Clinical and pathological features in patients with Nakajo-Nishimura syndrome and inclusion body myositis

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Introduction

- Nakajo-Nishimura syndrome (NNS) is an autosomal recessive disease characterized by remittent fever, skin rash, emaciation of the face and upper body, and long gnarled fingers with contractures. Mutation of the gene encoding the β5i subunit of the immunoproteasome causes the accumulation of ubiquitinated or oxidative protein due to proteasomal dysfunction [1].
- Inclusion body myositis (IBM) is a form of inflammatory myositis characterized by weakness and atrophy of the quadriceps femoris (QF) and flexor digitorum profundus (FDP) [2].
- Although the pathogenesis of IBM is unknown, proteasomal dysfunction is thought to be a major mechanism. In this study, we investigated the clinical and pathological features of NNS and IBM.

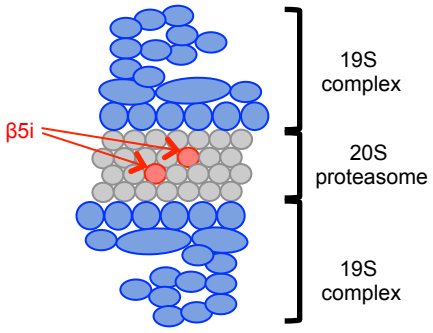
Tentative criteria for the clinical diagnosis of NNS [3]

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

1. Autosomal recessive inheritance
2. Pernio-like purplish rash on the hands and feet
3. Haunting nodular erythema with infiltration and induration
4. Repetitive spiking fever
5. Long clubbed fingers and toes with joint contractures
6. Progressive partial lipomuscular atrophy and emaciation (marked in the upper body)
7. Hepatosplenomegaly
8. Basal ganglia calcification

Pathogenesis of NNS

Mutation of G201V in the *PSMB8* gene
↓
Reduction of the chymotripsin-like activity in β5i
↓
Altered conjugation of the β4 and β6 subunits
↓
Deformation of immunoproteasome complexes
↓
Decrease in mature immunoproteasomes
Reduction of the tripsin-like activity in β1i and the caspase-like activity in β2i
↓
Accumulation of ubiquitinate proteins, leading to the increase of oxidative proteins



Methods

- We examined the clinical symptoms (e.g., region of weakness), muscle magnetic resonance imaging(MRI) findings, and laboratory data of 4 NNS patients.
- Immunohistological studies of muscle biopsy specimens from 2 NNS patients and 4 IBM patients were also performed.
- We prepared frozen sections of IBM and NNS muscles and paraffin sections of NNS muscles for immunostaining.
- We used hematoxylin-eosin (HE), anti-p62 antibody, anti-lys 63-linked polyubiquitin antibody, and anti-lys 48-linked polyubiquitin antibody for staining.

Results

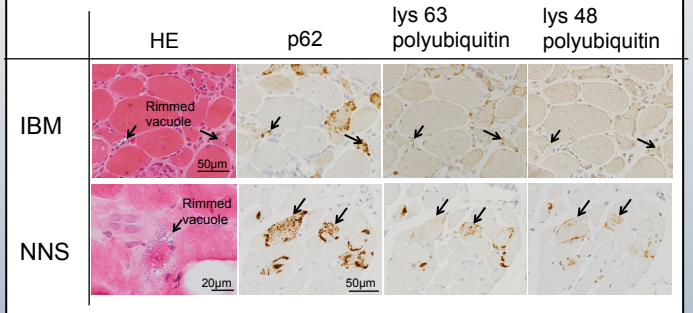
Demographic data of NNS patients

	Case 1	Case 2	Case 3	Case 4
Age (years)	11	41	37	39
Sex	Male	Male	Female	Male
Mutation	Homozygous G201V mutation, *PSMB8* gene			
Age at onset	3 months	2 years	6 months	2 years
Symptoms at onset	Fever Skin rash	Fever Skin rash (chilblain)	Chilblain	Swelling of cervical lymph nodes Erythema
Muscle weakness	Flexors of fingers, Quadriceps	Flexors of fingers, Quadriceps	Proximal part of upper limb, Flexors of fingers	Proximal parts of upper and lower limbs, Flexors of fingers
Impairment of the opening of the cricopharyngeal muscle	Not examined.	(-)	(-)	(+)
Muscle MRI (muscles of high intensity)	FDP	FDP	FDP, Quadriceps	FDP, Quadriceps
Treatment	Betamethasone	Prednisolone	Tocilizumab, Prednisolone	Prednisolone

∗ Muscles highlighted in red are also affected in IBM

- FDP and Quadriceps showed high intensity in T2-weighted images of both NNS and IBM patients.

Muscle pathology of NNS and IBM patients



- Rimmed vacuoles and p62-, lys63 polyubiquitin-, and lys48 polyubiquitin- positive deposits are seen in both NNS and IBM specimens.

Conclusions

- We identified rimmed vacuoles and p62-, lys63-linked polyubiquitin-, and lys48-linked polyubiquitin-positive deposits in both NNS and IBM patients.
- It is known that p62 and lys63-linked polyubiquitin are related to selective autophagy [4], and lys48-linked polyubiquitin works as the signal of proteasomal protein degradation [5]. Thus, both in NNS and IBM, dysfunction of autophagy and proteasome may occur, leading to accumulation of abnormal proteins.
- Our results support that the previously reported hypothesis that proteasomal dysfunction is one of the causes of IBM [6].

References

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COI disclosure: Principal presenter is Megumi Mori
No potential COI to disclose