DIFFUSION TENSOR IMAGING IN NIEMANN-PICK C DISEASE ON 3T

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Introduction:

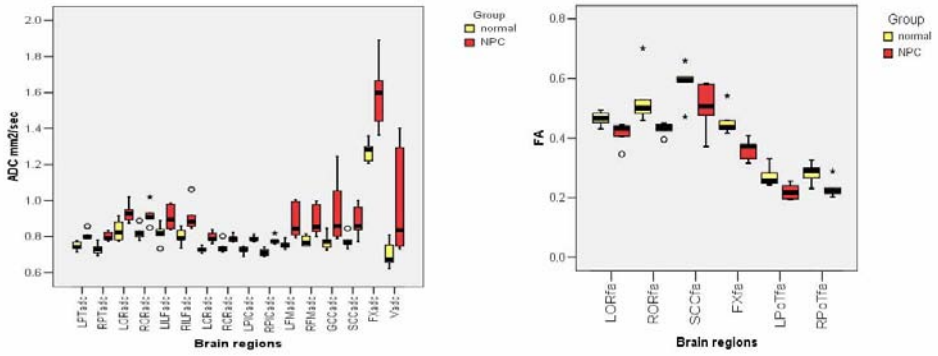
Niemann-Pick C (NPC) disease is an autosomal recessive neurovisceral lipid storage disorder characterized at the cellular level by accumulation of unesterified cholesterol and glycolipids in the endosomal/lysosomal system. The phenotype of NPC is remarkably variable, ranging from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. In recent years, NPC1 and NPC2 genes have been identified[1]. Although the role of the identified proteins in the intracellular cholesterol is not yet well understood, new drug therapies are beginning to emerge. Imaging findings of the brain include cortical, brainstem, and cerebellar atrophy, sometimes with corpus callosum atrophy, without obvious signal abnormalities on MRI[2]. As atrophy is not easily monitored, a quantifiable imaging method should be sought to enable therapeutic monitoring. We now attempt to assess feasibility of quantifying brain abnormalities in NPC by diffusion tensor imaging. We measured the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) of 6 NPC patients and compared them to a group of normal volunteers on a 3T magnet.

Methods:

6 patients (age 4 to 21 years) diagnosed with Niemann-Pick C Disease, were imaged with parental consent under an IRB approved protocol. The MR studies were performed on a 3.0T MR system (Philips Intera with SENSE head coil, software release 6.1.5; Philips Medical Systems, Best, The Netherlands). 6 healthy volunteers (mean age 31, range 24 – 40) were recruited as normal controls. Diffusion tensor MR imaging was performed using a single-shot, spin echo, echo planar DTI sequence. 32 directions (max b factor = 1000) were used. Matrix = 128 x 128; FOV = 240 mm; slice thickness 2.5 mm; TR = 6000 ms; TE = 76 ms; no. of averages = 1; acquisition time = 3:36 min. The study was repeated 3 times, and registered to 1 set of data set using Philips PRIDE tool. The same tool was used to compute the FA and ADC maps. Regions of interest (ROIs) were drawn in 21 different regions of the brain, including in the brainstem, cerebellum, cerebral white matter, and deep grey nuclei, to measure the FA and ADC. To maintain consistency, the ROIs were drawn by a single radiologist. Mann-Whitney U tests were used to determine significant differences between NPC patients and the normal cohort in the FA and ADC in the different regions of the brain. Linear correlation analysis was used to examine for correlation between age and either FA or ADC in the normal volunteers.

Results:

The results show that in the NPC patients there is significant elevation of ADC in many regions of the brain compared to the normal volunteers, including the brainstem (pyramidal tract), cerebellum (vermis), and corpus callosum. This correlates well with reported imaging findings[2,3]. The abnormality in the ADC of the motor tracts, including the pyramidal tract in the brainstem, posterior limb of the internal capsule, and corona radiata, may relate to the spasticity seen in these children. Fornix is affected as well, which has not been described in the literature. Abnormal ADC was also seen in the optic radiations and inferior longitudinal fasiculus. The only tracts that showed significant abnormalities in the FA were the optic radiations, posterior thalamus, and fornix. No correlation was found between age in either FA or ADC in the normal volunteers, and literature reports suggest that FA and ADC are stable after 2 years of age[4], suggesting that the difference between the patients and normals was due to the disease rather than different age distribution of the two populations.



Figures. Boxplots showing the differences in ADC (**left**) and FA (**right**) in different regions of the brain. LPT=left pyramidal tract; RPT=right pyramidal tract; V=vermis; LOR=left optic radiation; ROR=right optic radiation; LILF=left inferior longitudinal fasiculus; RILF=right inferior longitudinal fasiculus; LCP=left cerebral peduncle; RCP=right cerebral peduncle; LFM=left forceps minor; RFM=right forceps minor; LPIC=left posterior internal capsule; RPIC=right posterior internal capsule; Fx=Fornix; GCC=genu corpus callosum; SCC=splenium corpus callosum; LCR=right corona radiata; RCR=right corona radiata.

Table 1. ADC in patients compared to normal volunteers

	NPC ADC (mean ± sd)	Normal ADC (mean ± sd)	P-value
L pyramidal tract	0.77 ± 0.02	0.74 ± 0.02	.004
R pyramidal tract	0.80 ± 0.02	0.73 ± 0.03	.006
Vermis	0.97 ± 0.29	0.57 ± 0.27	.037
L optic radiation	0.93 ± 0.05	0.85 ± 0.05	.016
R optic radiation	0.91 ± 0.05	0.82 ± 0.08	.006
L inferior longitudinal fasciculus	0.90 ± 0.06	0.81 ± 0.05	.025
R inferior longitudinal fasciculus	0.90 ± 0.08	0.79 ± 0.04	.016
L forceps minor	0.88 ± 0.09	0.75 ± 0.02	.004
R forceps minor	0.88 ± 0.08	0.77 ± 0.02	.010
L posterior internal capsule	0.78 ± 0.01	0.72 ± 0.01	.004
R posterior internal capsule	0.77 ± 0.02	0.71 ± 0.01	.004
Fornix	1.59 ± 0.18	1.27 ± 0.05	.004
Corpus callosum genu	0.93 ± 0.18	0.67 ± 0.26	.016
Corpus callosum splenium	0.88 ± 0.08	0.77 ± 0.03	.016
L corona radiata	0.79 ± 0.02	0.72 ± 0.01	.004
R corona radiata	0.79 ± 0.01	0.74 ± 0.03	.037

Table 2. FA in patients compared to normal volunteers

	NPC FA (mean±sd)	Normal FA (mean±sd)	P-value
L optic radiation	0.41 ± 0.03	0.46 ± 0.02	.025
R optic radiation	0.43 ± 0.01	0.42 ± 0.16	.004
L posterior thalamus	0.21 ± 0.02	0.26 ± 0.03	.016
R posterior thalamus	0.22 ± 0.03	0.28 ± 0.03	.010
Fornix	0.36 ± 0.03	0.45 ± 0.04	.004

Conclusions:

Preliminary studies show significant differences in several regions of the brain between NPC patients and normal volunteers, especially in ADC, but also in FA. Following this, we plan a longitudinal study to follow the evolution of these changes, and hopefully map out the natural history of this disease quantitatively in the brain. We hope this study has raised the potential of diffusion tensor imaging as a means of quantification of changes in the brain in NPC patients, and thus be used as a means of disease monitoring and subsequently therapeutic monitoring.

References:

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