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REVIEW

Nakajo–Nishimura syndrome and related proteasome-associated autoinflammatory syndromes

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Abstract: Nakajo–Nishimura syndrome (NNS) is a rare hereditary autoinflammatory disorder with lipodystrophy. This disease is caused by a homozygous mutation of *PSMB8* gene, which encodes immunoproteasome subunit β5i. Phenotypes of NNS patients are periodic fever, pernio-like rash, nodular erythema-like eruptions, and lipomuscular dystrophy, especially in the upper body, leading to the characteristic long, clubbed fingers. NNS was considered to be endemic to the Kansai area of Japan, but patients with similar phenotypes and the mutation of *PSMB8* gene were reported in other countries, and named Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome and joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy (JMP) syndrome. These syndromes are now called proteasome-associated autoinflammatory syndromes (PRAASs), and their main pathophysiological mechanism seems to be interferonopathy. In this review, the history, characteristics, and the pathophysiological mechanism of PRAASs will be discussed, focusing mainly on NNS.

Keywords: Nakajo-Nishimura syndrome, PSMB8, autoinflammatory syndrome, proteasome, lipodystrophy, interferonopathy

Introduction

Nakajo–Nishimura syndrome (NNS) is a rare hereditary autoinflammatory disorder, mainly found in the restricted area of Japan. Causal genetic mutation was found to be *PSMB8*,[1,2] which was the same responsible gene as the cause of Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome[3] and joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy (JMP) syndrome.[4] *PSMB8* codes β5i subunit of the immune proteasome and other genetic mutations related to proteasome were recently found to show the similar phenotype to *PSMB8*-related disorders. Now, these disorders are called proteasome-associated autoinflammatory syndromes (PRAASs) and NNS is no more an endemic disease. I think it is a good time to overview NNS and the related disorders to understand the mechanism of PRAASs.

History and characteristic of NNS

NNS was first reported by Dr. Nakajo in 1939.[5] A brother and sister, the children of close relatives, showed a secondary hypertrophic osteoperiostosis with pernio. In 1950, Dr. Nishimura and his colleagues reported three similar cases in two consanguineous

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families and proposed that this syndrome is a hereditary disorder.[6] The first paper describing NNS in English was published in 1985, reporting 12 cases who presented nodular erythema, elongated and thickened fingers and emaciation.[7] This led to registration of the syndrome in international hereditary disease databases: MIM as Nakajo syndrome (MIM256040), and ORPHANET as Nakajo-Nishimura syndrome (ORPHA2615).

NNS is characterized as periodic fever, pernio-like rash, nodular erythema-like eruptions, and lipomuscular dystrophy especially in the upper body with elongated clubbed fingers. At least 28 cases have been reported, mainly in the Japanese literature (summarized in[8]). The symptoms and laboratory findings of the 28 cases are summarized in Table 1. Although NNS shows autosomal recessive heritability, only half of the reported cases have a family history. Onset is at around 2 years old, on average, but some patients develop their first symptoms only when they reach 6–12 years. The most common symptoms are pernio-like rash, nodular erythema-like eruption, elongated clubbed fingers, and lipodystrophy. Fever is not always concomitant, and mental retardation can occur in some cases. Erythrocyte sedimentation rate and C-reactive protein (CRP) are always elevated, and, interestingly, calcification of the basal ganglia occurs frequently. Immunological abnormalities such as hypergammaglobulinemia and anti-nuclear antibody are present in many cases. Autoantibodies include anti-double strand DNA antibody, anti-SS-A (Ro) antibody, and anti-myeloperoxidase antibody (MPO-ANCA). Although osteoperiostosis was noted in the first report of NNS, it is not so frequent. Creatine kinase (CK) is elevated in about one-third of patients, and some show a heliotrope-like rash on the eyelids, so some cases were initially diagnosed with dermatomyositis even after muscle biopsy.

Table 1 Frequency of clinical characteristics in Nakajo–Nishimura syndrome

	Pt # assessed	Pt # positive	Frequency (%)
Symptom			
Pernio	19	19	100
Erythema nodosum	28	28	100
Elongated clubbed finger	27	27	100
Lipodystrophy	26	26	100
Muscle dystrophy	16	14	88
Periodic fever	20	17	85
Joint contracture	18	14	78
Lymphadenopathy	12	8	67
Mental retardation	22	8	36
Clinical examination			
ESR elevation	26	26	100
Basal ganglia calcification	16	14	88
Hypergammaglobulinemia	25	21	84
ANA positive	17	12	71
Hepatosplenomegaly	20	14	70
CPK elevation	16	6	38
Osteoperiostosis	20	3	15
Consanguineous marriage	27	19	70

Abbreviation: ESR, erythrocyte sedimentation rate.

Identification of responsible gene

In 2011, the gene mutation responsible for NNS was reported almost at the same time by two Japanese laboratories.[1,2] A homozygous mutation in proteasome subunit beta type 8 gene (*PSMB8*: NM_148919 in the NCBI database) was identified in all of the affected patients at the same position (c.602C>T: G201V) of the β5i subunit of the immune proteasome. Haplotype analysis around the mutation suggested that all NNS patients are derived from a single founder. Proteasomes are huge protein complexes that degrade polyubiquitinated unneeded or damaged proteins.[9,10] This complex contributes not only to degrading misfolded or harmful proteins but also to signal transduction and to the cell cycle. As shown in Figure 1A, the proteasome is composed of a 20S core particle (CP) and two 19S regulatory particles (RP). The 20S CP is composed of two α rings, each of which consists of 7 α-subunits (α1-7), and two β rings, each of which consists of 7 β-subunits (β1–7). 19S RP catches polyubiquitinated proteins and leads them to 20S CP, which degrades them to peptides. The β1 (PSMB6), β2 (PSMB7), and β5 (PSMB5) subunits have enzymatic activity (caspase-like, trypsin-like, and chymotrypsin-like, respectively). Although these complexes are well conserved from yeasts to mammals, vertebrates have additional β subunits, ie, β1i (PSMB9), β2i (PSMB10), and β5i (PSMB8). When vertebrate cells are exposed to interferon (IFN) γ, β1i, β2i, and β5i subunits are strongly induced and incorporated into the proteasome complex instead of β1, β2, and β5, creating "immunoproteasome". Immunoproteasome is constitutively produced in the immune cells. β5i (PSMB8) subunit shows stronger chymotrypsin activity than β5, but G201V mutant β5i shows reduced chymotrypsin activity due to positional shift of adjacent Thr73 and Lys105 which are within the catalytic center. Moreover, G201V substitution changes the conformation of interface between β4 and β5i, which affects the assembly of the 20S proteasome, leading to further reductions in β1i and β2i enzymatic activities. As a result, ubiquitinated or oxidized proteins accumulate in the macrophages of skin lesions, and

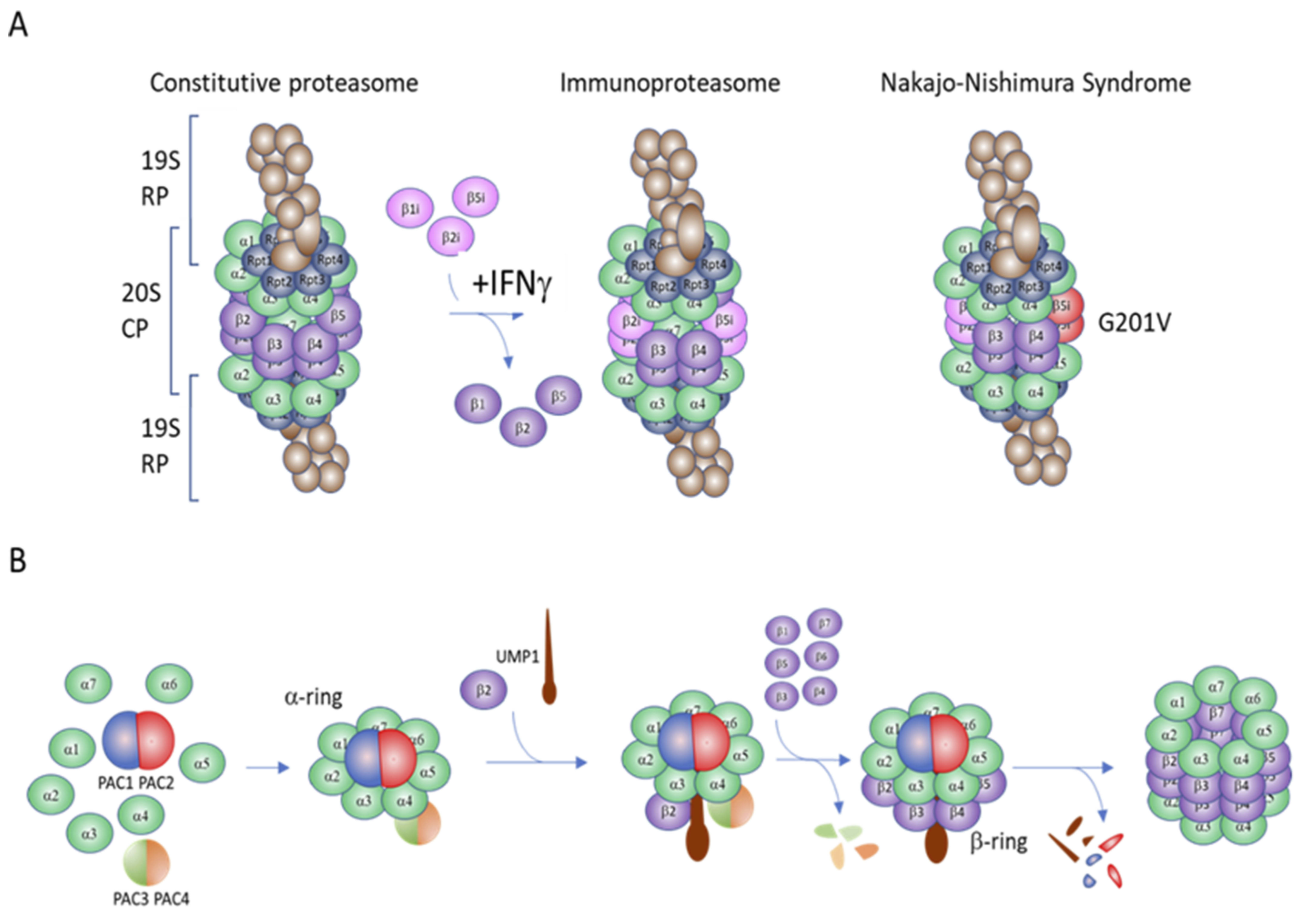

Figure 1 Illustration of proteasome structure and assembly.

Notes: (**A**) Proteasome is formed by the assembly of a 20S core particle (CP) and two 19S regulatory particles (RP), and is called 26S constitutive or standard proteasome. 20S CP consists of two α-rings (light green) and β-rings (purple); each α-ring has seven subunits (α1-7) and each β-ring seven subunits (β1-7). When the cells are stimulated with IFNγ, β1i, β2i, and β5i are incorporated into the β-rings by replacing β1, β2, and β5, which forms immunoproteasome. G201V mutation in β5i subunit leads to proteasome dysfunction, causing Nakajo–Nishimura syndrome. (**B**) Assembly of 20S proteasome. Proteasome assembling chaperone 1 (PAC1)–PAC2 heterodimers and PAC3–PAC4 heterodimers assist α-ring formation. Ubiquitin-mediated proteolysis 1 (UMP1) assists β-ring formation sequentially from β2 subunit, and during and after assembly of all the other β subunits, all the PACs and UMP1 chaperones degrade and active 20S proteasome CP is formed.

interleukin (IL)-6 and IFN-inducible protein (IP)-10 are increased in the sera of NNS patients.[1,2]

Diagnosis and differential diagnosis

Diagnostic criteria of NNS have been proposed in Japan and is used for certification of patients as having intractable disease for the patients' welfare (Box 1) (http://www.nanbyou.or.jp/entry/4583). Patients with five or more of the eight clinical characteristics are diagnosed with NNS. When homozygous *PSMB8* mutations are detected, NNS is considered definite regardless of the number of clinical characteristics. In patients with five or more of the eight clinical characteristics but with no mutations in *PSMB8* gene, a diagnosis of probable NNS is made. Important differential diagnoses are as follows: Lipodystrophy occurs in patients with mutations in *LMNA, PPARG, AKT2, CIDEC, CAV1*, and *ZMPSTE24* genes,[11] but these patients basically do not develop fever or show inflammation markers such as CRP. Basal ganglia calcification and pernio-like rash occurs in Aicardi-Goutières syndrome (AGS) with mutations in *TREX1, RNASEH2B*, etc., but AGS patients do not show lipodystrophy.[12] Weber-Christian disease shows panniculitis with recurrent fever and sometimes shows localized lipodystrophy, but the distribution of lipodystrophy is different. Polymyositis/dermatomyositis and inclusion body myositis (IBM) are important to exclude. CK is often elevated and a heliotrope-like rash on the eyelids is common in NNS patients.[1] Muscle biopsy of NNS shows typical polymyositis histological findings, and in some cases rimmed vacuoles were identified and DM or IBM was diagnosed.[13] Other differential diagnoses are systemic lupus erythematosus and

Box 1 Diagnostic criteria of Nakajo–Nishimura Syndrome (NNS)

1. Autosomal Recessive heritability (consanguineous marriage or patients with family history)
2. Pernio-like rash on hands and feet (develops in winter from infancy)
3. Recurrent remittent fever or periodic fever (not always present)
4. Nodular erythema with strong infiltration appear and disappear (sometimes annular)
5. Progressive localized lipomuscular dystrophy or emaciation (dominant in face and upper limbs)
6. Elongated clubbed fingers or joint contracture
7. Hepatosplenomegaly
8. Calcification in the basal ganglia

Notes: Patients with five or more of the eight clinical characteristics are diagnosed with NNS. When homozygous *PSMB8* mutations are detected, NNS is considered definite regardless of the number of clinical characteristics. In patients with five or more of the eight clinical characteristics but with no mutations in *PSMB8* gene, a diagnosis of probable NNS is made.

other autoinflammatory syndromes such as cryopyrin-associated periodic syndrome and TNF receptor-associated periodic syndrome.[14]

In 2010, two syndromes with similar phenotypes to NNS were reported,[15,16] and the responsible mutated genes were *PSMB8* in both cases.[3,4] CANDLE syndrome was reported by a group from Spain, the United States, and France,[15] and a group from Israel[17] showed most of the characteristics of NNS. In contrast, a group from the United States, Mexico, and Portugal reported patients with joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy (JMP) syndrome.[16] JMP syndrome is similar to NNS, but is different in that JMP syndrome showed seizure, anemia, and strong joint contracture, but no fever and no mental retardation. The similarities and differences among these three *PSMB8* gene-related syndromes are shown in Table 2.

Table 2 Comparison of clinical characteristics among three *PSMB8*-related diseases

Characteristics	NNS	JMP	CANDLE
Fever	+	–	+
Pernio-like rash	+	–	+
Erythema nodosum	+	+	+
Elongated clubbed finger	+	+	+
Lipomuscular dystrophy	+	++	+
Hepatosplenomegaly	±	+	+
Basal ganglia calcification	±	+	±
Seizure	–	+	–
Joint contracture	+	+++	–
Anemia	±	++	+

Abbreivations: NNS, Nakajo–Nishimura syndrome; JMP, joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature.

NNS/CANDLE/JMP as PRAASs

JMP syndrome appears to be a more severe phenotype of NNS or CANDLE syndrome, possibly due to the difference in mutation. *p*.G201V mutation of NNS causes a conformational change of the β5i subunit, which affects not only the chymotrypsin activity of the β5i subunit but also affects the binding of the adjacent β4 and β6 subunits, leading to less mature immunoproteasome and reductions of trypsin-like and caspase-like activity of β1i and β2i subunits.[1,2] In contrast, the p.T75M mutation in JMP syndrome specifically reduces the chymotrypsin activity of the β5i subunit, but the expression of immunoproteasome does not decrease.[14] It thus seems that the conformational abnormality of immunoproteasome complex is not essential for the development of JMP syndrome. The genetic mutation of CANDLE syndrome varies.[3] Many patients were homozygous for the p. T75M mutation of *PSMB8* gene, which is the same as in JMP syndrome.[13] However, other mutations such as p.C135X (stop codon) homozygous, p.A94P homozygous, and p. M117V homozygous of *PSMB8* were reported. Interestingly, combinations of heterozygous mutations of *PSMB8* and another proteasome subunit (PSMA3 or PSMB4) were also reported.[3,18] Furthermore, combinations of heterozygous *PSMB4* and other *PSMB4* hetero or *PSMB9* hetero were reported in CANDLE syndrome. There were even some patients with no mutations in any of the proteasomes after intensive sequencing. Recently, novel mutations in a proteasome assembly chaperone were found in a CANDLE patient.[19] This chaperone is called PAC2 (coded by *PSMG2*), and works with PAC1, 3, and 4 to aid in assembly of the α-ring subunits of proteasome (Figure 1B). The *PSMG2* mutations reduced all chymotrypsin-, trypsin-, and caspase-like enzymatic activities, ubiquitin accumulated in the cells, and the interferonopathy signature was upregulated to a level similar to that in confirmed CANDLE syndrome patients. Mutations in another chaperone, UMP1 (coded by *POMP*), for assembly of proteasome subunits were also reported in a CANDLE syndrome case and two infant cases of CANDLE-like syndrome with neutrophilic dermatosis, thrombocytopenia, and immunodeficiency with autoantibodies.[3,20] From these results, NNS, JMP, and CANDLE syndromes can be considered as PRAASs, and could be caused by a combination of various genetic mutations in the subunits of proteasome and related chaperone molecules.

In addition to the mutations in the 20S subunit of proteasome, there is a report of 10 patients who have mutations or deletions in *PSMD12* gene encoding Rpt5 of 19S subunit.[21] Of interest is that these patients showed neurological abnormalities and congenital malformations. Thus, depending on the subunit affected within proteasome complex, the phenotype seems to be completely different.

NNS as a type I interferonopathy

Due to the defect of immunoproteasome, ubiquitinated proteins and oxidized proteins accumulate in macrophages, epidermal keratinocytes, muscle cells, and so on. As a result, the expressions of various cytokines and chemokines are increased. Cytokines and chemokines were screened in the sera of four NNS and three CANDLE syndrome patients.[1,3] In almost all cases, IP-10 was extremely elevated, and IL-6 was modestly elevated in both NNS and CANDLE syndrome. IL-1β and TNFα were not elevated, and MCP-1 was slightly elevated in both NNS and CANDLE syndrome. In NNS, other cytokines including IL-2, IL-4, IL-5, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, eotaxin, FGF, G-CSF, GM-CSF, IFN-γ, MIP-1α, MIP-1β, and VEGF were not elevated. Although RANTES was slightly elevated in CANDLE patients, it was not elevated in NNS patients.

The induction of type I IFNs and related genes in NNS and CANDLE syndrome seems to be the key pathophysiological mechanism of inflammation,[3] and CANDLE syndrome is now listed as a type I interferonopathy by the International Union of Immunological Societies.[22] IFN is now classified into type I, type II, and type III; type I consists of IFN-α, β, ε, τ, κ, ω, δ, ζ, type II has only IFN-γ, and type III consists of IFN-$\lambda_{1\text{-}4}$. Type I IFNs are produced mainly from dendritic cells and macrophages, and usually act as anti-virus factors. Their expressions are regulated by interferon regulatory factors (IRF), and IRF3 and IRF7 are especially important.[23,24] Type I IFNs bind to interferon hetero receptors (IFNAR1/2) and activate Jak1/Tyk2, which phosphorylate STAT1 and STAT2, leading to the hundreds of IFN stimulated genes (ISGs) by the STAT1/STAT2/IRF9 complex. This IFN response is mainly induced by various pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through pattern recognition receptors such as toll-like receptors, RIG-I-like receptors, OAS-like second-messenger receptors, AIM2-like receptors, and DNA-dependent activators of IRFs. Excess amounts of nucleic acid, like DNA and RNA, in the cytoplasm and endosome, may induce strong ISG expression through such nucleic acid sensors. A representative type I interferonopathy is AGS, which is characterized by progressive brain atrophy, basal ganglia calcification, meningeal abnormality, and microcephalus. Several genetic mutations have been reported to be responsible for the development of AGS. These are *TREX1* (AGS1), *RNASEH2B* (AGS2), *RNASEH2C* (AGS3), *RNASEH2A* (AGS4), *SAM HD1* (AGS5), *ADAR1* (AGS6), and *IFIH1* (AGS7). All of these molecules are DNA or RNA binding proteins and act on the nucleic acid metabolism or nucleic acid signal transduction. Defects of these molecules lead to the accumulation of nucleic acids in the cells and act as DAMPs, causing interferonopathies. NNS and related PRAASs show increased expression of IFN signature, and type I IFN blockade treatment is effective as described later. Although it is not currently clear how the type I IFN signature is upregulated in PRAASs, accumulation of DAMPs or PAMPs in the cytosol due to reduction of immunoproteasome activity may trigger type I interferonopathy.

Treatment and prognosis of PRAASs

There are no gold standard treatment protocols for NNS and other PRAASs, but systemic corticosteroid treatment is usually used (daily prednisolone equivalent dose of 1–2 mg/kg for children, 0.4–1 mg/kg for adults, maintain the prednisolone dose at 5–10 mg/day in adults). This works for fever and skin rash, but is not effective for lipomuscular dystrophy. The disease easily relapses the following reduction of the corticosteroid dose, and although methotrexate, calcineurin inhibitor, and tocilizumab (anti-IL-6 receptor antibody) have been used, their efficacies were also partial.[25,26] Of special note is that baricitinib, a JAK1/2 inhibitor, was used in 10 CANDLE syndrome patients for a mean duration of 3 years, and was effective in more than 80% of the patients with 50% achieving remission despite no corticosteroid treatment.[27,28] One more case report of CANDLE syndrome effectively treated with baricitinib was published recently.[29] Although it is still not clear whether baricitinib is effective for lipodystrophy, baricitinib is currently a most promising treatment option for NNS/PRAASs.

Prognosis of PRAASs including NNS varies from patient to patient. Some die in infancy, but many grow to adulthood. Many of the adult cases develop severe lipodystrophy. Activity of daily living of patients decreases during the disease course due to muscle atrophy and joint contracture, and many die aged around 60 years, but some cases are very severe and patients die suddenly in their 30s.

Concluding remarks

The detection of mutations in the components of proteasome in NNS, CANDLE, and JMP syndromes opened doors to a new disease entity called PRAASs, having two major aspects of autoinflammation and lipodystrophy. The major key mechanism of autoinflammation seemed to be type I interferonopathy. Although the molecular mechanisms of lipodystrophy are still far from being understood, it seems that immunoproteasome is definitely related to lipodystrophy because siRNA-mediated downregulation of *PSMB8* disturbs adipocyte differentiation.[2] Further investigation will increase our understanding of these rare diseases and lead to new treatments.

Disclosure

The author reports no conflicts of interest in this work.

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