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 proteins due to proteasomal dysfunction.
- Inclusion body myositis (IBM) is a form of inflammatory myositis characterized by weakness and atrophy of the face and upper body, and long gnarled fingers with contractures. Mutation of the gene encoding the β4i subunit of the immunoproteasome causes the accumulation of polyubiquitin and oxidative proteins due to proteasomal dysfunction.
- 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

- 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 limb muscle 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 tripapsin-like activity in β1i and the caspase-like activity in β2i
- Accumulation of ubiquitinated 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 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

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Mutation</td>
<td>Homozygous G201V mutation, PSMB8β5i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>3 months</td>
<td>2 years</td>
<td>6 months</td>
</tr>
<tr>
<td>Symptoms at onset</td>
<td>Fever, Skin rash</td>
<td>Fever, Skin rash (chilblain)</td>
<td>Chilblain</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Flavors of fingers, Quadriceps</td>
<td>Flavors of fingers, Quadriceps</td>
<td>Proximal part of upper limb, Flavors of fingers</td>
</tr>
<tr>
<td>Impairment of the opening of the orocricopharyngeal muscle</td>
<td>Not examined.</td>
<td>(-)</td>
<td>(−)</td>
</tr>
<tr>
<td>Muscle MRI (muscles of high intensity)</td>
<td>FDP</td>
<td>FDP</td>
<td>FDP, Quadriceps</td>
</tr>
<tr>
<td>Treatment</td>
<td>Betamethasone</td>
<td>Prednisolone</td>
<td>Tocilizumab, Prednisolone</td>
</tr>
</tbody>
</table>

- *Muscles highlighted in red are also affected in IBM

Muscle pathology of NNS and IBM patients

<table>
<thead>
<tr>
<th>HE</th>
<th>p62</th>
<th>lys 63 polyubiquitin</th>
<th>lys 48 polyubiquitin</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBM</td>
<td>Rimmed vacuoles and p62-, lys63 polyubiquitin-, and lys48 polyubiquitin-positive deposits are seen in both NNS and IBM specimens.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 6, and lys48-linked polyubiquitin works as the signal of proteasomal protein degradation. 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