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Allergology International. 2012;61:197-206
DOI: 10.2332/allergolint.11-RAI-0416

REVIEW ARTICLE

Review Series: Primary Immunodeficiency and Related Diseases

Nakajo-Nishimura Syndrome: An Autoinflammatory Disorder Showing Pernio-Like Rashes and Progressive Partial Lipodystrophy

Nobuo Kanazawa[1]

ABSTRACT

Nakajo-Nishimura syndrome (ORPHA2615; also registered as Nakajo syndrome in OMIM#256040) is a distinct inherited inflammatory and wasting disease, originally reported from Japan. This disease usually begins in early infancy with a pernio-like rash, especially in winter. The patients develop periodic high fever and nodular erythema-like eruptions, and gradually progress lipomuscular atrophy in the upper body, mainly the face and the upper extremities, to show the characteristic thin facial appearance and long clubbed fingers with joint contractures. So far about 30 cases have been reported from Kansai, especially Wakayama and Osaka, Tohoku and Kanto areas. At present, about 10 cases are confirmed to be alive only in the Kansai area, including one infant case in Wakayama. However, more cases are expected to be added in the near future. Although cause of the disease has long been undefined, a homozygous mutation of the *PSMB8* gene, which encodes the β5i subunit of immunoproteasome, has been identified to be responsible in 2011. By analyses of the patients-derived cells and tissues, it has been suggested that accumulation of ubiquitinated and oxidated proteins due to immunoproteasome dysfunction causes hyperactivation of p38 mitogen-activated protein kinase and interleukin-6 overproduction. Since similar diseases with *PSMB8* mutations have recently been reported from Europe and the United States, it is becoming clear that Nakajo-Nishimura syndrome and related disorders form proteasome disability syndromes, a new category of autoinflammatory diseases distributed globally.

KEY WORDS

immunoproteasome, Nakajo-Nishimura syndrome, partial lipodystrophy, pernio, PSMB8

DEFINITION OF THE DISEASE

Nakajo-Nishimura syndrome (NNS) was first reported as "secondary hypertrophic osteoperiostosis with pernio" in 1939 by Dr. Nakajo, a medical staff of Tohoku University Department of Dermatology and Urology.[1] He described a brother and a sister cases of a consanguineous family showing pernio and clubbed fingers accompanied with periosteal thickening and suspected that peripheral circulatory failure due to cardiac insufficiency was the disease cause. In 1950, Dr. Nishimura, the first professor of Wakayama Medical University Department of Dermatology and Urology, and colleagues further reported three cases of two consanguineous families showing the similar phenotype and pointed out a possibility that this disease was a primary inherited disease.[2] Several cases were subsequently reported by dermatological groups mainly in Kansai area and, in 1985, Dr. Kitano and colleagues of Osaka University Department of Dermatology summarized 12 cases of 8 families including their own 4 cases and reported them in Archived of Dermatology as a novel "syndrome with nodular erythema, elongated and thickened fingers, and emaciation".[3] According to this report, this disease has been registered in Online Mendelian Inheri-

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Conflict of interest: No potential conflict of interest was disclosed.
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Received 20 December 2011.

Table 1 Tentative criteria for the clinical diagnosis of NNS

A clinical diagnosis of NNS can be made if at least 5 of the following 8 features are positive.

1. Autosomal recessive inheritance (parental consanguinity and/or familial occurrence)
2. Pernio-like purplish rash in hands and feet (appearing in winter since infancy)
3. Haunting nodular erythema with infiltration and induration (sometimes circumscribed)
4. Repetitive spiking fever (periodic, not necessarily)
5. Long clubbed fingers and toes with joint contractures
6. Progressive partial lipomuscular atrophy and emaciation (marked in the upper part of body)
7. Hepatosplenomegaly
8. Basal ganglia calcification

tance in Man (OMIM), an international online database of human genes and genetic diseases, as Nakajo syndrome (OMIM#256040) and in ORPHANET, an European website collecting rare diseases and orphan drugs, as Nakajo syndrome (ORPHA1953: nodular erythema-digital changes) and Nakajo-Nishimura syndrome (ORPHA2615: amyotrophy-fat tissue anomaly).

In the field of internal medicine, a sporadic case of "collagen disease-like disease with skin eruption, muscular atrophy, splenomegaly, hyper γ-globulinemia and decreased IgA" was reported as an atypical dermatomyositis by a group of Nihon University in 1971 and raised physicians' attention.[4] The report of this case was later published as "a case of partial lipodystrophy with erythema, dactylic deformities, calcification of the basal ganglia, immunological disorders and low IQ level.[5]" Three cases of two consanguineous families with a similar disease were further reported as a particular lipodystrophy by groups of Akita University Department of Internal Medicine and Niigata University Department of Neurology.[6,7] After it was pointed out that the disease of these cases seemed to be the same as the one formerly reported by dermatologists, they were unified as "hereditary lipo-muscular atrophy with joint contracture, skin eruptions and hyper-γ-globulinemia" and reported in Japan Medical Journal in 1991 and in Internal Medicine in 1993.[8,9]

On the other hand, from the field of pediatrics, the first reported case was an adult case of a consanguineous family, originally described as lupus profundus in 1985 and revised as a lipodystrophy-like hereditary disease with basal ganglia calcification in 1989, by a group of Kochi University.[10,11] However, a series of child cases have only been reported in a meeting by Dr. Sugino and colleagues of Wakayama Medical University in 1986.[12] They reported four child cases, three of whom were born in consanguineous parents, of a hereditary disorder showing partial lipodystrophy-like appearance, pernio-like eruptions, long clubbed fingers, basal ganglia calcification and positive inflammatory reactions, and proposed a new disease entity. In 2006, they focused on the characteristic periodic fever and limited localization of the disease and proposed the designation "familial Japanese fever", in contrast to the major autoinflammatory disorder, familial Mediterranean fever.[13]

Thus, although this disease was considered as an autosomal recessively-inherited disease uniquely reported in Japan, its causative gene has long been unidentified. In 2006, Dr. Ida of Nagasaki University Department of Internal Medicine and Kanazawa of Wakayama Medical University Department of Dermatology, who are expertized at autoinflammatory syndromes, found this disease and started a genetic analysis. By a collaborative research with Dr. Yoshiura of Nagasaki University Department of Human Genetics, a homozygous missense mutation of the *PSMB8* gene encoding the β5i subunit of immunoproteasome (IP) has finally been identified in 2009, and the proteasome disability has proven to be associated with this disease.[14] At the same time, Dr. Yasutomo and colleagues of Tokushima University have independently identified the same mutation in cases of Akita and Niigata.[15] Furthermore, phenotypically similar cases with joint contractures, muscular atrophy, microcytic anemia and panniculitis-associated lipodystrophy (JMP) syndrome (formally registered in OMIM as 613732) and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome were reported in 2010 from groups of the United States and Spain, respectively.[16,17] Since other mutations in *PSMB8* reducing the IP activity have been identified in both syndromes, NNS and these diseases are now considered to form proteasome disability syndromes, a new category of autoinflammatory diseases, distributed globally.[18,19]

EPIDEMIOLOGY

Following the acceptance of this disease under the designation of Nakajo-Nishimura syndrome as one of the 177 diseases listed for the promoting division of Research Project to Overcome Intractable Diseases among grants from the Japan Ministry of Health, Labor and Welfare in 2009, national surveillance was performed.[20] To this aim, tentative criteria for clinical diagnosis of NNS were determined as shown in Table 1. At first, eight common characteristic features were

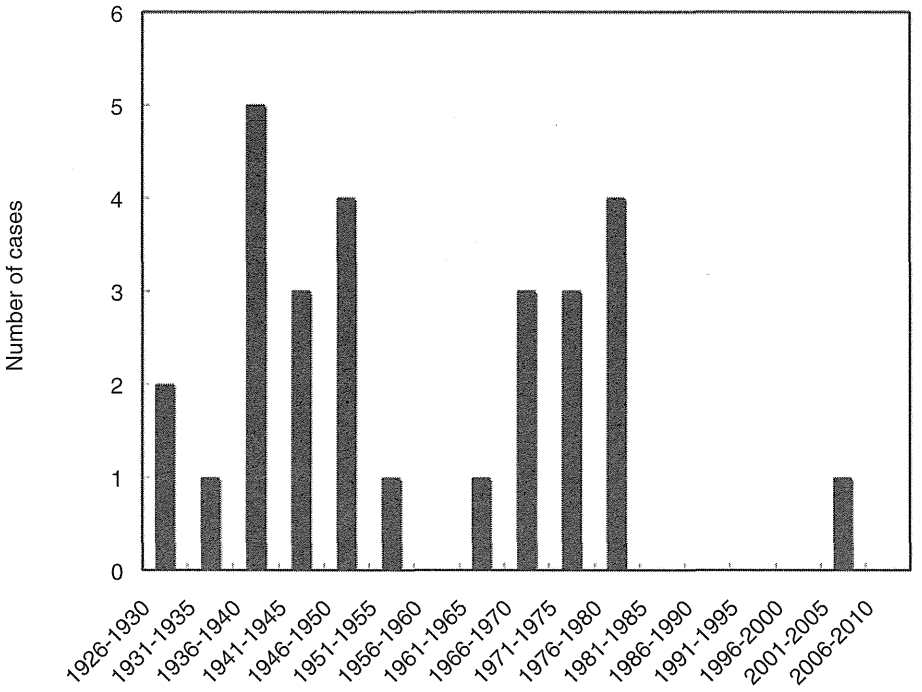

Fig. 1 Years at birth of the identified 28 NNS cases.

selected for the list of criteria, according to the summary of 11 NNS cases in Wakayama; parental consanguinity and/or familial occurrence, pernio-like purplish rash in hands and feet, haunting nodular erythema with infiltration and induration, repetitive spiking fever, long clubbed fingers and toes with joint contractures, progressive partial lipomuscular atrophy and emaciation, hepatosplenomegaly, and basal ganglia calcification. Then, it was proposed that, among these features, cases showing at least five are definite, while cases showing more than two are suspected, to be NNS. A questionnaire asking experience of such cases in the last five years was sent to Departments of Metabolic Medicine, Endocrinology, Rheumatology, Neurology, Dermatology, Pediatrics and Orthopedics in all University Hospitals (623 Departments) and General Hospitals equipped with more than five hundreds beds (1193 Departments). Although answers were returned from 371 Departments of University Hospitals and 433 Departments of General Hospitals, none of new cases, definite or suspected, have been informed other than previously reported cases or those who were already referred to us. Already reported and known cases include 7 cases of 5 families in Tohoku and Kanto (Miyagi, Akita, Niigata and Tokyo) and 20 cases of 17 families in Kansai area (Wakayama, Osaka and Nara). Many of them have not been followed and still followed were only 10 cases in Kansai.

At the same time, a 5-year-old boy followed since 3 years before in Departments of Dermatology and Pediatrics of Wakayama Rosai Hospital with three hundreds beds has been revealed to be a new case of NNS which appeared at 20 years' interval after the last case, because he satisfied its diagnostic criteria and actually harbored the homozygous *PSMB8* mutation. Accordingly, surveillance was further performed by sending the same questionnaire to the Departments in General Hospitals with more than three hundreds beds in Tohoku and Kansai areas (761 Departments), but no other novel cases have been discovered. As shown in Figure 1, years at birth of these 28 cases are concentrated in 1930/40's and 1960/70's. If most cases were actually born at 30 years' interval, new cases born in 1990/2000's might appear in the near future.

CLINICAL FEATURES AND LABORATORY FINDINGS

28 cases include 19 male and 9 female and therefore male cases are twice more than female ones. Consanguinity or familial history is observed in about seventy percent of the affected families. Clinical features of a female case born in consanguineous parents are shown in Figure 2.[21] All cases except for one case onset in infancy at the age from 2 months to 8 years old and most of them show pernio-like rash as the first symptom (Fig. 2a). Typically, severe pernio appears in the first winter after birth and repeats every year, and therefore in some cases the underlying disease was not recognized by either of the patient or the doctor. As a skin manifestation, so-called nodular erythema-like eruptions which can be palped as red, slightly swollen, well-defined, hard nodules or infiltra-

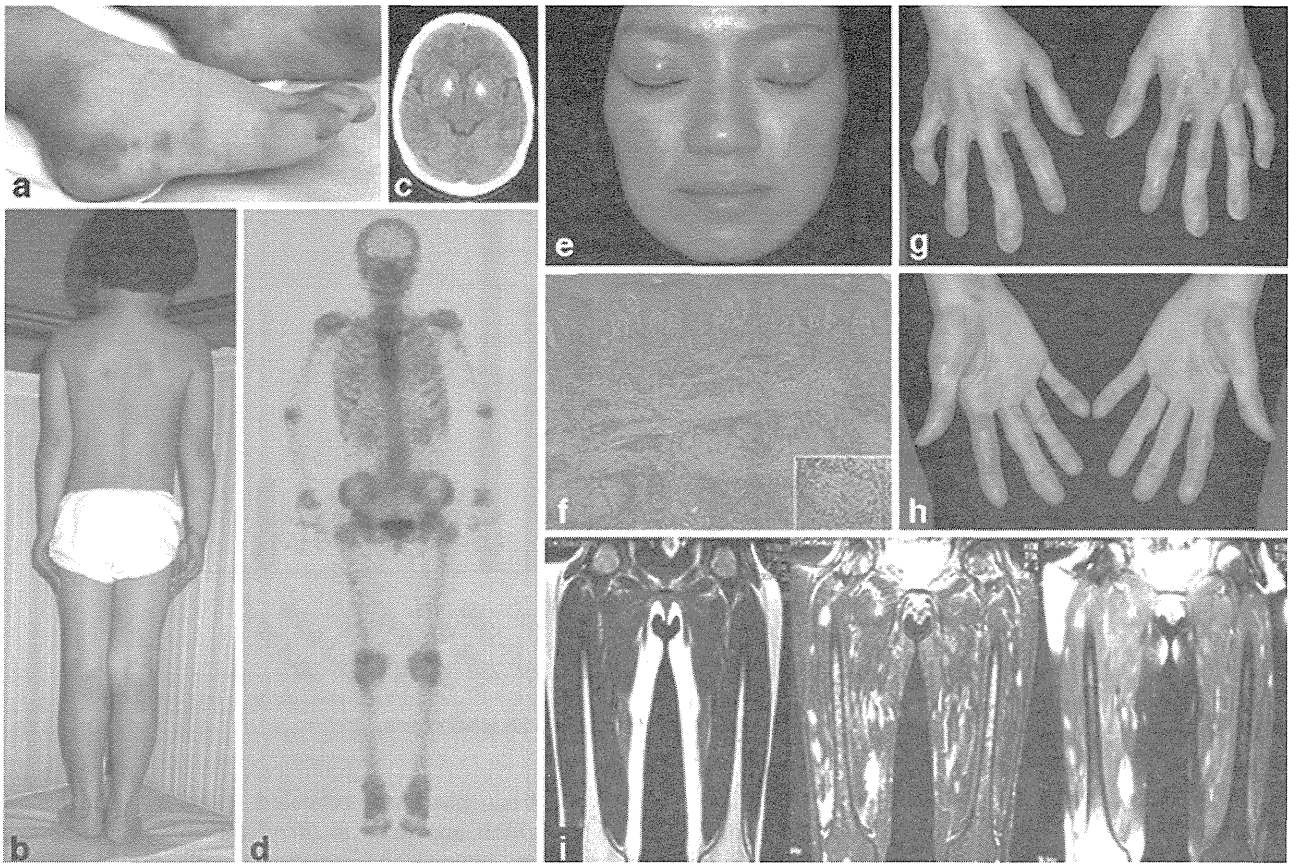

Fig. 2 Clinical features of an NNS case. **a**) Pernio-like purplish rashes on feet at 5 years of age. **b**) Equinus position caused by myositis in lower extremities. **c**) Basal ganglia calcification on cranial computed tomography at 24 years of age. **d**) Technetium uptake in multiple joints shown by bone scintigram. **e**) Angular facial appearance with emaciation and helliotrope-like periorbital rash at 27 years of age. **f**) Dense infiltration of inflammatory cells throughout dermis and vasculopathy with endotheial proliferation. **g**) Long clubbed fingers. **h**) Nodular erythema-like eruptions on hands and wrists. **i**) Multiple focal myositis revealed by magnetic resonance imaging. T1, T2, and T1 with gadlinium enhancement, from left to right.

tive rashes, seem to be rather characteristic and are actually found in all NNS cases (Fig. 2h). Notably, as these eruptions are worsened in winter and reportedly induced by cold stimulation test, Dr. Nishimura and colleagues reported them as pernio-like eruptions.[2] Indeed, both of pernio-like and nodular erythema-like skin eruptions seem to be caused by the common mechanism of inflammatory changes due to vasculopathy. However, dark-purplish edematous rashes, which appear in winter on fingertips and earlobes and resemble typical pernio, have been defined as pernio-like rashes distinct from nodular erythema-like eruptions, as they can be the first symptom but are easily overlooked. Periodic fever is not necessarily observed in all cases, but description of various types of fever can be found in most of the previous reports. Some cases were even accompanied with lymphadenopathy. Pertussis might be a trigger of the disease onset in one case reported by Nakajo, and also reported were a case which onset after middle otitis and a case which onset together with cytomegalovirus infection.[1] Long clubbed fingers and partial lipomuscular atrophy mainly in the upper body are the most characteristic for NNS and observed in almost all the cases (Fig. 2e, g). These features usually become apparent with age, but can also be the first symptom in some cases and thus attention should be paid from the early stage. In contrast, mental retardation was detected in only 8 cases, and therefore it is unlikely to be caused by NNS. Other characteristic symptoms observed in some cases include heliotrope-like rash in eyelids, myositis, short statue, hyperhidrosis in hands and feet, and severe tyrosis on feet.

In laboratory findings, erythrocyte sedimentation rate is elevated in almost all cases. Anemia, which is microcytic and usually accompanied with iron deficiency, is unresponsive to iron preparation and possibly caused by chronic inflammation and splenomegaly. Thrombocytopenia is also seen in some cases. Increased serum creatine phosphokinase level is due to myositis but is not necessarily correlated

with muscular atrophy, although a neurogenic examination shows myogenic changes in many cases. Hyper-γ-globulinemia, which is also observed in almost all cases, is considered to be a result of chronic inflammation. Although serum IgG level is always elevated, some cases with low serum IgA level or with abnormally high IgE level were reported. Furthermore, although no cases show positive serum autoantibodies at the disease onset, anti-nuclear antibody and some other specific autoantibodies such as anti-double stranded DNA antibody become detectable in the serum of not a few cases during the course of the disease. In contrast, for estimation of cellular immunity, lymphocyte blastoid formation with mitogen shows normal reaction, while tuberculin test shows negative in not so many but all examined cases. Regarding natural killer (NK) activity, remarkable impairment was detected in three cases, while remarkable increase of the NK cell number with normal or even high activity was reportedly observed in one case, and therefore further examination should be required. As the visceral involvement, hepatosplenomegaly and calcification of basal ganglia are recognized in most cases. Especially, the latter symptom is considered highly specific for NNS and cranial computed tomography should be checked if NNS is suspected (Fig. 2c). Various levels of conduction block and ischemic changes were frequently detected with electrocardiogram and considered a cause of precmature or sudden death. Although no abnormalities are usually found by an endocrinological analysis, growth hormone was administered for short stature in one case.

Hyperperiostosis, which was considered characteristic for NNS soon after the first report, has never been detected in most of the following reports. In contrast to the characteristic appearance of long clubbed fingers, neither of lytic bone lesions or narrowing of interphalangeal joints are detected by roentgenogram and serum matrix metalloprotease-3 level is within normal range. Cold stimulation test was originally described by Nakajo, by which perniolike erythematous nodules are induced on the forearm along the superficial vessels within several hours after soaking hands for 15 minutes in cold water of 4 degree centigrade.[1] Even though positivity of the test is not high, it is considered important for investigating the pathogenesis of NNS. By an analysis of serum cytokine levels, interleukin (IL)-6 and interferon (IFN) γ-induced protein-10 (IP-10) levels are commonly and significantly higher in NNS patients compared with healthy controls, while IL-1β and tumor necrosis factor (TNF)α are not.[14] Serum lipid levels were analyzed in relation to lipodystrophy to reveal high triglyceride level in many cases, while total cholesterol level was not stable. Gallium scintigram, bone scintigram, positron-emission tomography and magnetic resonance imaging are beneficial for systemic search of inflammatory lesions in bones, joints and muscle (Fig. 2d, i).

HISTOPATHOLOGY

On biopsy specimen of pernio-like or nodular erythema-like eruptions, focal dense infiltration of inflammatory cells in perivascular or periadnexal areas, especially around sweat glands, is observed from superficial dermis to subcutaneous fat, sometimes to the muscle layer (Fig. 2f). Infiltrating cells mainly include lymphocytes and histiocytes, and in some cases neutrophils and eosinophils with nuclear dusts. However, typical leukocytoclastic vasculitis with fibrinoid necrosis cannot be found but rather observed is an obstructive change by thickening of the vessel walls with endothelial cell proliferation and hyaline deposit. Slight atypia is detected in infiltrating cells but a variety of cells including CD4, CD8, CD68 and myeloperoxidase-positive cells infiltrate without monoclonality.

As a result of the autopsy of a NNS case who died with cardiac failure at 47 years old, severe, discrete, multifocal atrophy and fibrosis of skeletal muscles which replaced several primary fascicules were observed.[22] In the remaining muscle fibers, many rimmed vacuoles and lobulated fibers were revealed. On electron microscopy, myofibrillary necrosis, intramitochondrial paracrystalline bodies and cytoplasmic and myeloid bodies were revealed, whereas intramuscular peripheral nerves and neuromuscular junctions of the remaining muscle fibers looked well preserved. No evident regenerating fibers, central nuclei, myophagia or inflammatory cell infiltration were observed. Fundamentally identical but less severe lesions were observed in the tongue and the heart.

Although restricted to the very severely atrophic fascicules of the affected muscles, peculiar morphological changes were observed in blood vessels. Arteries and veins showed hyperplasia of the media with obstruction of the lumen, while most small vessels showed hypertrophy of endothelial cells with luminal obstruction. By electron microscopy, arterioles showed hyperplasia of smooth muscle cells containing centrioles and hypertrophied or degenerating endothelial cells. Terminal arterioles frequently showed centriols in endothelial and smooth muscle cells and narrowing of the lumen by debris of necrotic endothelial cells. Increased Weibel-Palade bodies and filaments were obvious in endothelial cells, whereas no evident increase of collagen, discontinuity of internal elastic lamina, fibrinous deposition, atherosclerotic changes, viral infection bodies or inflammatory cell infiltration were observed.

In the brain, no evident pathological changes were observed except for ferocalcium deposition in the small vessels of the globus pallidus and centrum semiovale. Myocardial hypertrophy with patchy fibrosis was observed in the heart. The aorta and large ar-

teries showed patchy calcification of the media adjacent to the internal elastic lamina, whereas no atheroma or intimal fibrosis were present around these lesions. Central fatty degeneration with acute cell necrosis was observed in the liver. The spleen was congested and the pancreas showed chronic pancreatitis. Subcutaneous fat was reduced and the fat around the visceral organs was increased, whereas the fat cells did not show remarkable pathological changes ultrastructurally.

DIFFERENT DIAGNOSIS

The characteristic angular facial appearance was described as gargoil-like in some reports and congenital metabolic diseases such as mucopolysaccharidosis might be suspected. This characteristic facial appearance and long clubbed fingers due to lipoatrophy are really the partial lipodystrophy in itself. Partial lipodystrophy includes the familial type with a mutation in either gene of *LMNA*, *PPARγ*, *AKT2*, *CIDEC* or *ZMPSTE24*, and the second type, mostly with hypocomplementemia and rarely with autoimmune diseases such as systemic lupus erythematosus (SLE), dermatomyositis and Sjogren's disease.[23,24] Actually, some NNS cases were first diagnosed as dermatomyositis, lupus profundus and SLE. Notably, a case of NNS, who had originally been diagnosed as SLE, further developed myositis with muscle weakness and was then diagnosed as inclusion body myositis by the histological findings of muscle biopsy. As previously discussed, histological differentiation of inclusion body myositis from NNS seems to be quite difficult. As a disease showing both pernio and basal ganglia calcification since early infancy, Aicardi-Goutieres syndrome caused by a mutation of the endonuclease gene such as *TREX1* should be considered for differentiation.[25] Progeria such as Werner syndrome is also suspected by progressive lipoatrophy with severe clavus, however, early-onset cataract and gray hair are not observed in NNS.

Some NNS cases were diagnosed as Weber-Christian disease (WCD), which shows relapsing febrile attacks with erythematous nodules caused by lobular panniculitis with lipophagy and leaves local collapses after healing of nodules. Defect of α1-antitrypsin or α1-antichymotrypsin also shows nodular erythema with lobular panniculitis. Lipoatrophy in NNS shows systemic loss of fat from periphery and thus can be distinguished from collection of collapses in WCD and related diseases. However, since exclusion of other diseases is required for the diagnosis of WCD, active diagnosis of NNS is fundamentally required. The tentative criteria for clinical diagnosis of NNS satisfy more than 5 features of the listed 8 ones in all the recent 23 cases. However, further improvement would be necessary to enable the early diagnosis of NNS before development of the full features and to exclude other diseases showing pseudopositive.

Among autoinflammatory diseases with periodic fever, cryopyrin-associated periodic syndrome (CAPS) seems to be the most similar to NNS, because both diseases are induced or worsened by cold stimuli and have common features of unstable pattern of febrile attacks and characteristic angular facial appearance.[26] However, arthritis and IL-1β overproduction are not revealed in NNS. As there is a case of tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), which was originally reported as WCD, genetic analysis might be required for the definite diagnosis.[27]

In 2010, a group of Spain, France and the United States and a group of Israel reported 5 cases with CANDLE syndrome, which satisfies 7 features (familial occurrence, nodular erythema-like eruptions, periodic fever, long clubbed fingers, partial lipodystrophy, hepatosplenomegaly and basal ganglia calcification) of the diagnostic criteria and resembles NNS very well.[17,28] Although neutrophilic infiltration is remarkable on histology and neutrophilic dermatosis is used for the designation of the disease, the main infiltrating cells include atypical histiocytes with large nuclei and thus such histopathology is fundamentally the same as that of NNS. Furthermore, another group of the United States, Mexico and Portugal reported 3 cases with JMP syndrome.[16] They pointed out the similarity between this disease and NNS but finally differentiated them, because seizures and anemia are specifically detected in JMP while mental retardation is specifically reported in NNS. JMP syndrome does not show fever and looks severer than NNS, because of the systemic lipodystrophy and severe contracture of wrist and phalangeal joints, but satisfies 6 features (familial occurrence, nodular erythema-like eruptions, long clubbed fingers with joint contractures, partial lipodystrophy, hepatosplenomegaly and basal ganglia calcification) of the diagnostic criteria for NNS. Comparison of these three syndromes is summarized in Table 2.

THERAPIES AND PROGNOSIS

Skin lesions disappear by administration of systemic steroid but can reappear after tapering. Furthermore, systemic steroid is ineffective for lipodystrophy but rather worsens the central obesity. Long-term administration of systemic steroid since infancy can cause severe side effects including growth retardation and glaucoma, and therefore, adaptation of this medication should be carefully determined. It was reported that kallikrein and DDS (dapson) were effective for NNS, however, the effect should be temporal. Administration of biological drugs such as anti-TNFα and anti-IL-1β antibodies might be effective, but has not been applied yet.

In cases with CANDLE syndrome, various antirheumatic and immunosuppressant drugs, including

Table 2 Comparison of the three proteasome disability syndromes

	Nakajo-Nishimura syndrome	JMP syndrome	CANDLE syndrome
Parental consanguinity	-/+	-	-
Family history	-/+	-/+	-/+
Age at onset of pernio	2 m-5 y	-	-/1 m?
Eruptions in trunk	-/++	+	+
Age at onset of fever	-/3 m-8 y	-	1m-1y
Long clubbed fingers	+	+	+
Joint contractures	-/+++	+++	-
Hyperhidrosis	-/+	-	-
Partial lipoatrophy	+-/+++	++	+
Loss of muscle power	-/+	+	-
Dyspnea	-/+	-	-
Hepatosplenomegaly	-/+	+	+
Microcytic anemia	-/+	++	+
Basal ganglia calcification	+	+	+
Seizures	-	+	-
Electrocardiogram	np/LVH, LAE, CRBBB	?	np
PSMB8 mutation	p.G201V	p.T75M	p.T75M, p.C135X, none

m, month(s); y, year(s); np, nothing particular; LVH, left ventricular hypertrophy; LAE, left atrial enlargement; CRBBB, complete right bundle branch block.

methotrexate, hydroxychloroquine, azathioprine, cyclosporine, tacrolimus, infliximab, adalimumab, etanercept, anakinra, tocilizumab, rituximab, were administered but satisfying effect has never been obtained, especially on progressive lipodystrophy.[19]

IDENTIFICATION OF THE RESPONSIBLE GENE

After informed consents were obtained, typing of single nucleotide polymorphisms (SNPs) in the whole genomic DNA extracted from peripheral blood of five NNS patients and unaffected three siblings was performed using Affimetrix GeneChip Human Mapping 500k array set.[14] As a result of homozygosity mapping using Partek Genomics Suite v6.4, an 1.1 Mb region on chromosome 6p21.31-32 was identified for the candidate locus, where homozygous SNPs were continuously present commonly in the patients whereas not continuously in unaffected siblings. By direct sequencing of all exons with exon-intron boundaries of 53 genes located on this locus, one missense mutation has been identified in exon 5 of the *PSMB8* gene, which is homozygously present only in the patients but is absent in 272 healthy controls. This homozygous c.602 G > T mutation causing p.G201V transition of the *PSMB8* gene, encoding the β5i subunit of IP, was actually observed in all examined NNS patients. Furthermore, all SNPs located in the genomic region between 15 kb before and 15 kb after the mutation were all homozygous in all examined NNS patients, and thus the strong founder effect has been revealed. Surprisingly, at the same time, a group of Tokushima University has identified the same mutation by homozygosity mapping of three patients in Akita and Niigata.[15]

By homozygosity mapping of three cases with JMP syndrome, another homozygous missense mutation of the *PSMB8* gene, c.224C > T in exon 2 causing p.T75M transition was identified to be responsible for all cases.[18] Homozygosity mapping was further performed on five cases with CANDLE syndrome and the homozygous p.T75M transition of the *PSMB8* gene was also detected in four cases and another homozygous c.405C > A in exon 3 causing p.C135X nonsense mutation was detected in one case of an Ashkenazi-Jewish origin.[19] Interestingly, no mutation was identified in one case and only the heterozygous p.T75M transition without any second mutation was detected in two cases, including one case who had not shown the similar homozygosity with other 4 cases at the original mapping.

PATHOGENESIS

Proteasome is the intracellular protease complex specialized for degradation of polyubiquitinated proteins.[29] The full complex called 26S is formed by one 20S core and two 19S regulatory units. The 20S core unit is composed of 2 sets of 2 rings with 7 α and 7 β subunits, including catalytic β1, β2 and β5 subunits with caspase-like, trypsin-like and chymotrypsin-like activities, respectively. The ubiquitin-proteasome system not only degrades unnecessary proteins and controls the protein quality, but also works on various cellular functions, including cell cycle regulation, gene repair and signal transduction such as nuclear factor (NF)-κB activation. Immunoproteasome, in

which inducible β1i, β2i and β5i subunits are incorporated instead of β1, β2 and β5 subunits, respectively, is constitutively expressed in immune cells and induced in other cells by inflammatory stimuli such as IFNγ, to effectively present the digested peptides on MHC class I.[30] The *PSMB8* gene encodes this β5i subunit and, after maturation with cleavage of the N-terminal 72 amino acids, exposed Thr73 acts as the catalytic center. Computer simulation for tertiary structure of the mature β5i has shown that Gly201 is located very close to Thr73 and transition of Gly201 to valine alters the localization of Thr73 and Lys105, which form the catalytic center with Asp89 and Asp 91, and thus its enzymatic activity is possibly affected.[14] Furthermore, the tertiary structure of the interface with the neighboring β4 and β6 subunits is also changed and the assembly of the IP complex is predictably affected. Actually, by analysis of the proteasome enzymatic activities of the proteins, which were obtained from NNS patient-derived immortalized B cells and fractionated with glycerol gradient, not only remarkable impairment of the β5i-responsible chymotrypsin-like activity but significant decrease of the β1i- and β2i-responsible caspase-like and trypsin-like activities were observed as expected. Interestingly, heterozygous parent-derived cells show the intermediate proteasome activities between the homozygous patient's cells and those of a healthy control, although the parents show no phenotype. By Western blotting of the same series of fractionated proteins, reduced amount of the mature 26S containing β5i and retained immature 20S containing β1i and β2i but not β5i were revealed. Moreover, observed were retention of hUmp1, a chaperon molecule which is temporally incorporated during immature 20S formation and degraded after completion, and immature β5i, which still contains uncleaved N-terminal amino acids. Thus, defective assembly of IP complex in NNS cells has been clearly indicated. Consequently, accumulation of ubiquitinated proteins was revealed in NNS patient-derived immortalized B cells and primary fibroblasts by Western blotting and in $CD68^+$ macrophages infiltrating in the lesional skin of an NNS patient by immunofluorescent double staining. In addition, accumulation of oxidated proteins was shown in the patient-derived fibroblasts by Western blotting. Notably, it was reported by another group that accumulation of ubiquitinated proteins was also immunohistochemically detected in epidermal keratinocytes, hair follicular cells and sweat glands' secretary cells of another NNS patient.[15]

Regarding NF-κB activation, although hyperactivation reflecting autoinflammatory phenotypes and hypoactivation due to defective cleavage of inhibitor of NF-κB caused by proteasome deficiency were both predicted, no remarkable change of p50/65 activation was observed in NNS patient-derived fibroblasts compared with those of a healthy control with electrophoresis mobility shift assay and Western blotting.[14] Rather, by analysis of mitogen-activated protein kinase (MAPK) cascades, accumulation of phospho-p 38 was specifically observed in the nucleus of NNS patient-derived fibroblasts and peripheral blood lymphocytes by Western blotting. By an exhaustive analysis of serum cytokine levels of four NNS patients with multiplex bead-based enzyme-linked immunosorbent assay on a suspension array, levels of IL-6, IP-10 (formally called CXCL10), monocyte chemoattractant protein (MCP)-1 (CCL2) and granulocyte-colony stimulating factor (G-CSF) were significantly higher than those of healthy controls. IL-6 level was also higher in the culture supernatant of NNS fibroblasts compared with that of control cells after TNFα stimulation and even without stimulation, whereas CXCL10 level was not. Therefore, IL-6 overproduction induced by nuclear accumulation of phospho-p38 is considered to have a role on repetitive/constinuous inflammation in NNS. The similar pathway has also been proposed to be involved in TRAPS, in which intracellular accumulation of aggregated TNF receptor 1 causes inflammation.[31] As a whole scheme, in NNS, ubiquitinated and oxidated proteins, produced by various stress such as cytokines and infectious stimuli, are accumulated due to defective digestion with IP and inhibit dephosphorylation of phospho-p38, and the resultant relative activation of p38 MAPK causes IL-6 overproduction (Fig. 3).

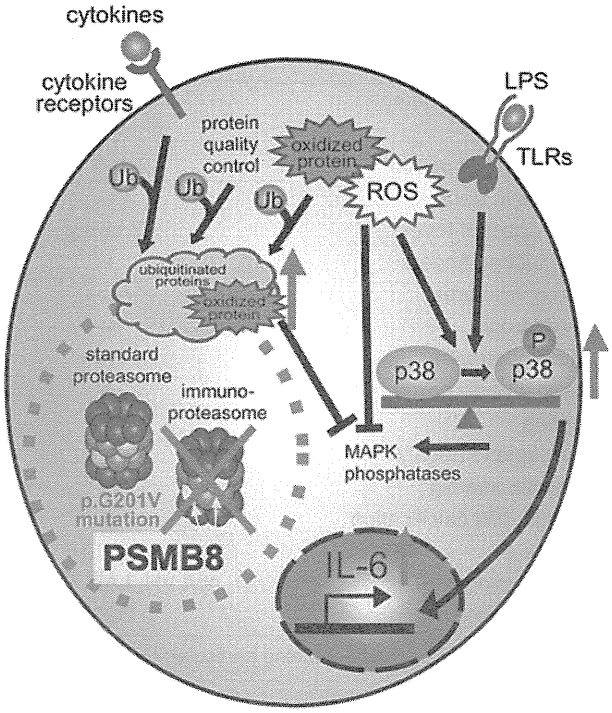

Fig. 3 A schematic view of the mechanism of autoinflammation in NNS.

On the other hand, distinct mechanism might underlie both JMP and CANDLE syndromes with other mutations of the *PSMB8* gene.[18,19] In contrast to the p.C135X nonsense mutation, which deletes a large portion of C-terminal residues and predictably obstructs the assembly of the IP complex, p.T75M transition seems to affect only the chymotrypsin-like activity of the β5i subunit. Interestingly, serum cytokine profiling of three CANDLE cases with the homozygous or heterozygous p.T75M or without mutation showed highly elevated level of CXCL10 and significantly high levels of CCL2, RANTES (CCL5), IL-6 and IL-1 receptor antagonist in all cases. The transcriptome by whole blood microarray analysis of these cases identified the IFN pathway as the most differentially regulated pathway among canonical ones and the pattern of altered gene expression, including IP-10 as the IFN-inducible upregulated gene, was quite similar among the cases. As stronger phosphorylation of signal transducers and activators of transcription (STAT)-1, a downstream mediator of IFN signaling, was actually observed in the patients' monocytes after IFNγ stimulation compared with the healthy control cells, tofacitinib as a Janus kinase inhibitor, which decreased the STAT-1 phosphorylation and IFNγ-induced IP-10 production of the patients' cells, is proposed as the specific and effective treatment for CANDLE syndrome.

It has not yet been clarified whether progressive lipodystrophy is dependent or independent on repetitive/continuous inflammation in these diseases. Although it remains to be estimated whether early intervention with intensive anti-inflammatory therapy can inhibit the progression of lipodystrophy, so far no effective treatment for lipodystrophy has been reported, including tocilizumab as anti-IL-6 receptor antibody. Surprisingly, small interfering RNA for PSMB8 inhibited the differentiation of murine and human preadipocytes into mature adipocytes *in vitro* and, when injected subcutaneously into the murine skin, induced atrophy of subcutaneous adipose tissue and reduced the number of hair follicles.[15] Although development of lipodystrophy has never been reported in PSMB8-deficient mice, these results suggest a critical and direct involvement of the β5i subunit in adipocyte differentiation.

FUTURE PROSPECTS

A new disease category of proteasome disability syndrome has been defined by our own and related studies. However, there still remain many questions to be addressed. Bortezomib as a specific β5i proteasome inhibitor, which has recently been applied for the treatment of multiple myeloma, is reportedly effective for rheumatoid arthritis and expected to be further applied for the treatment of autoimmune diseases.[32] Such a situation seems to be inconsistent with our observations. Since repetitive inflammation and progressive atrophy caused by congenital proteasome disability is considered as one aspect of the effects by inhibition of proteasome functions, clarification of the underlying mechanisms is urgently required. However, from the beginning, why NNS patients do not show immunodeficiency in spite of defective IP function? The way of antigen presentation and the status of immunological tolerance should be elucidated because IP should reportedly be critical for MHC class I presentation and CD8 T cell proliferation.[30] As some NNS cases produce various autoantibodies after progression of the disease, analysis of the whole mechanisms for development of NNS may elucidate a way from autoinflammation to autoimmunity. To this aim, further studies using the patient-derived induced pluripotent stem cells and the mutation-knockin mouse, rather than the simple knockout mouse would be desired. It is highly expected that a new research on inflammation and immunity will be expanded using this disease as a model, which has been originally reported and precisely described by many clinicians in Japan.

ACKNOWLEDGEMENTS

I would like to thank Drs. Hirotoshi Sugino (Sugino Pediatric Clinic), Michio Koike and Masahiro Matsunaka (Wakayama Medical University), Shimpei Kasagi and Seiji Kawano (Kobe University), Sachiko Miyagawa and Makito Hirano (Nara Medical University), Akihiro Fujisawa and Koichiro Ohmura (Kyoto University), Toru Momoi (Red Cross Wakayama Medical Center), and Kayo Kunimoto, Ayako Kimura and Koji Uede (Wakayama Rosai Hospital) for collection of NNS patients, Drs. Kazuhiko Arima, Akira Kinoshita, Hiroyuki Mishima and Koh-ichiro Yoshiura (Nagasaki University) and Dr. Hiroaki Ida (Kurume University) for fruitful collaborations, and Dr. Fukumi Furukawa (Wakayama Medical University) for continuous encouragement. I also would like to thank NNS patients and their parents and siblings for their kind cooperation. This work was supported by grants from the Ministry of Health, Labour and Welfare and the Japan Society for the Promotion of Science (23591651).

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