals to achieve social accountability. However, the Japanese healthcare system has been established through profit-sharing among specific groups, including the revision of the fee-for-service system, without fulfilling its social responsibility to weigh social advantage and costs objectively [7]. This system was formed on the basis of rapid economic growth after World War II and a pyramidal population structure.

With the slowdown in economic growth and the coming unprecedented aging society, it will not be possible to keep the current system anymore. Under these circumstances, reconfiguring the system only for a cost reduction will end up affecting its fair accessibility and the quality of the health care. First, whether the values of systematic evaluations based on verified data in the NCD will be suitable for the new society will be validated, and second, resource allocation and the development of a system structure to fulfill the values will be considered. The NCD was built as a platform not only for medical providers, but also for stakeholders, such as administrators, legislators and insurers, to allow them to provide better healthcare and to seek roles in collaboration. Using the nationwide platform, the collaboration among the stakeholders in Japan will also allow them to give useful suggestions to other countries that will face aging societies in the near future. We herein evaluate the significance and issues related to database initiatives that impact various aspects of society.

Social significance and issues related to the database initiatives

We herein evaluate the social impact of the clinical database initiatives from the perspectives of utility, feasibility and propriety standards [8]. The utility standard involves understanding the values of those involved in the initiatives, as well as those affected by it, determining their needs and evaluating whether services are offered that address these needs. The utility standard is assessed from the perspectives of (a) clarification of the central issue, (b) comprehension of the values of those involved, (c) comprehension of the process and outcomes and (d) consideration of the impact that the initiatives have. The feasibility standard relates to verifying whether the initiatives are realistic and economically reasonable. This standard is discussed herein from the perspectives of (a) political validity, (b) realistic progression, (c) project management and (d) resource use. The propriety standard relates to whether the initiatives are carried out lawfully and ethically and whether they pay due consideration to those affected by the results, as well as those involved in the initiatives. The propriety standard is assessed from the perspectives of (a) respect for basic human rights, (b) transparency and information disclosure and (c) maintaining balance.

The utility standard

The central issue

Just as the United States (US) Institute of Medicine identified the concept of "healthcare for the patient" as the chief provision of the twenty-first century medical revolution [9], patient-centric considerations are also an important aspect of future healthcare. Reducing medical costs is often a central policy issue in healthcare. However, the primary aim of healthcare should be to provide the best service to patients, rather than to curb medical costs [10]. High-quality healthcare services must be provided to patients, and considering how to design and coordinate practical approaches and the healthcare provision system, such as that for remuneration, is important to achieve this goal.

A key consideration when discussing the topic of improvements in healthcare quality is to define, understand and evaluate the quality that brings to fruition the values of the patients. The existence of "specialists" in various fields implies that a different result is expected when such specialists are involved in healthcare, compared with when non-specialists are involved. Thus, to fully grasp the quality of healthcare, the different effects that result from specialist involvement must be explained from the patient's perspective. Also important is the understanding of how each specialty is defined and the extent of their involvement. This can be achieved through continuous measurements and evaluations of the structure (e.g., human and material resources, organizational structure and operational management policy), the healthcare process (e.g., diagnosis/examinations, judging treatment indications, patient transport and admission and surgery/treatments) and healthcare outcomes (e.g., short-term mortality, complications, mid- and long-term prognoses and patient quality of life) for each specialty. In this context, the central goal of the NCD is to serve as the foundation for the development of a system that provides long-term, high-quality

healthcare by interfacing with the clinical setting in terms of systematic data collection and practical analyses.

The value of the NCD to stakeholders

Patients and the general public

The benefits of the NCD for patients and the general public include their ability to receive high-quality healthcare through the improvement of the healthcare service throughout Japan. This is achieved through directives by the NCD for improvement, with the clinical setting at the forefront. By reviewing the NCD data, patients can choose facilities that suit their preferences, whether it be the presence of board certified physicians of a relevant field, or the certification of a particular facility.

Health care providers

By unifying the standards of data management, health care providers in clinical settings can compare their approaches with peers throughout Japan and gain an understanding of where they stand. A risk-adjusted analysis based on nationwide data allows for one to determine and provide feedback on the information of the risks patients have beforehand. On the basis of these objective data, health care providers can then determine treatment indicators and obtain informed consent. Standardized information can be reformulated as case reports and shared at conferences. Moreover, the use of the NCD at individual facilities can reduce the burden of paperwork, for example, by providing clinical organizations with access to data for applications of certification, such as those required for board-certified physicians [11, 12]. By adding additional items and using data from one's own facility, clinical research may progress more efficiently.

Participating institutions

Facility reports, in which the severity-adjusted clinical performance of a facility is contrasted with nationwide data, are periodically sent to the participating institutions. These reports can describe the characteristics of each institution and elucidate the issues that require solution. Moreover, knowing one's position among peers allows for strategic planning and proper staff management. The mere fact that a facility participates in a benchmarking project that uses NCD data is in itself a means to ensure stable quality as a facility [13, 14].

Clinical organizations

Maintaining a clinical database as per the unified standards and definitions allows clinical organizations to improve their understanding of the actual performance of various fields, particularly when unified standards and definitions exist. Not only do unified standards increase the reproducibility of the collected data, they also ensure scientific accuracy. The large sample size offered by the database further paves the way for various types of research designs. Moreover, accurate information, as well as insight into the implementation status of various treatments and their effects, allows clinical organizations to provide policies and recommendations on the evidence-based board certification of physicians, their effective placement, improvement of their work environments and setting remuneration schedules. By serving as the driving force for efforts to improve the quality of healthcare, clinical organizations, as groups of specialists, can broadly appeal to the utility of certified facilities and the significance of board certified physicians to society, and at the same time, achieve accountability to society.

International collaboration is important to evaluate the quality of healthcare and produce meaningful results. The aim of the collaboration is to compare the incidence rates of diseases, the treatment trends and the outcomes and to identify factors that explain the differences. The NCD was developed in collaboration with the leadership of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), which adopted a similar goal of developing a standardized surgery database for quality improvement and investigation. The core members of the NCD joined the meetings and seminars of the ACS NSQIP to discuss various issues related to a large clinical database, including the data collection methods, data feedback and public relations. In addition, the NCD implemented the same variables as those of the ACS NSQIP to facilitate future international cooperative studies. This collaboration is expected to lead to potential global benchmarking and further collaborative efforts to evaluate and improve clinical practices.

Pharmaceutical/medical device companies

Research collaborations with clinical organizations will allow pharmaceutical and medical device companies to more rapidly carry out trials and post-marketing surveillance of pharmaceutical products and medical devices. Trials based on the NCD will decrease the costs associated with clinical trials and provide opportunities to obtain information on unregistered patients, thereby improving the scientific quality of the research. Moreover, when randomization is ethically difficult, data from the cases in the clinical database can be used to generate a control group, making it easier to determine the effects of interventions. For post-marketing surveillance, information on the effects and use of medical devices and drugs is valuable

for the development and promotion of more effective drugs and devices.

Government and insurance companies

A lack of understanding regarding healthcare quality indicators may result in the provision of low-quality care that increases the overall costs because it results in expensive postoperative adverse effects and higher rates of complications and mortality. Previous studies have reported that decreases in the mortality rates and incidence of adverse events through benchmarking activities can help cut down medical costs [15, 16]. Therefore, taken together, the coordinated efforts of the NCD, which carries out clinically led benchmarking activities, may benefit the government and insurers.

Processing and reporting results

Benchmarking reports

As discussed above, a report is periodically distributed to participating facilities and provides data on each facility's severity-adjusted clinical performance in comparison with the national data. The report is formatted in a way that makes the patient characteristics evident. In the cardiac surgery field, a web-based program already provides feedback on severity-adjusted clinical performance [17]. Real-time feedback through the web provides an opportunity to observe changes within facilities and shifts in clinical performance instantaneously.

NCD and the board certification system

Data registered with the NCD can be used to design evidence-based board certification systems. In addition to easy tracking of clinical performance, source data acquisition will also become easier, as the system streamlines the need to apply for source data and its usage. Through appropriate data registration, it will also be easier for facilities to become certified or considered an "associated facility" by achieving stable performance. With an effective certification system, the clinical performance data required for the certification process can be readily obtained, and performance comparison and on-site audits using source data can be conducted. For the most part, the current Japanese system focuses on the clinical experience of board-certified physicians. Coordinating with the NCD may enable these organizations to operate on the basis of the parameters that better reflect the clinical reality, including the severity-adjusted clinical performance and the rate of use of appropriate clinical treatments.

Communication within the clinical settings

From various perspectives, including reporting the results of the data analyses, status of database operations, policy measures through the NCD, improvements in entry items and interfaces and supporting each facility's efforts, the NCD and facilities of various fields will need to share information and communicate to operate at an advanced level. Periodic meetings, such as symposia and scientific conferences, in addition to the use of the web and e-mail, provide opportunities to share information and increase awareness. Furthermore, the formation of region- or topic-specific groups will promote NCD-related activities. These activities will enable organizations to introduce and share the best practice recommendations in the participating clinical departments.

Progress reports to patients and the government

Periodic reports for patients and government officials will ensure the impartiality of NCD-related activities. To this end, the NCD has established a group of outside experts (e.g., patients and specialists of law and information) to provide such reports. Moreover, when outside organizations provide funding, conflicts of interest must be considered. When institutional support is required to provide high-quality healthcare, policy recommendations must be coordinated among the members of the government, legislature and patients.

Considering various influences

In addition to prioritizing and appropriately designing NCD benchmarking efforts in various disciplines, an understanding of the overall clinical performance and the temporal transition of clinical processes is important. For instance, when a new treatment is widely used, the database must be kept current to understand and follow the impact of this treatment. For clinical performance evaluations, if inter-facility differences in perioperative mortality become small, the focus will need to be placed on a different complication with a larger disparity between facilities, and initiatives that consider this new area of investigation will be needed. Negative influences must be considered as well. In other countries, different benchmarking stances have had a major impact on patient selection, for example, the treatment of critically ill patients may be avoided, or patients may be discharged early or transferred to different departments [18, 19]. Continuous assessment of the impact of the NCD may help to prevent such occurrences in Japan. When clinical organizations offer recommendations to the government or other institutions, the consequences and effects of these recommendations must be monitored. This would allow for

before-and-after comparisons of certified facilities with regard to patient transfer and the impact of certification on the clinical performance [20, 21].

The feasibility standard

Political validity

The NCD was established in April 2010 as a general incorporated association in partnership with several clinical organizations (http://www.ncd.or.jp). By participating as members of various NCD divisions, leaders of various organizations and those in charge of the board certification system can continuously guarantee partnerships with the leadership of various disciplines and the board certification system. However, NCD operations are free from the influence of other stakeholders, such as the government and businesses. Although donations from businesses and government research grants can help fund NCD-related activities, these are used in a manner that secures the independence of NCD operations.

Realistic progression

In order for NCD operations to continue successfully, it may be beneficial for the various specialty divisions to divide roles among themselves and to collaborate in performing the day-to-day operations. Independent NCD divisions are already in place for continuous coordination with the board certification system in each field. The data management and analysis secures the scientific quality of the data and analysis, systems management ensures the continuity and security of information systems and investigation of the legality and ethicality of activities aids in securing resources and preparing budget plans.

Particularly important is the development of a system that allows for easy data entry and reduces the burden on those entering the data. To this end, case registration in the NCD is based on an easy-to-use web system. The results of a questionnaire survey of various clinical departments registered with the NCD indicated that 63 % of respondents entered information directly via the web while referring to medical records (i.e., source data: Table 1), and 52 % entered information in real-time or immediately upon finalization of the information without delay (Table 2). Moreover, the survey revealed that data entry was performed at common hospital computer terminals or on individuals' personal computers in most cases. In 3.1 % of clinical departments, data entry was performed at an operating room computer terminal (Table 3); however, entering data onto the web while referring to source data was difficult for some departments. Therefore, information was written on paper first and entered into the system later (Table 1). The Case Report Form developed by the NCD is useful in such situations.

Table 1 The input method (multiple answers allowed, $n = 2,123$)

	n	%
Direct data entry via the Web while referencing medical records	1,344	63.3
Data entry after first accumulating data in the department's database (e.g., FileMaker, Access)	458	21.6
Data are first written on case report forms (CRFs; data entry manuals) and then registered	438	20.6
Departmental information systems, such as electronic medical charts, are first revised to be compatible with the NCD before data entry	175	8.2
Others	37	1.7

Table 2 Timing of data entry ($n = 2,123$; as of January 13, 2012)

	n	%
Register case information in real-time to the extent possible	503	24
Register case information upon finalization of information	598	28
Case information is collected and entered periodically	1,022	48

Table 3 Location of data entry (multiple answers allowed, $n = 2,123$)

	n	%
Common terminal other than a hospital terminal	1,156	54.5
Personal computer	1,081	50.9
Hospital terminal outside the operating room	325	15.3
Operating room terminal	65	3.1
Others	50	2.4

In order to avoid the burden on physicians, the NCD allows data entry by various medical staff members in each department. NCD data entry privileges allow people other than physicians to enter the data. Table 4 lists the data entry workers utilizing the NCD as of January 13, 2012. Although the department chair entered information in 58 % of the departments, a medical information manager entered information in 10.2 % and a medical administrative assistant did so in 35.1 % of departments. Importantly, either the department chair or a physician designated by the department chair must approve each case for data entry when somebody other than a physician enters the data to secure the data accuracy. Before the initiation of the database, tests were conducted in various relevant areas to determine the user needs. As a result, an easy-to-use

Table 4 Data enterer (multiple answers allowed, $n = 2,123$)

	n	%
Department chair	1,125	53.0
Department-affiliated physician (other than department chair)	1,232	58.0
Department-affiliated resident	113	5.3
Physician affiliated with different department	7	0.3
Nurse	13	0.6
Medical information manager	216	10.2
Medical administrative assistant	745	35.1
Others	60	2.8

system with an error identification component was developed. Efforts to improve the system continue today in the form of a questionnaire on the web that solicits comments on how to improve the system.

Management plan

A database cannot operate on its own if no data are entered, regardless of whether the system is ready for operation. As its name suggests, a clinical database requires the entry of technical and clinical information, which can be time-consuming. Securing funds for labor costs associated with data entry for each department is no simple task in Japan. Therefore, consistent with this, data are often entered by the physicians themselves. In the NCD, data entry is performed by workers of various backgrounds (Table 4). Continuous sharing of high-quality data requires the securing of funding and personnel to enter the data. In addition, the data must be verified. To address this issue, NCD-registered hospitals throughout Japan have been requested to provide continuous support and understanding of the processes involved in maintaining such a huge database. For example, large hospitals may perform examinations that might not be carried out at small-scale facilities. Therefore, data from such examinations cannot be included as entry items in the database. Thus, an important consideration is the verification of whether entry items and the entry system are realistic for each participating institution. Moreover, because the clinical database documents medical treatments, database items and options inevitably change with advances in surgery and changes in treatment. Depending on when the entry items are revised, the entered data may no longer be used; therefore, frequent revisions without careful planning must be avoided. This underscores the importance of entry item management.

Resource use

By unifying the standards and digitizing the medical record systems in each participating facility, the costs related to data collection may be minimized. In addition, incorporating a program that extracts clinical information other than that requiring a physician's judgment into the database would decrease the burden associated with data entry. In this way, the clinical database may be most efficiently developed in conjunction with developments in medical record systems.

The propriety standard

Respecting basic human rights and consensus building

Ethical guidelines and study types

The NCD is grounded on the framework of observational studies. Therefore, no additional tests or surgery, or even a prolonged length of stay, are required for the institution to participate, and the registration of patient information does not influence the treatments. Projects that do not involve documenting actual events are bound by the Ethical Guidelines for Epidemiological Research developed by the Japanese Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour and Welfare [22]. For interventional studies, such as randomized-controlled trials, comprehensive registration in the NCD may be desirable [23]. In such cases, a new review based on the Ethical Guidelines for Clinical Research must be conducted [24]. Even within the framework of observational studies, broadening registration details and targeting certain disorders can change the nature of the management and operation of clinical databases. Changes that are particularly pronounced may warrant further ethical review, and project implementation may be reconsidered in light of independent valuations.

Patient consent

The patient intentions must be respected when considering the pros and cons of data registration. This can involve obtaining explicit verbal or written consent from participants (opt-in) [23], or not obtaining consent, but accepting a patient's explicit refusal to participate (opt-out) [25]. Only when these conditions are satisfied can clinical databases adopt the opt-out system. A few points are worth noting in this regard. First, clinical databases operate for the purpose of medical and public health research [26]. Second, clinical databases operate under the principle that the risk to participating patients is minimal [27]. Finally, clinical databases must guarantee that patients are given the opportunity to learn about the purpose of registration and the type of information registered [28]. The NCD has adopted the opt-out system and broadly discloses the

purpose of registration and the type of registered information. Moreover, to support the efforts of various clinical departments, the NCD provides web-based templates and explanatory material. However, when interventional studies (e.g., clinical trials) are conducted using the NCD infrastructure, a sufficient explanation must be provided to patients, and their explicit consent must be obtained.

Information security

The NCD data entry system is managed and operated via the web. Occasionally, a tradeoff may exist between the benefits of using the web and the associated risks, such as information leakage. The NCD data entry system uses an ID and password system, and the department chair of every participating facility has the authority to issue IDs. Users are notified about the password management policy; however, given that desirable security standards change as technology advances, the possibility that the evaluation standards at one point may not necessarily be valid in the future must be considered. In such situations, clearly articulating new policies on information management and operations is important. By complying with the disclosed policies, and the contents and measures therein, when issues arise, information system managers and operators can achieve a certain degree of accountability.

Use of personal information

Clinical databases must adhere to laws related to the protection of personal information. Various types of personal information, including (1) identifiable non-anonymous data, (2) identifiable anonymous data and (3) non-identifiable anonymous data require different considerations. In addition to patient information, the NCD includes information on participating facilities, as well as the health care providers involved in the treatment. Thus, the data management system and data use must be carefully considered. The American Association of Thoracic Surgery accepts analysis plans from applicants, and rather than source data, it principally feeds back the results of the analyses [29]. The Japanese Association of Thoracic Surgery has adopted a similar policy.

In view of the sensitivity of such information, the parent operating body of the NCD has established an ethics committee comprising outside experts. This committee includes members of the Japanese Surgical Society ethics board, lawyers, patient representatives and experts on information security. This ethics committee was requested to consider the ethical propriety of the entire initiative, and the progress of the review process was made public on the Japan Surgical Society website [30]. Thus, rather than merely undergoing a review, the contents of the discussion were made public, clarifying for the public the measures taken to address ethical issues. In addition, the NCD requested that the participating facilities undergo a review of ethical propriety regarding case registration in the form of facility director approval or a review from the facility's ethics committee. Because some participating facilities may not have ethics committees, the NCD made it possible to submit to a review by the NCD ethics committee. Since the review of ethical propriety must occur without delay, an application template was designed for ethics committee review and is available on the NCD website. As of January 2012, most participating facilities had received approval from a facility director.

Transparency and disclosure

Data usage

It becomes necessary to accept/adopt a fair stance for data usage. For example, in particular, covering up information that would be disadvantageous for certain facilities or businesses, or disclosing only advantageous information, may lead to conflicts of interest. Transparency must be guaranteed. Therefore, disclosure of information regarding the standards for data usage and rule of publication are important.

Publicizing the results of the data analyses

Further, the standards for publicizing the results of the data analyses need to be established. When performing severity adjustments, as in the US, where additional remuneration is provided on the basis of a department's clinical performance, the details and how severity adjustment is carried out must be disclosed [31]. In some cases, applicants who wish to use data may retain the results as internal documents without publicizing them. It is difficult to determine whether such decisions are made because secrecy would be advantageous, or whether the results are simply not worthy of public disclosure. However, certain standards need to be in place from the perspective of fairness.

Maintaining balance

Unifying the standards for evaluating clinical performance

Standards must be applied for evaluating the clinical performance of departments whose data are registered with the NCD. For instance, when choosing "mortality rate" as a clinical performance indicator, one facility may narrowly define the mortality rate as intraoperative mortality, whereas others may broadly define it as the 30-day postoperative mortality. Some facilities may even exclude periods in which an abnormally high number of deaths

Table 5 Participating facilities/number of departments (as of April 5, 2012)

	Facilities	
	n	%
Hokkaido/Tohoku	437	13.0
Kanto	942	27.9
Chubu	495	14.7
Kinki	650	19.3
Chugoku	252	7.5
Shikoku	142	4.2
Kyushu/Okinawa	454	13.5
Total	3,372	

occur. Even with raw mortality rates, the meaning differs between facilities that treat severe illnesses and those that only treat mild ailments. Therefore, the clinical performance must be fairly evaluated to avoid distrust among the participating facilities. Balanced information sharing can achieve this goal.

Fairness of participation

The NCD intends to improve the quality of healthcare throughout Japan. Because data registration is a condition for obtaining board certification, securing fairness is particularly important. In the US, many businesses pay millions of dollars each year to participate in clinical databases. However, in payment-based systems, the fairness of participation cannot be guaranteed, and coordination with board certification systems is difficult as well. Given the large number of small facilities in Japan, purchasing software for each department within a participating facility is not economically feasible. The NCD data entry software program was developed for use by all facilities and is distributed for free. Therefore, since the beginning of registration on January 1, 2011, more than 3,300 participating facilities have registered with the NCD as of April 2012 (Table 5).According to an administrative cross-country study of medical facilities by the Ministry of Health, Labour and Welfare, surgery under general anesthesia was conducted in 4,519 facilities in Japan [32]. The number of registered facilities by the Japan Surgical Society was 2,143 as of March 2012. [33] Therefore, a large proportion of the Japanese facilities in which surgeries are conducted participate in the NCD.

Conclusions

The coordination of a nation-wide clinical registry, such as the NCD in Japan, with board certification systems in various medical disciplines will positively impact society through their activities. The social implications of the activities must be considered. By identifying and addressing issues that arise from analyzing data, the clinical setting will drive improvements in healthcare quality. The central theme of clinical database activities is the provision of high-quality healthcare to patients and the general public. Clinical research and evidence-based policy recommendations based on the data from this database may positively impact businesses, the government and insurers. Initiatives may be evaluated to assess whether they are realistic and reasonably economical in comparison with the previous initiatives, in order to guarantee that they are conducted lawfully and ethically and to ensure that they pay due consideration to all the stakeholders involved. To ensure this, the continuity and responsibility of activities require continuous evaluation.

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