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European Journal of Radiology 49 (2004) 224–228

EJR
EUROPEAN JOURNAL OF RADIOLOGY

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Brain MR spectroscopy in children with a history of rheumatic fever with a special emphasis on neuropsychiatric complications

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Received 17 April 2003; received in revised form 10 June 2003; accepted 11 June 2003

Abstract

Purpose: To investigate whether there are metabolite changes in basal ganglia of children with complete healing of rheumatic fever (RF), history of Syndenham chorea (SC) and obsessive compulsive-tic disorder (OCTD) developed after RF when compared with healthy controls and each other. *Material and methods:* A total of 49 children with history of RF and 31 healthy controls were included into the study. All patients and control group underwent a detailed neuropsychiatric evaluation. Children with the history of RF were classified into three groups as; group 1: with history of RF without neuropsychiatric complications (NCRF), group 2: only with history of SC (HSC), group 3: with HSC and OCTD (OCTD). After MR imaging, single voxel MR spectroscopy was performed in all subjects. Voxels ($15 \times 15 \times 15$ mm) were placed in basal ganglia. *N*-acetyl aspartate (NAA)/creatin (Cr), and choline (Cho)/Cr ratios were calculated. *Results:* OCTD were detected in 13 children with HSC. NAA/Cr ratio was found to be decreased in these children when compared with NCRF (*n*:29), HSC without OCTD (*n*:7) and control groups (*n*:31). No significant difference was found in metabolite ratios of children with HSC without OCTD when compared with NCRF and control groups. There were no significant differences in Cho/Cr ratio between patient and control groups. *Conclusion:* Although MR imaging findings was normal, MR spectroscopy findings (decreased NAA/Cr ratio) in our study support the neuronal loss in basal ganglia of children with OCTD and could indicate the development of permanent damage.

Keywords: Rheumatic fever; Chorea; Obsessive compulsive disorder; Magnetic resonance spectroscopy

1. Introduction

Rheumatic fever (RF) is still an important health problem in children of developing countries. RF related neuropsychiatric complications like Syndenham's chorea (SC) and obsessive compulsive and tic disorders (OCTD) were reported to occur at about 15–26% [1,2]. Neurologic and psychiatric sequale and central dopaminergic hypersensitivity have been reported in patients with SC in long term follow-up studies [1,3,4]. Basal ganglia involvement has been reported in children with SC and OCTD [1,4–9].

MR spectroscopy (MRS) is a noninvasive tool to investigate the biochemical alterations in neural structures caused by various brain disease processes. It is increasingly being used to aid in diagnosis and clinical management. MRS provides additional information independent of conventional MR imaging [10]. In the literature neuropathological studies about the changes in basal ganglia of children with RF related SC and OCTD [11–15]. However, to the best of our knowledge, there are no MRS studies in these patients.

Our aim in this study was to determine whether there are metabolite changes or not in basal ganglia of children with history RF, and investigate its relationship with neuropsychiatric symptoms such as OCTD.

2. Material and methods

A total of 49 children with history of RF were included in our study (27 female, 22 male, age range: 5–16 years, mean

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doi:10.1016/S0720-048X(03)00177-3

age: 11.4 ± 2.8 years). 20 children with history of SC (HSC) (11 females, nine males, age range: 6–16 years, mean age: 11.3 ± 3.5 years), and age matched 29 children with history of RF without neuropsychiatric complication (NCRF) (16 females, 13 males, age range: 5–16 years, mean age: 11.5 ± 2.3 years) who were being followed-up by pediatrics department were underwent clinical, neuropsychiatric and MR imaging reevaluation. In NCRF group, none of the children had neuropsychiatric symptoms (i.e. OCTD) and their RF was completely healed. Thirty one healthy volunteers (16 females, 15 males, age range: 8–17 years, mean age: 13.1 ± 2.2 years) constituted the control group. Informed consents were obtained from parents of juvenile patients, and healthy controls. The mean duration of ARF history was 21.8 ± 17.8 months (range: 6–45 months). There was no difference in all patient groups from the point of duration of RF history. The mean duration of SC diagnosis was 15.4 ± 2.7 months. None of the children had active SC and involuntary movement. All patients and controls were underwent a detailed medical history and neuropsychiatric examination. In the neuropsychiatric examination, all patients and controls were evaluated for OCTD according to DSM IV criteria (Diagnostic and Statistical Manual of Mental Disorders). OCTD were detected in 13 children with history SC according to DSM IV criteria.

Children with the history of RF were classified into three groups as; group 1: with history of RF without neuropsychiatric complications (NCRF) (*n*:29), group 2: only with HSC (*n*:7), group 3: with HSC and OCTD (OCTD) (*n*:13).

The MRI examination consisted of routine imaging and single voxel spectroscopy (SVS). MRI was performed on a 1.5-T system (Philips, Gyroscan Intera Master, Best, the Netherlands). T1 weighted images (TR: 560, TE: 15) were obtained in the axial and sagittal planes. T2 weighted images (TR: 4530, TE: 100) were obtained in the axial and coronal planes. Since none of the patients had active SC and involuntary movements, no difficulty was encountered during MR imaging and MRS. SVS was performed in all patients by using a point-resolved spectroscopy sequence (PRESS) (TR: 2000/TE: 136 ms) with 128 averages; voxel sizes of 15 × 15 × 15 mm were used. Voxels were placed in basal ganglia. Prior to MRS, shimming was performed to optimize field homogeneity and water suppression was optimized using automated routines provided by manufacturer. The water signal was suppressed by a chemical-shift selective saturation pulse. A spectral sweep width of 1000 Hz was used with data size of 1024 points. The magnitude spectra were processed automatically using baseline correction and curve-fitting procedures to determine the resonance areas of *N*-acetyl aspartate (NAA), creatine (Cr) and choline (Cho). Analysis of the spectra was performed with the manufacturer supplied spectroscopy software package of the MR system. Resonances were assigned as follows: NAA, 2.0 ppm; Cr, 3.02 ppm; Cho, 3.2 ppm. Peak area metabolite ratios (NAA/Cr, and Cho/Cr) were calculated. For each patient, two authors (AA, RK) assessed whether the spectra were diagnostic.

Table 1
Metabolite ratios of patient and control groups obtained from basal ganglia

Metabolite ratios	HRF (*n*:49)			Control (*n*:31)
	NCRF (*n*:29)	HSC (*n*:7)	OCTD (*n*:13)	
NAA/Cr	1.33 ± 0.09	1.26 ± 0.13	1.10 ± 0.13*	1.34 ± 0.11
Cho/Cr	0.79 ± 0.12	0.77 ± 0.13	0.74 ± 0.11	0.82 ± 0.12

HRF, history of RF. NCRF, history of RF without neuropsychiatric complications. OCTD, obsessive compulsive and tic disorders. HSC, history of Sydenham's chorea without OCTD. $P<0.05$ OCTD vs. control, NCRF, and HSC.

All statistical analyses were performed using a commercially available SPSS release 10.0 software package (SPSS Inc., Chicago, IL). The results are presented as mean ± standard deviation in order to facilitate comprehension of the tables. One sample Kolmogorov–Smirnov test demonstrated normal distribution of metabolite ratios in patient and control groups. One Way Analysis of Variance (ANOVA) test was utilized for the general comparison of metabolite ratios of groups. Tukey HSD test was used for the assessment of metabolite ratio differences among healthy control and patient groups. The interrelation among them also evaluated. A *P*-value below 0.05 was considered statistically significant.

3. Results

There was no age difference between patient and control groups.

Routine MR imaging was normal in all patients.

Metabolite ratios obtained from basal ganglia of patient and control groups were presented in Table 1.

No significant difference was found in NAA/Cr ratio between HSC and NCRF and control groups ($P>0.05$) (Fig. 1A, B).

NAA/Cr ratio was found to be significantly decreased in group with OCTD when compared with control, NCRF and HSC groups (*P*: 0.0001, *P*: 0.0001, *P*: 0.007, respectively).

There were no significant differences in Cho/Cr ratio between patient and control groups.

4. Discussion

SC is a major diagnostic criterion of RF that is known to be related with group A betahemolytic streptococci (GABHS) infection [1,3,16]. It is a member of poststreptococcal basal ganglia syndromes caused by antibasal ganglia antibodies (ABGA) against GABHS bacteria which cross-react with neurons in the basal ganglia, leading to inflammation and dysfunction [1,5–7]. Vasculitis, perivasculitis, and exudation of circulating streptococcal–antistreptococcal immune com-

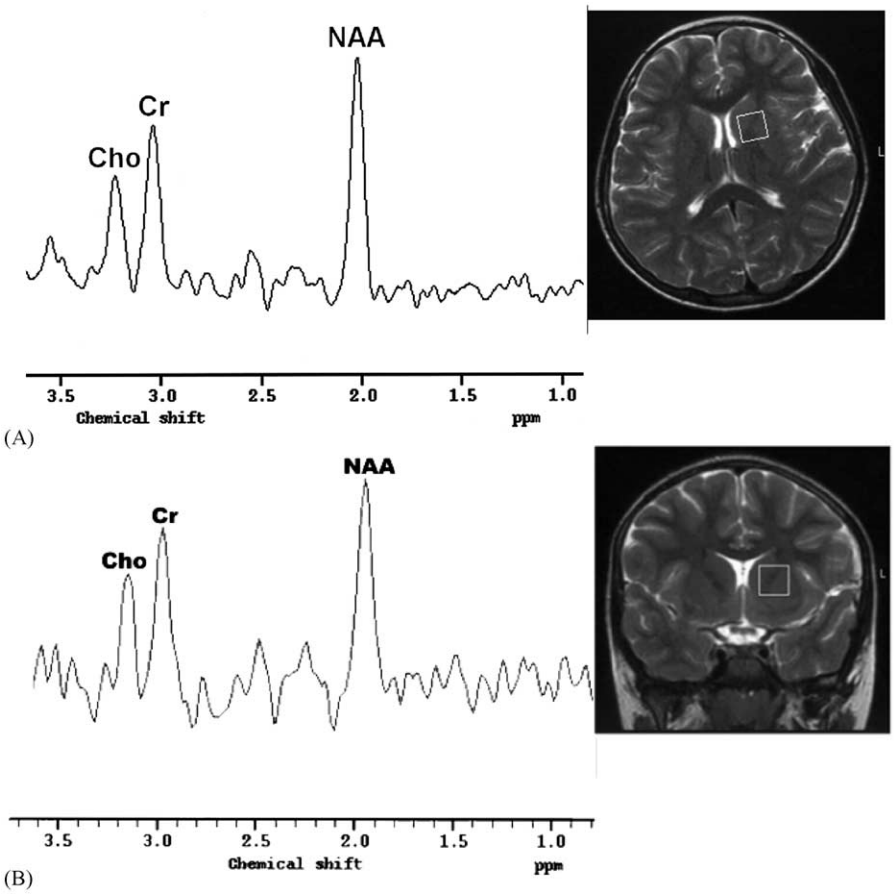

Fig. 1. (A) An 8-year-old male child with history of completely healed RF. MR spectrum (PRESS; 2000/136/128) obtained from left basal ganglia shows normal metabolite peaks. (B) An 11-year-old male child with history of Syndenham's chorea without OCTD. MR spectrum (PRESS; 2000/136/128) obtained from left basal ganglia shows normal metabolite peaks.

plexes are likely to initiate an immune reaction against neuronal tissues [8]. SC is characterized by sudden, involuntary, aimless movements, and behavioral disturbances like emotional lability, obsessive–compulsive disorders, anxiety, impulsivity, and inattentiveness [3,16]. Pathological studies demonstrated specific changes, like cellular infiltration and neuronal loss, arteritis, endothelial swelling, perivascular round cell infiltration and petechial hemorrhages in the basal ganglia [9,11–15].

Basal ganglia enlargement and increased signal intensity on T2-weighted images in the caudate, putamen, and globus pallidus has been reported in MR imaging studies [4,13,16,17]. These imaging abnormalities could occur only during the acute phases of SC. In the literature, resolving of these abnormalities 6–14 months of after the onset of symptoms has been reported [3,4]. Since none of our cases was in the acute phase of SC, there were no detectable MR imaging findings. The cause of basal ganglia involvement has been established as an autoimmune in nature. The antibodies developed against antigens on GABHS may cross-react with certain host tissues in the cardiac, skeletal or central nervous systems [18,19]. A certain type of these antibodies, i.e. ABGA, is reported to be the main cause of CNS involvement in SC by altering the corticostriatal circuits [1,20]. The alterations of these circuits lead to basal ganglia dysfunction in SC which causes motor symptoms by putamen involvement and behavioral disturbances (like difficulties, emotional lability, and obsessive–compulsive symptoms) by caudate involvement and cortical dysfunction [3,21,22]. Poststreptococcal autoimmunity has been regarded as one of the etiologic factors for OCTD in children. Following GABHS infections, the symptoms of these children exacerbate dramatically [22–24]. In our study, OCTD was detected in 13 (65%) of 20 children with HSC.

It is possible to detect metabolite changes in the normal appearing basal ganglia by diffusion weighted imaging (DWI) and MRS. Since DWI is sensitive to the random translational motion (diffusion) of water molecules in tissue, even subtle pathological damages disrupting the tissue architecture, increasing the mobility of water molecules could be detected. Therefore, diffusion imaging has the potential to probe structural changes that are inaccessible to conventional MR techniques [25].

MRS is a noninvasive tool to investigate the biochemical alterations in neural structures caused by various brain disease processes [10,26]. It is increasingly being used to aid

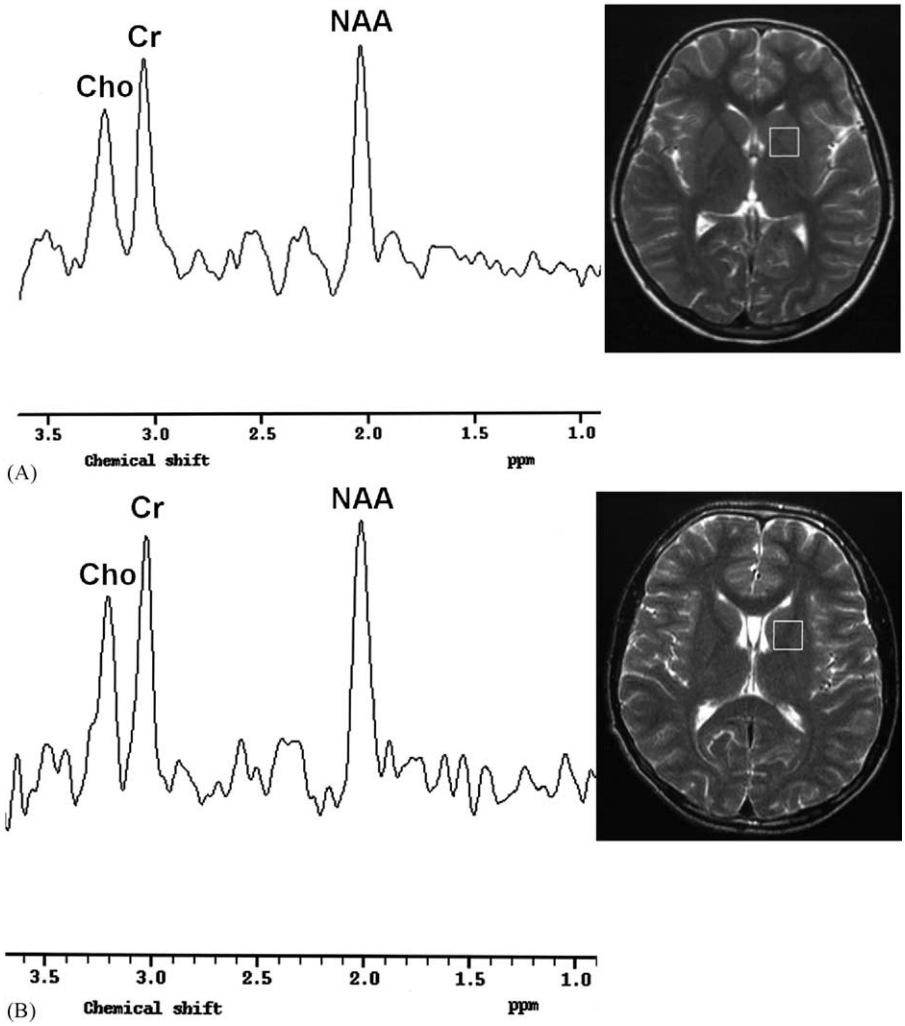

Fig. 2. (A) A 10-year-old male child with obsessive compulsive and tic disorders. MR spectrum (PRESS; 2000/136/128) obtained from left basal ganglia shows decreased NAA/Cr ratios. (B) An 11-year-old female child with obsessive compulsive and tic disorders. MR spectrum (PRESS; 2000/136/128) obtained from left basal ganglia shows significant decrease in NAA/Cr ratios.

in diagnosis and clinical management. The prominent resonances detected on MRS in normal brains include NAA, Cho, and Cr. NAA is the most sensitive central nervous system metabolite. Since it is a neuroaxonal marker, abnormalities of neuronal structures, like reduced neuronal density or viability, lead to the reductions in NAA. Therefore, it is an important predictor of neuronal dysfunction [10,26]. There was a significant decrease in NAA/Cr ratio in basal ganglia of children with OCTD. This reduction could indicate neuronal loss in basal ganglia (Fig. 2A, B). The finding of no difference in metabolite ratios between HSC and NCRF and control groups might reveal absence of permanent neuronal loss in basal ganglia. The decrease in NAA/Cr ratio could be the explanation of permanent basal ganglia damage in children with OCTD group.

Cho resonance might be an indication of membrane turnover. The increase in the Cho/Cr ratio might point to an inability to properly incorporate Cho-containing molecules into myelin. Also, loss or disruption of normal myelin increases the level of Cho-containing compounds. Thus, increase in Cho/Cr ratio could indicate demyelination [10]. In the present study, there was no significant difference in Cho/Cr ratio between patient and control groups. These findings might indicate absence of disturbances of membrane metabolism in patients with history RF.

5. Conclusion

The decrease in NAA/Cr ratio obtained from basal ganglia of children with HSC with OCTD may support the functional and morphological abnormalities reported previously in histopathologic studies. The demonstration of decreased NAA/Cr ratios suggesting neuronal loss in the basal ganglia of these children with MRS could indicate the development of permanent damage.

Acknowledgements

We thank Associate Professor Cemal Ozcan and Associate Professor Mucahit Egri for their critical review and statistical evaluation of the manuscript.

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