Patients and Methods/Material and Methods: We detected a novel heterozygous MFN 2 gene mutation (733A>C:S245R) in a family lineage of CMT2A, which presented the abnormality of visual evoked potentials. In the next step we have generated a transgenic mouse expressing this mutant (S245R) MFN 2 protein in neurons and observed the optic nerves of these transgenic mice.

Results: We have found that in the optic nerves of these mice, the pathological changes of mitochondria appeared significantly smaller than those of control mice and the mitochondria in the state of incomplete fusion were observed only in the transgenic mice.

Conclusion: MFN 2 gene encodes a mitochondrial outer membrane protein that participates in mitochondrial fusion. Although pathogenesis of CMT2A in part has been described as the abnormality in mitochondrial axonal transport and its distribution in vitro studies, our results suggest that abnormality in mitochondrial fusion may also contribute to the disease process.

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1275

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SHIFT 3 - NEUROGENETICS

Effects of GFAP promoter polymorphism on age at onset of Alexander disease

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Background: Alexander disease (AxD) is a rare neurodegenerative disorder caused by mutation of the glial fibrillary acidic protein (GFAP) gene. It has been reported that a -250-bp C/A single-nucleotide polymorphism (SNP) of the *GFAP* promoter (rs2070935) influences the level of transcription: higher *GFAP* expression in the C compared with A allele. Our previous study showed the possibility of the C/C genotype of rs2070935 being associated with an earlier onset and the more rapid progression of ambulatory disability than the other genotypes among ten AxD patients.

Objective: To confirm the relationship between rs2070935 and the age at onset by recruiting additional patients.

Patients and Methods/Material and Methods: We genotyped rs2070935 in 20 additional AxD patients and combined the data with those of the 10 previous patients. The age at onset was compared, focusing on rs2070935 genotypes, using ANOVA and the t-test.

Results: In the total of 30 patients, there was no significant difference in the age at onset among three genotypes. A reason for this negative finding may be the difference in *GFAP* mutations. Therefore, we subsequently focused on a subgroup patients with an identical *GFAP* mutation. Among five patients with N386S or three with R79H, the C/C allele of rs2070935 was associated with a younger age at onset.

Conclusion: The results suggest that the rs2070935 C allele is associated with an early age at onset among AxD patients with identical *GFAP* mutations.

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1276

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SHIFT 3 - NEUROGENETICS

Revised guidelines for diagnosing Alexander disease and their validity

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Background: Alexander disease (AxD) is a rare neurodegenerative disorder characterized by white matter degeneration and the formation of cytoplasmic inclusions, caused by heterozygous mutations in *GFAP*, encoding the glial fibrillary acidic protein (GFAP). We conducted a nationwide survey in Japan and proposed guidelines for the diagnosis of AxD based on neurological and MRI findings (Yoshida T, et al. J Neurol 2011).

Objective: The definite diagnosis of AxD based on these guidelines includes the detection of *GFAP* mutations and/or presence of the characteristic pathological findings. However, a genetic test of *GFAP* can only be performed at a few facilities in Japan, and brain biopsy of living patients for diagnosing AxD is seldom performed. Therefore, we have revised the guidelines and established "probable AxD" to provide a diagnostic clue even without these two definitive diagnostic methods (Table 1).

Table 1: Revised guidelines for diagnosing Alexander disease

A. Neurological findings
1. convulsions
2. macrocephaly
3. psychomotor developmental delay/mental retardation, convulsions
4. motor symptoms: muscle weakness, spastic paresis, cerebellar ataxia, muscle rigidity
5. bulbar/pseudobulbar palsy: dysphagia, dysarthria, dysphonia
6. autonomic dysfunction: orthostatic hypotension, sphincter abnormalities, sleep apnea
7. palatal myoclonus
8. episodic vomiting

B. MRI findings
1. cerebral white matter abnormalities with frontal lobe predominance
2. periventricular rim b) supportive features
3. signal abnormalities with swelling or atrophy of the basal ganglia and thalami
4. contrast enhancement
5. brainstem lesions
1) signal abnormalities in midbrain
2) signal abnormalities or atrophy of the medulla oblongata and/or cervical cord
6. signal abnormalities in the hilum of the dentate nucleus

C. Genetic and pathological tests
1. genetic test: *GFAP* mutation
2. pathological findings: existence of numerous Rosenthal fibers in addition to gliosis and loss of myelin

D. Differential diagnoses
Pelizaes-Merzbacher disease, megalencephalic leukodystrophy with subcortical cysts, adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe disease, vanishing white matter disease, Canavan disease, multiple sclerosis, neuromyelitis optica, progressive multifocal leukodystrophy, brain tumor, CADASIL, CARASIL, etc.

Definite: One of the items listed in 1. and 2. in C. and one of the items in a. and b. listed below must be satisfied:
a. more than one of the items from 1. to 3. in A. and more than one of the items from 1. to 5. in B.
b. more than one of the items from 4. to 8. in A. and item 5. 2) in B.

Probable: One of the items in a. and b. listed below and one of the differential diagnoses listed in D. must be satisfied:
a. more than one of the items from 1. to 3. in A. and more than four of the items from 1. to 5. in B.
b. more than one of the items from 4. to 8. in A and both of 5. 2) and 6. in B.

Patients and Methods/Material and Methods: To confirm the validity of the revised guidelines, we applied them to 78 consecutive patients, including 28 AxD patients with *GFAP* mutations and 50 patients with suspected AxD but without the detection of any *GFAP* mutations.

Results: The sensitivity and specificity were 57.1 and 94%, respectively.

Conclusion: The relatively low sensitivity may be due to only 41% of patients progressing to enhanced MRI, influencing criteria a. in "probable AxD", and due to difficulty in judging the characteristic MRI findings including brainstem atrophy and signal abnormalities, influencing criteria b. However, "probable AxD" facilitated high specificity, suggesting that we can make an accurate diagnosis even when neither genetic tests nor brain biopsy is available.

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SHIFT 3 - NEUROMUSCULAR DISORDERS

Preclinical biomarkers in spinal and bulbar muscular atrophy

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Background: Spinal and bulbar muscular atrophy (SBMA) is a hereditary neuromuscular disease characterised by progressive muscle weakness and antecedent signs including hand tremor.

Objective: To evaluate biological changes during the preclinical progression of SBMA.

Patients and Methods/Material and Methods: We analysed longitudinal changes in biochemical parameters obtained during periodic health examinations before and after the diagnosis of SBMA. We estimated trajectories of clinical markers across years from the onset of weakness using linear mixed models and compared these trajectories with those estimated for control subjects. Moreover, we examined the relationship between serum creatinine level and the onset of symptoms using Kaplan-Meier curves.

Results: Twenty subjects with genetically confirmed SBMA and 20 healthy male control subjects were included in the analysis. In SBMA patients, we evaluated data for a period of 19.6 $\pm$ 7.8 years including 13.2 $\pm$ 7.1 years of preclinical SBMA. Decreases in serum creatinine occurred more than ten years before the onset of subjective muscle weakness. The mean serum creatinine concentration was 0.58 mg/dl at the onset of weakness in SBMA patients compared to 0.93 $\pm$ 0.09 mg/dl upon final evaluation in control subjects. Moreover, in SBMA patients, the onset of tremor corresponded to the time at which serum creatinine levels decreased below 0.8 mg/dl. Serum levels of alanine transaminase and aspartate transaminase also showed tendencies to increase in the preclinical phase of SBMA.

Conclusion: Serum creatinine begins to decrease prior to the onset of weakness in SBMA, and could be a potential biomarker for disease progression as well as the efficacy of therapeutics in preclinical SBMA.

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1278

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SHIFT 3 - NEUROMUSCULAR DISORDERS

Quantitative muscle ultrasound is useful for evaluating secondary axonal degeneration in chronic inflammatory demyelinating polyneuropathy

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Background: The presence or absence of secondary axonal degeneration may be important for prognostication of chronic inflammatory demyelinating polyneuropathy (CIDP). It can be evaluated by nerve conduction study (NCS), needle electromyography or nerve biopsy, although each method has limitations. In muscle ultrasound (MUS), increased echo intensity (EI) and decreased muscle thickness (MT) represent muscle denervation due to axonal degeneration in neurogenic disorders. Hence, MUS would be a new tool to detect secondary axonal degeneration in CIDP.

Objective: To examine the utility of MUS in evaluating secondary axonal degeneration in CIDP.

Patients and Methods/Material and Methods: Subjects consisted of 16patients with CIDP. EI and MT were measured quantitatively in the abductor pollicis brevis, abductor digiti minimi, and first dorsal interosseous. Raw values were converted into z-scores using the data from 60 normal controls (NCs).

Results: Six out of 45 muscles showed abnormally high EI and low MT suggesting denervation following secondary axonal degeneration. These six muscles belonged to two patients with long history, unresponsiveness to treatment and long interval from onset to initial therapy. There were no significant differences between the CIDP and NC groups regarding EI and MT ($P = 0.23$ and 0.67 respectively) although NCS showed obvious demyelinating abnormalities in all CIDP patients.

Conclusion: The fact that MUS parameters remained normal in most CIDP patients may suggest that they are preserved unless secondary axonal degeneration occurs. MUS is a promising tool for evaluating prognosis and treatment effect in patients with CIDP.

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SHIFT 3 - NEUROMUSCULAR DISORDERS

Anti-Mi-2 antibody positive myositis: Clinical and histopathological features in three patients

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Background: Anti-Mi-2 antibody have been detected dominantly in patients with dermatomyositis and characterized by typical cutaneous lesions, mild muscle weakness, and well-response to corticosteroid treatment.

Objective: The aim of this study is to describe the clinical and histopathological features of anti-Mi-2 antibody positive myositis.

Patients and Methods/Material and Methods: Three patients with anti-Mi-2 antibody positive myositis (1 female and 2 male) diagnosed in Yamaguchi University from 2015 to 2016 were included. Clinical, laboratory, and histopathological features were evaluated.

Results: Patient's age were 57, 69, 80 years old. Two of 3 patients presented skin eruptions. All patients had severe proximal and trunk muscle weakness with dysphagia. No patients had muscle pain. Serum creatine kinase levels ranged from 2125 to 14885 IU/L. Muscle biopsies showed necrotic and regenerative muscle fibers in all 3, infiltrates of lymphocytes in 2, perifascicular atrophy in 1, and diffuse high expression of major histocompatibility complex class 1 in all 3. Although administration of high dose corticosteroid showed no effect, combination therapy of corticosteroid and intravenous immunoglobulins improved the muscle weakness and dysphagia in two patients. All patients had neither malignant tumor nor interstitial pneumonia.