Received:
26 November 2015

Revised:
11 October 2016

Accepted:
18 October 2016

<https://doi.org/10.1259/bjr.20151007>

Cite this article as:

Dogan F, Sen Dokumaci D, Yildirim A, Bozdogan E, Boyaci FN, Koca B, et al. Brain diffusion changes in Eisenmenger syndrome. *Br J Radiol* 2016; **89**: 20151007.

FULL PAPER

Brain diffusion changes in Eisenmenger syndrome

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Objective: This preliminary study aimed to evaluate whether there are changes in the apparent diffusion coefficient (ADC) values of the brain in patients presenting with Eisenmenger syndrome (ES).

Methods: This cross-sectional study included 10 consecutively recruited patients with ES and 10 healthy control subjects. In the patients and controls, eight distinct neuroanatomical locations were selected for analysis. Quantitative measurements of ADC values of the frontal white matter (FWM), occipital white matter, lentiform nucleus (LN), thalamus, frontal cortex, anterior and posterior limbs of the internal capsule and caudate nucleus were measured. Statistical analysis was performed using SPSS® (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) for Windows v. 20. Data were presented as mean ± standard deviation values. The

Kruskal-Wallis test was used to assess differences in the ADC values of each brain location between the ES group and the control group. Statistical significance was accepted at the level of $p < 0.05$.

Results: The ADC values of the FWM and LN were significantly higher in the ES group than that in the control group. The mean ADC levels of other brain regions were not significantly different between the groups.

Conclusion: Chronic hypoxia in patients with ES may lead to diffusion changes in the brain tissue. There is a need for further studies to assess the clinical significance of cerebral ADC values in patients with ES.

Advances in knowledge: The ratio of extracellular volume to intracellular volume in the FWM and LN can be considered to be increased in patients with ES.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a common complication of congenital heart disease (CHD). Most cases occur in patients with congenital cardiac shunts. If a left-to-right shunt remains uncorrected, increased pulmonary pressure results in vascular remodelling and dysfunction over time. As a result, there are increases in pulmonary vascular resistance and pressures in the right heart. Finally, reversal of the shunt may occur and may lead to the development of Eisenmenger syndrome (ES).^{1,2} There are various types of CHD including simple and complex defects. Simple defects include pre-tricuspid shunts, such as atrial septal defect and simple post-tricuspid shunts, including ventricular septal defects, while complex CHD includes truncus arteriosus, complete atrioventricular septal defect and single ventricular physiology with unobstructed pulmonary blood flow and transposition of the great arteries with ventricular septal defects.³

ES affects multiple organ systems, including the haematological, skeletal, renal and neurological systems, as

a result of erythrocytosis and hyperviscosity due to chronic hypoxaemia. Besides PAH, haemorrhage, haemoptysis, cholelithiasis due to hyperbilirubinemia, susceptibility to infections (central nervous system abscesses, endocarditis), thrombosis, iron deficiency anaemia, heart failure, arrhythmias, gout due to hyperuricemia and pulmonary artery aneurysms can also be seen during the course of this disease.⁴

Chronic hypoxia and ischaemia have serious effects on brain cells. In a state of ischaemia, brain cells become depolarized, and while sodium and calcium ions move into the cell, potassium ions move into the extracellular space.⁵ Owing to the increased ion gradient between the intracellular and extracellular compartments, water enters the cell, causing cytotoxic oedema.^{5,6} Then, depolarized cells release glutamate, which is toxic to neural cells.⁷ Moreover, chronic hypoxia can lead to myelin destruction, resulting in reduced tissue barriers, ion and protein leakage into the extracellular space and vasogenic oedema. All these factors contribute to increased mean diffusion values.^{6,8}

Several neuroradiological studies have shown structural changes non-invasively.⁹ Conventional imaging, such as MRI, seems to be inadequate in demonstrating the expected cerebral damage due to hypoxia.¹⁰

Diffusion-weighted imaging (DWI) mainly depends on the microstructural characteristics of water diffusion in tissues.¹¹ It provides valuable information about certain pathologies of the brain and reliably distinguishes vasogenic oedema from cytotoxic oedema. DWI provides qualitative information regarding the movement of water molecules in the brain tissue. The apparent diffusion coefficient (ADC) is a quantitative measurement of the diffusion of water molecules that is altered in pathological conditions.^{12–14} The diffusion is related to the molecular microscopic movement of water molecules and reflects tissue properties such as the size of the extracellular space, viscosity and cellularity. Restricted diffusion is encountered in tissues with high cellularity. Relatively free diffusion is seen in tissues with tissue injury.^{6,15,16}

As in acute ischaemia in the brain, restriction of water diffusion is revealed within minutes. The biophysical basis of this change has not yet been clarified.^{5,17–19} Diffusion values are known to increase in eclampsia, hypertensive encephalopathy and venous thrombosis-like syndromes owing to reversible vasogenic oedema.¹⁶

In this study, an investigation was made of the diffusion changes in different regions of the brain in patients with ES and these were compared with a control group.

METHODS AND MATERIALS

Patient selection

Approval for the study was granted by the local ethics committee. Between January 2015 and June 2015, 10 patients (aged 5–16 years) with ES underwent brain MRI. This prospective two-centre study group included 10 children with CHD whose pulmonary vascular resistance was calculated to be >8 Wood units/m², obtained during cardiac catheterization, and who were diagnosed with ES in our Pediatric Cardiology Department. Patients with any brain disorders including stroke, infection and multiple sclerosis, which could affect diffusion changes, were excluded from the study. ES is defined as the process in which a long-standing left-to-right cardiac shunt caused by a congenital heart defect causes pulmonary hypertension and eventual reversal of the shunt into a cyanotic right-to-left shunt. Patients with additional diseases, which could cause PAH, such as pulmonary, liver and kidney diseases and connective tissue disorders, were also excluded from the study.

The patient ages were obtained from the medical records of the patients at the time of the diagnosis. The cardiac catheterization and angiography records of the patients with ES were reviewed. All echocardiography examinations were performed with a commercially available echocardiography device, the Vivid™ S5 (GE Vingmed Ultrasound AS Strandpromenaden 45, N-3191 Horten, Norway), equipped with 4- and 7-MHz transducers. Measurements were taken through the parasternal window as long-axis and short-axis and through the apical window as 4- and

5-chamber views. Post-diastolic and post-systolic volumes and diameters of the left ventricle, ejection fraction, left atrium diameter and right atrium diameter and their volumes were measured. The diameters of the left and right atrium were measured in the apical 4-chamber window. Post-systolic left and right atrium areas were measured. PAH was defined as tricuspid regurgitant jet velocity ≥ 2.7 m s⁻¹ on echocardiography.

The control group consisted of 10 age- and gender-matched, healthy children without PAH, who were screened for headache.

MRI examination

The MRI examination consisted of routine non-contrast brain scanning, including DWI. MRI was performed on a 1.5-T Magnetom Avanto (Siemens Healthcare, Erlangen, Germany). Fast-spin-echo T_2 weighted images (repetition time = 4530 ms, echo time = 100 ms) were obtained in the axial and coronal planes. Subjects with normal MRI findings were included. For DWI, a single-shot spin-echo pulse sequence (TR = 3216 ms, TE = 89 ms, FOV = 230 mm, matrix of 128 × 128, number of acquisitions = 2, slice thickness = 5 mm, interslice gap = 1 mm) was used in all 8 patients with two b -values (0 and 1000 s/mm²). The ADC maps were reconstructed with commercially available software.^{14,20,21} For the patients and control subjects, eight distinct neuroanatomical locations were selected for analysis. Regions of interest (ROIs) were drawn by two experienced radiologists on the regions identified, and the ADC values were calculated automatically from the ADC map. A circular ROI was used for quantitative measurements of ADC values of the frontal white matter (FWM), occipital white matter, lentiform nucleus (LN), thalamus, frontal cortex, anterior and posterior limbs of the internal capsule and caudate nucleus (Figure 1). Partial-volume effects were minimized by inspecting the slices above and below the region to avoid averaging with the cerebrospinal fluid. Similar ROIs were used for an individually selected region in all patients, which were carefully evaluated by the same radiologist, who was blinded to the condition of the subjects. The mean values of the two investigators were calculated for each region. The interrater reliability tests for ADC were evaluated.

Statistical analysis

Statistical analysis was performed using SPSS® (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) for Windows v. 20. Data were presented as mean $\pm$ standard deviation (SD). The Kruskal–Wallis test was used to assess differences in the ADC values of each brain location between the ES group and the control group. A value of $p < 0.05$ was accepted as statistically significant.

The paired Student's t -test was used to analyze the difference between two measurements of physicians.

RESULTS

A total of 10 children with ES and 10 control subjects were included for evaluation in the study, with a mean age of 11.4 years (range 5–16 years). No statistically significant difference was determined between the ES subjects and the control group with respect to age and gender.

Figure 1. Apparent diffusion coefficient values in the frontal ($877 \times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$) and occipital ($805 \times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$) white matter of a 9-year-old male patient with Eisenmenger syndrome. Std Dev, standard deviation.

The mean ADC values of the ES and control groups are shown in Table 1. The mean ADC values in the FWM and LN in the ES group were 846.0 ± 63.1 and $777.5 \pm 43.4 \times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$ (mean $\pm$ SD $\times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$), respectively. The mean ADC values in the FWM and LN in the control group were 768.3 ± 41.3 and $739.7 \pm 34.7 \times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$ (mean $\pm$ SD $\times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$), respectively.

The ADC values of the FWM and LN were significantly higher in the ES group ($n = 10$) than that in the control group ($n = 10$).

No statistically significant difference was determined between the groups with respect to the mean ADC levels of other brain regions. The interrater reliability tests for ADC were not significant. The results obtained from both physicians are summarized in Table 2.

DISCUSSION

To the best of our knowledge, this is the first report to evaluate the ADC measurements taken from cerebral deep white matter and other brain locations of patients with ES. The main findings of this study were: (1) ADC values were different in the ES and control group; and (2) in the ES group, the ADC values of the FWM and LN were significantly higher compared with the control group.

ES is the most advanced form of PAH associated with CHD.³ Long-standing cyanosis has effects on multiple organ systems and can be a source of significant morbidity and mortality. Haematological, neurological, renal, hepatic and skeletal systems are affected by chronic cyanosis. In addition to cyanosis, heart failure also contributes to brain hypoxia in the long term in patients with ES.²²

Diffusion is related to the molecular microscopic movement of water molecules and shows tissue features such as the size of the extracellular area, viscosity and cellularity.

Restricted diffusion is encountered in tissues with high cellularity, e.g. tumours, abscesses and cytotoxic oedema. Relatively free diffusion is seen in tissues with tissue injury, such as damage to the myelin, axons, cell bodies and membranes.^{6,15,16} When acute ischaemia occurs in the brain, the restriction of water diffusion is revealed within minutes.^{5,17–19} Acute hyponatraemic encephalopathy (without ischaemia) can lead to cytotoxic oedema and occurs in restricted diffusion.²³

Syndromes with reversible vasogenic oedema, which lead to elevated diffusion, include eclampsia, hypertensive encephalopathy, cyclosporin toxicity, other posterior leukoencephalopathies, venous thrombosis, human immunodeficiency virus

Table 1. Apparent diffusion coefficient values ($\times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$) of eight brain regions of both groups

Neuroanatomical Locations	ES group ($n = 10$) mean $\pm$ SD (minimum–maximum)	Control group ($n = 10$) mean $\pm$ SD (minimum–maximum)	p -value
FWM	846.0 ± 63.1 (753–928)	768.3 ± 41.3 (696–818)	<0.05
OWM	816.2 ± 57.2 (706–889)	815.3 ± 50.6 (759–905)	NS
ALIC	748.7 ± 68.4 (644–871)	711.0 ± 53.3 (637–805)	NS
PLIC	737.2 ± 72.2 (653–902)	738.3 ± 43.9 (655–814)	NS
CN	774.7 ± 53.8 (669–832)	761.9 ± 34.3 (715–808)	NS
LN	777.5 ± 43.4 (723–868)	739.7 ± 34.7 (664–775)	<0.05
T	783.4 ± 43.4 (735–857)	744.2 ± 63.8 (629–817)	NS
FC	817.7 ± 71.6 (722–958)	776.0 ± 48.2 (684–850)	NS

ALIC, anterior limbs of the internal capsule; CN, caudate nucleus; ES, Eisenmenger syndrome; FC, frontal cortex; FWM, frontal white matter; LN, lentiform nucleus; NS, non-significant; OWM, occipital white matter; PLIC, posterior limbs of the internal capsule; SD, standard deviation; T, thalamus.

Table 2. Mean apparent diffusion coefficient (ADC) values ($\times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$) and standard deviation (SD) deviation of eight brain regions of Physicians 1 and 2

Neuroanatomical Locations	Physician 1 (Mean ADC value $\pm$ SD)	Physician 2 (Mean ADC value $\pm$ SD)	p-value
FWM	846.00 $\pm$ 63.16	843.63 $\pm$ 60.21	NS
OWM	816.20 $\pm$ 57.28	815.98 $\pm$ 57.95	NS
ALIC	748.74 $\pm$ 68.44	746.91 $\pm$ 68.88	NS
PLIC	737.26 $\pm$ 72.29	736.48 $\pm$ 75.53	NS
CN	774.79 $\pm$ 53.82	772.83 $\pm$ 55.80	NS
LN	777.53 $\pm$ 43.46	779.44 $\pm$ 44.31	NS
T	783.41 $\pm$ 43.47	782.42 $\pm$ 44.97	NS
FC	817.70 $\pm$ 71.60	814.63 $\pm$ 70.89	NS

ALIC, anterior limbs of the internal capsule; CN, caudate nucleus; FC, frontal cortex; FWM, frontal white matter; LN, lentiform nucleus; NS, non-significant; OWM, occipital white matter; PLIC, posterior limbs of the internal capsule; T, thalamus.

encephalopathy and hyperperfusion syndrome after carotid endarterectomy.¹⁶

Cullu et al²⁴ reported that the ADC values from the measurements taken from the frontal, temporal, parietal and occipital deep white matter of a chronic obstructive pulmonary disease group were found to be significantly high compared with those of the control group.

Other studies have explained that chronic obstructive pulmonary disease and lower arterial oxygen saturation (SaO_2) are linked to severe periventricular white matter lesions. This finding shows that both cerebral hypoperfusion and hypoxaemia may contribute to the aetiology of periventricular white matter lesions.²⁵

In the present study, the ADC values of the FWM and LN were higher in the ES group than that in the control group. These findings could be considered to be due to cerebral tissue increasing free water content because of damage to the myelin and axons in chronic hypoxia. These increased ADC values were consistent with previous findings in literature.¹⁶ Hypoxaemia is known to strongly intensify ischaemic brain damage.²⁶ ADC has been reported to be increased in patients with Type 2 diabetes

compared with non-diabetic controls, thereby indicating vasogenic brain oedema in Type 2 diabetes. However, it is not understood whether this increase of ADC/vasogenic brain oedema is due to the alteration in extra/intracellular volume. Normally, the intracellular volume is much greater than the extracellular volume in the human brain. Atherosclerosis and chronic ischaemia are seen in Type 2 diabetes and these conditions decrease cerebral perfusion. Thus, the intracellular volume in the brain is decreased, resulting in a higher ratio of extracellular volume to intracellular volume. Chronic ischaemia and hypoxia can cause chronic damage in neurons, axons and medullary sheath, leading to heterogeneity in diffusion.²⁷ The extracellular volume to intracellular volume ratio of the FWM and the LN can be considered to be increased in patients with ES.

The limitations of this study were the small number of patients and that longer follow-up could not be applied owing to the relatively short lifespan of the patients. Another major limitation was the lack of pathological correlation with the imaging findings.

In conclusion, ES may affect the FWM and LN of the brain. There is a need for further studies to assess the clinical significance of cerebral ADC values in patients with ES.

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