White matter connection's damage, not cortical activation, leading to language dysfunction of mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes

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Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS) is a metabolic disorder characterized by hyperlactic acidemia and stroke-like symptoms.[1] The clinical symptoms of MELAS are complex and diverse, with an incidence of 39.47% of aphasia.[2] MELAS is often considered to be gray matter damage, little studies investigated its white matter changes. However, many studies have shown that for stroke patients, white matter played an important role in language dysfunction, especially in conductive aphasia.[3] Therefore, language function disorder is an ideal target for exploring white matter's role in MELAS. This study aimed to discover which damage caused the abnormal symptoms in a particular case. First, we measured grey and white matter sizes of the MELAS patient and controls. Second, we investigated the cortical activation's decrease (based on a Blood oxygenation level dependent functional magnetic resonance imaging [BOLD-fMRI], white matter connections' damage (based on diffusion tensor imaging [DTI]) and proposed a hypothesis about which of them may be the most likely cause by comparing the two together. This was first done worldwide.

A 35-year-old man complained about speech disorder and right-hand numbness for one day. One day before admission (January 9, 2018, at 10:00 AM), the patient had difficulty repeating and finding words, especially naming items. He could write Chinese characters, but not Chinese phonetic alphabet. At 11:00 AM, the patient had weakness with numbness in right hand and was difficult to write. At 3:00 PM, the patient was unable to understand others' words and text messages. These symptoms were significantly relieved after 1 min and occurred again within 1 min of the interval and worse than before. The patient had no dysphagia, choking when drinking water, dizziness, or limbs twitching. The patient had a history of diabetes mellitus for 5 years, hearing loss of the right ear for about 2 years, light smoking and alcohol intake. Physician examination: height of 172 cm, weight of 66.5 kg, right handed, conductive aphasia (West aphasia battery, AQ = 62.9, the score of information content and fluency, grammatical ability and wrong language in self-speaking were 7 and 5. And in oral understanding: the score of yes or no question was 57, the score of recognition of words was 58 and the score of sequential instruction was 46. The score of retelling was 61. Lastly, in naming part, the scores of object naming, spontaneous naming, complete sentences and reactive naming were 30, 8, 7, and 8), misreading disorder, left and right disorder, miscalculation, slight cognitive impairment (Mini-Mental State Examination [MMSE]: 30, Montreal Cognitive Assessment [MoCA]: 20, graduated, white-collar). Pure tone audiometry showed bilateral neurodeafness (right side: 60–80 dB, left side: 40–50 dB, acoustic impedance: type A). Bundle sensations of the right-side limbs were decreased compared to the left side. MRI showed abnormal signal shadow in bilateral occipital lobes and left temporal parietal lobe, especially in the cortex. "Lace sign" which is

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a characteristic marker of MELAS in diffusion weighted imaging (DWI) sequence was shown in Figure 1A. Blood lactic acid and gene examination were completed. The Sanger sequencing of the patient's urine found a mutation of chM3243 which is the most common mutation of MELAS.

From March 2018 to April 2018, 39 "healthy" subjects aged 30 to 60 years (controls) were recruited from the nearby community of Beijing Tiantan Hospital. The controls had already been confirmed with no abnormalities through MRI scan, cognition and language examination: no evidence for cerebral infarction, cerebral hemorrhage, neurodegenerative diseases, traumatic brain injury, multiple sclerosis, aphasia, *etc.*, no anxiety or depression (Hamilton Depression Scale [HAMD] and the Hamilton Anxiety Scale [HAMA]<8), and no mental or psychiatric diseases, no drug addiction. MRI scans included T1-weighted 3D structural, DTI and task fMRI. The subject was asked to think about the noun in his/her mind during MRI scan and then we add 15 more pictures and asked "have you seen this picture and if yes what did you think" to make sure that the subject really could do the task, the correct rates of this MELAS patient and controls were 67% and 95%, respectively.

The Voxel Based Morphometry (VBM8) toolbox of the Statistical Parametric Mapping software (http://www.fil.ion.ucl.ac.uk/spm/) was used to analyze the structural MRI data and task fMRI data. On the single-subject level, the data were analyzed according to the fixed-effects model. Contrast images were created by subtracting the fixation images from the picture naming images. On the second level, activation differences between the MELAS patient and controls were computed on the whole brain. And DTI image preprocessing was implemented using PANDA software (a pipeline tool for analyzing brain diffusion images, http://www.nitrc.org/projects/panda/), and calculating main diffusion metrics, that is, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (DA) and radial diffusivity (DR) were carried out successively. Subsequently, the Tract-Based Spatial Statistics (TBSS) analysis was carried out. The Singleton-*vs*-Group (Prediction Interval Test) design based on general linear model (GLM) in the FMRIB software library (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) combined with a permutation-based inference tool for nonparametric statistical thresholding (the "randomise" tool) was used to compare the differences between the single typical patient and controls. A $P < 0.05$ was considered as statistical significance (family-wise error [FEW] corrected for multiple comparisons) using the threshold-free cluster enhancement (TFCE) option in the "randomize" permutation-testing tool.

No statistical difference was found in grey and white matter sizes between the MELAS patient and controls. The brain area activated in MELAS patient decreased during the picture naming task, comparing with controls, but there was no statistical difference between 2 groups after multiple comparison correction. Compared to the controls, the FA value decreased significantly in the entire brain range, and MD value increased significantly in the

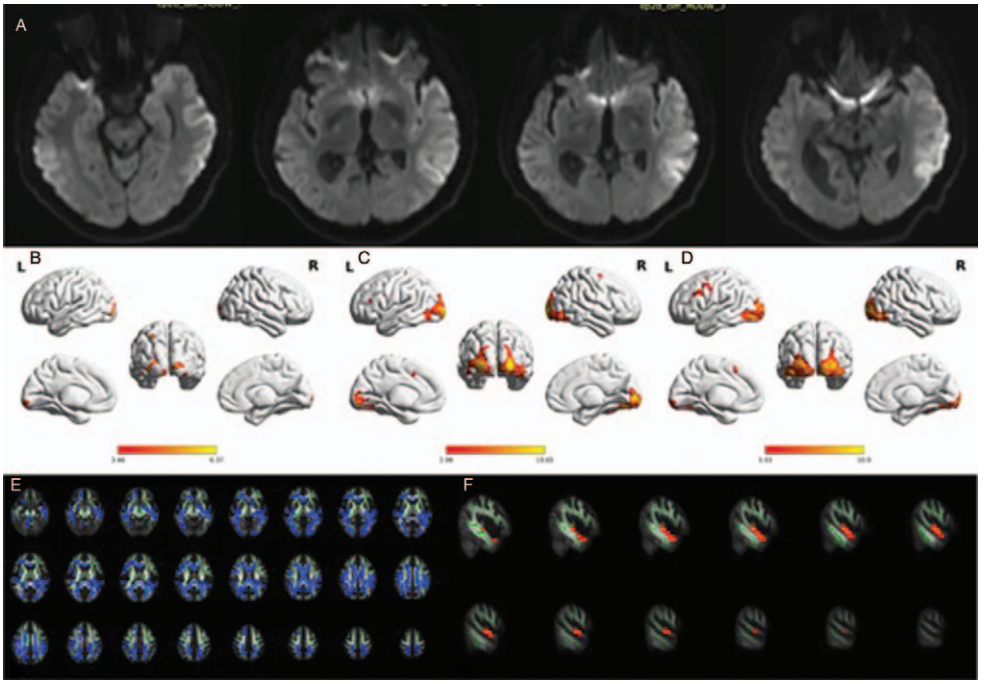

Figure 1: Imaging data of one MELAS patient and normal controls. (A) DWI sequence of brain MRI at January 12, 2018. (B) Active Brain Region for Picture Naming Task (SXY, a MELAS patient, $P < 0.05$, FDR correction). (C) Active Brain Region for Picture Naming Task (1 subject of control group, $P < 0.05$, FDR correction). (D) Active Brain Region for Picture Naming Task (control group, 1 sample *t* test, $P < 0.05$, FDR correction). (E) TBSS analysis: the FA value of MELAS patient decreased significantly in the entire brain range compared to control group ($P < 0.05$, TFCE-FEW correction). (F) TBSS analysis: MD value increased significantly in the lower longitudinal beam at the back of the left temporal lobe ($P < 0.05$, TFCE-FEW correction). DWI: Diffusion weighted imaging; FA: Fractional anisotropy; FDR: False discovery rate; FEW: Family-wise error; MELAS: Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes; MD: Mean diffusivity; MRI: Magnetic resonance imaging; TBSS: Tract-Based Spatial Statistics; TFCE: Threshold-free cluster enhancement.

lower longitudinal beam at the back of the left temporal lobe in MELAS patient in DTI study [Figure 1B–1F]. It's clearly understood that there was no difference of VBM in grey and white matter between MELAS and controls. This is because that brain atrophy would occur in chronic stage in MELAS, while brain edema could occur during acute stage in some MELAS patients.[4] So this finding might due to acute stage of the patient.

MELAS syndrome is a more common type of mitochondrial encephalomyopathy, and a recent study showed that MELAS patients had high perfusion and increased oxygenation ability in the acute phase, and decreased perfusion and oxygenation in the chronic period.[5] Therefore, the decreased cortical activation in our study could be explained as impaired oxygen utilization, which was consistent with previous studies. In DTI studies, FA value showed that white matter connections' damage was significant in the entire brain of the MELAS patient while MD value just significantly increased in the lower longitudinal beam at the back of the left temporal lobe. This might indicate that the FA value was more sensitive than MD value and the lower longitudinal beam at the back of the left temporal lobe may be most damaged and relative to the patient's conductive aphasia. For the retelling of language, there are 2 paths, one is the phonetic path and the other is the sematic path. The back of the left temporal lobe is believed in charge of the sematic path which can explain the conduction aphasia of this patient.[6,7] MELAS is easy to relapse, and the symptoms are always changeable. Patients often have multiple symptoms that interfere with each other, with their conditions change unexpectedly and shortly. First onset, single stable symptom of conductive aphasia, concentrate lesion, all these make the patient an ideal sample for studying white matter connections and raising a brand-new hypothesis, though the cause-effect relationship unclear and unproven for the moment.

MELAS is believed as a cortical disease,[8] but in this study, there was no cortical activations' statistic difference in the picture naming task fMRI while the damage to white matter was so remarkable especially by FA value. So we came up with a hypothesis that "it's not cortical activation but white matter connection's damage leading to language dysfunction of MELAS". Studies have shown that dendrites (white matter) produced nearly 10 times more electrical pulses than the cell body, accounting for more than 90% of the nerve tissue and they were the main forms of perception, learning, and memory formation.[9] We did not know why this happened, and what we wanted to emphasize was that we should pay more attention to the white matter in MELAS patients. More researches on white matter and its neuromuscular pathology are needed to be done to confirm this. The causality between white matter connections' damage and functional abnormality like aphasia is hopefully remedied by follow-up of this patient and a cohort study of more cases.

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Conflicts of interest

None.

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