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Investigation of Alterations in Brain White Matter of Individuals Diagnosed with Smith-Lemli-Opitz Syndrome and Sjögren-Larsson Syndrome

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Background

Smith-Lemli-Opitz Syndrome (SLOS) and Sjögren-Larsson Syndrome (SLS) are sterol and isoprenoid disease caused by recessive autosomal mutations to genes DHCR7 and ALDH3A2 respectively. Both mutations cause disruption of lipid biosynthesis.

Clinical symptoms:
Neurological
Cognitive
Physical

Currently, there is no cure for either disorder.

Recent incorporation of Magnetic Resonance Imaging (MRI) in the investigation of SLOS and SLS has resulted in evidence suggesting brain atrophy and decreases in white matter density with progression of the diseases; however, it has never been quantitatively studied.

Objective

To monitor the white and gray matter alteration in individuals diagnosed with SLOS and SLS by the use of quantitative MRI.

Hypotheses

1. We predict lower white matter volumes in SLOS and SLS when compared to healthy controls.
2. We anticipate a decrease in white matter volume over time in SLOS and SLS patients with longitudinal follow-up.

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METHODS

Study participants:
SLOS (n=2) and SLS (n=16) subjects, healthy controls (n=97)

MRI image analysis:
T1-weighted images were processed through FreeSurfer (FS) Image Analysis Suite version 5.3

Statistics:
t-test with unequal variance and Welch degrees of freedom was used to evaluate discrepancies between SLOS + SLS patients and controls

Separating each of the group, a one way ANOVA was used to assess statistical significance

A univariate analysis of variance was used to control for the covariate of age

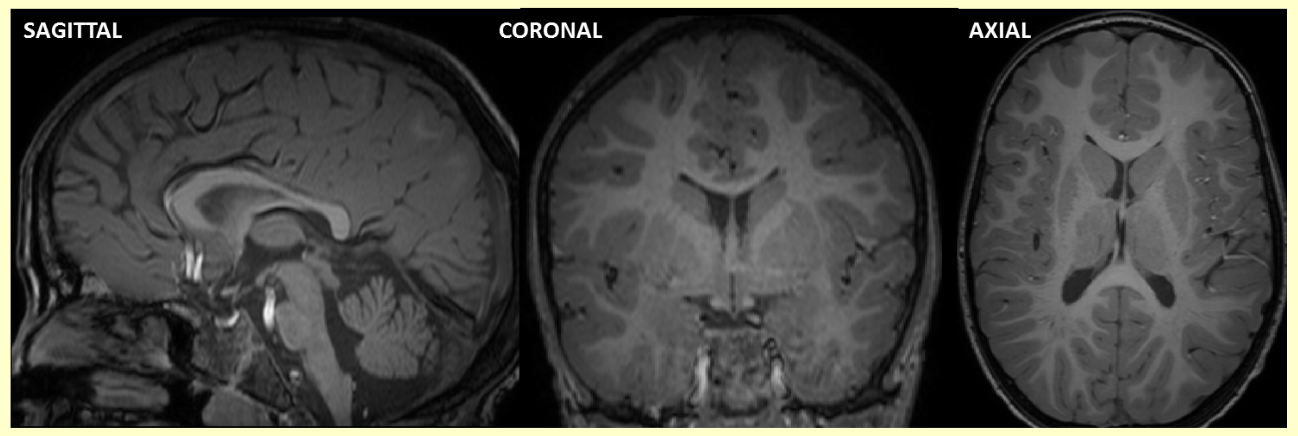

Figure 1. T1-weighted image in three anatomical planes; SLS male, 7 year old

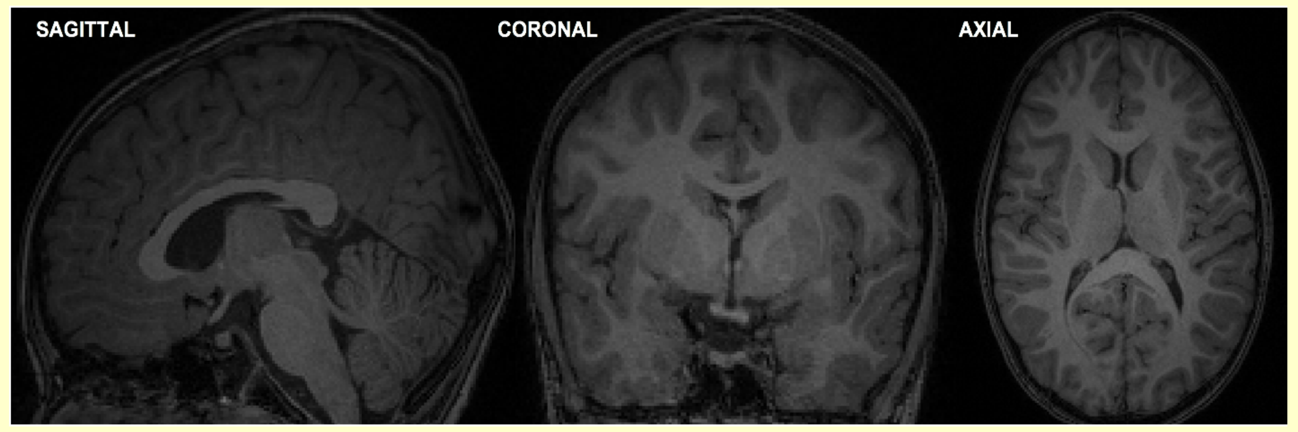

Figure 2. T1-weighted image in three anatomical planes; healthy control male, 7 year old

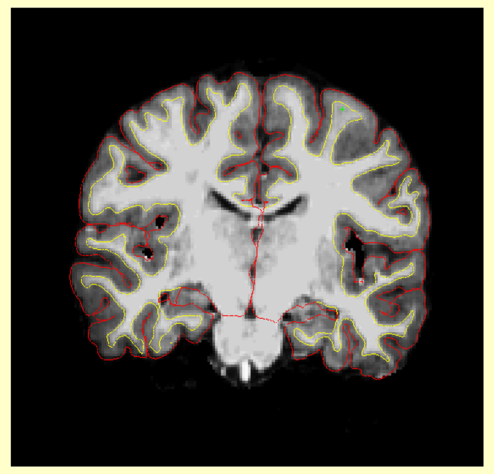

Figure 3. FS pial and white matter surface

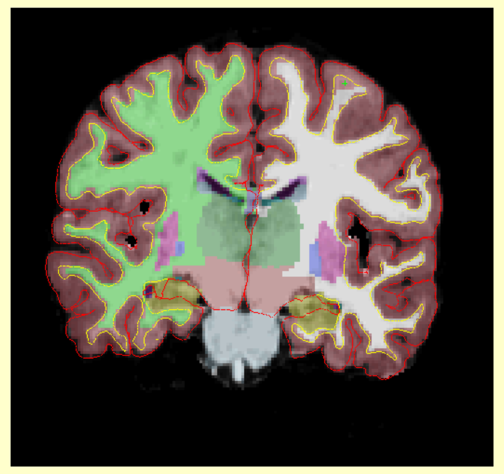

Figure 4. FS segmented brain, pial white matter surface

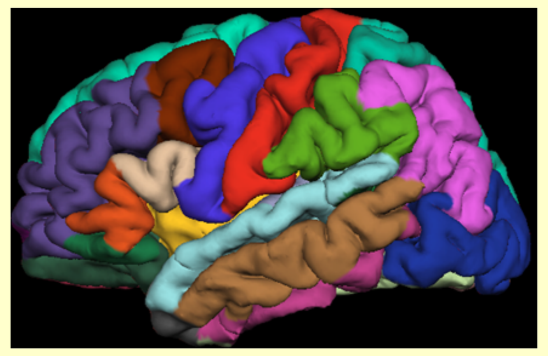

Figure 5. FS 3D surface model

Figure 6. Ratio of cerebellar white matter to total intracranial volume across age

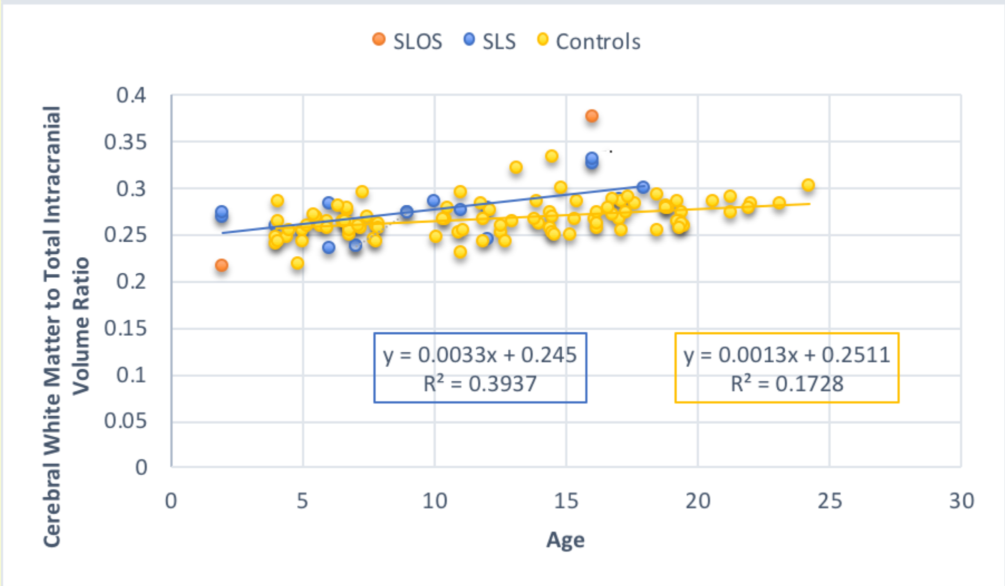

Figure 7. Ratio of cerebral white matter to total intracranial volume across age

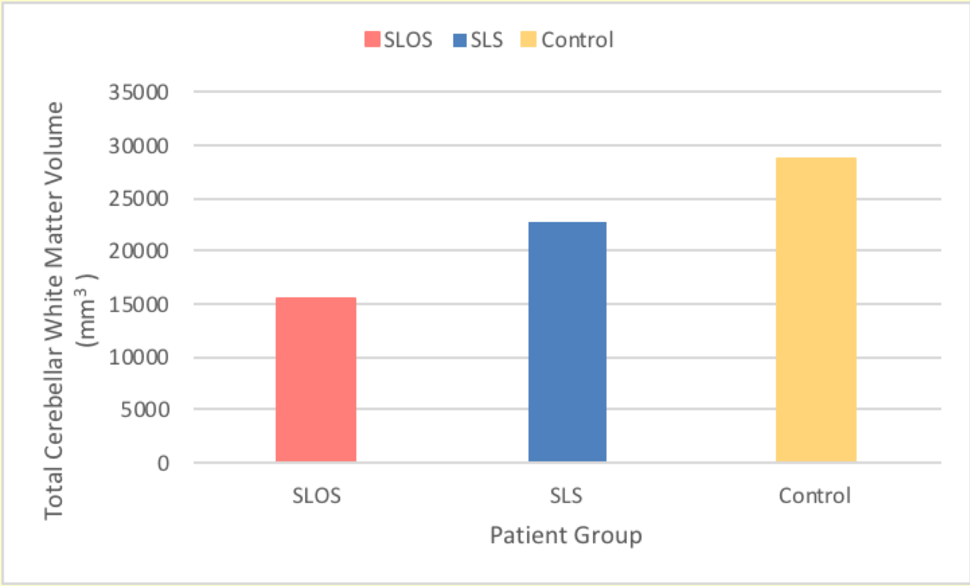

Figure 8. Comparison of total cerebellar white matter volume between patient groups

Figure 9. Average cortical thickness versus age

RESULTS

SLS and SLOS affected individuals displayed lower volumetric values of cerebellar white matter compared to controls. Difference in cerebellar white matter between SLOS + SLS and controls was found to be statistically significant with a $p < 0.001$ (Figure 6).

Volumetric values for cerebral white matter were consistent between SLS, SLOS, and healthy control subjects (Figure 7).

Estimated means of cerebellar white matter volume showed statistically relevant differences, $p < 0.001$ (Figure 8).

Average cortical thickness displayed a declining value with respect to age (Figure 9).

CONCLUSIONS

Comparisons of individuals with SLS, SLOS, and healthy controls revealed lower cerebellar white matter volume across age.

Lower cerebellar volumes in SLOS and SLS individuals suggest a possible cerebellar involvement.

Cortical thickness and cerebral white matter volumes for individuals with SLOS, SLS, and healthy controls illustrated a typical pattern seen in normally developing brains.

Future directions:
Analysis of longitudinal MRI data.

Employing techniques sensitive to white matter microstructure and neuronal integrity such as diffusion tensor imaging and magnetic resonance spectroscopy.

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