NeuroImage: Clinical 4 (2014) 319–325

Contents lists available at ScienceDirect
NeuroImage: Clinical
journal homepage: www.elsevier.com/locate/ynicl

Brain Volumetrics, Regional Cortical Thickness and Radiographic Findings in Adults with Cyanotic Congenital Heart Disease☆

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ARTICLE INFO

Article history:
Received 24 September 2013
Received in revised form 22 December 2013
Accepted 24 December 2013
Available online 4 January 2014

Keywords:
Cyanosis
MRI
Brain volume
White matter
Gray matter
Cyanosis

ABSTRACT

Background: Chronic cyanosis in adults with congenital heart disease (CHD) may cause structural brain changes that could contribute to impaired neurological functioning. The extent of these changes has not been adequately characterized.

Hypothesis: We hypothesized that adults with cyanotic CHD would have widespread changes including abnormal brain volumetric measures, decreased cortical thickness and an increased burden of small and large vessel ischemic changes.

Methods: Ten adults with chronic cyanosis from CHD (40 ± 4 years) and mean oxygen saturations of 82 ± 2% were investigated using quantitative MRI. Hematological and biochemical parameters were also assessed. All subjects were free from major physical or intellectual impairment. Brain volumetric results were compared with randomly selected age- and sex-matched controls from our database of normal subjects.

Results: Five of 10 cyanotic subjects had cortical lacunar infarcts. The white matter (WM) hyperintensity burden was also abnormally high (Scheltens Scale was 8 ± 2). Quantitative MRI revealed evidence of extensive generalized WM and gray matter (GM) volumetric loss; global GM volume was reduced in cyanosed subjects (630 ± 16 vs. 696 ± 14 mL in controls, $p = 0.01$) as was global WM volume (471 ± 10 vs. 564 ± 18 mL, $p = 0.003$). Ventricular cerebrospinal fluid volume was increased (35 ± 10 vs. 26 ± 5 mL, $p = 0.002$). There were widespread regions of local cortical thickness reduction observed across the brain. These changes included bilateral thickness reductions in the frontal lobe including the dorsolateral prefrontal cortex and precentral gyrus, the posterior parietal lobe and the middle temporal gyrus. Sub-cortical volume changes were observed in the caudate, putamen and in the thalamus ($p \leq 0.005$ for all regions). Cortical GM volume negatively correlated with brain natriuretic peptide ($R = -0.89$, $p = 0.009$), high sensitivity C-reactive protein ($R = -0.964$, $p < 0.0001$) and asymmetric dimethylarginine ($R = -0.75$, $p = 0.026$) but not with oxygen saturations, packed cell volume or viscosity.

Conclusions: We present the first comprehensive analysis of brain structure in adults with chronic neurocyanosis due to congenital heart disease. We demonstrate clear evidence for marked macro- and microvascular injury. Cyanotic patients show global evidence for reduced brain volume as well as specific foci of cortical thickness reduction. The GM volume loss correlated with hsCRP, BNP and ADMA suggesting that inflammation, neurohormonal activation and endothelial dysfunction may have important roles in its pathogenesis.

Abbreviations: ADMA, asymmetric dimethylarginine; CSF, cerebrospinal fluid; CHD, congenital heart disease; GM, gray matter; hsCRP, high-sensitivity C-reactive protein; MRI, magnetic resonance imaging pro-brain natriuretic peptide; BNP, NT pro-brain natriuretic peptide; VBM, voxel-based morphometry; WM, white matter.

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http://dx.doi.org/10.1016/j.nicl.2013.12.011

1. Introduction

Adults with cyanotic congenital heart disease (CHD) are the most physically impaired of the adult CHD cohort and have a markedly impaired quality of life and a reduced life expectancy (Engelfriet et al., 2005). The impact of chronic cyanosis on brain structure in these patients has not been adequately characterized. Although the cyanotic CHD group is phenotypically heterogeneous from a cardiac perspective, they share numerous features that are unavoidable consequences of chronic cyanosis such as hypoxemia, compensatory erythrocytosis, increased blood viscosity and endothelial dysfunction (Cordina and Celermajer, 2010). In childhood, reduced gray matter (GM volume), white matter (WM) injury and impaired cognitive outcomes have been well-documented in the setting of cyanotic CHD (Owen et al., 2011) however such neurological consequences are virtually uninvestigated in the adult population. Our study explores the long-term consequences of cyanotic CHD on brain structure in adults.

Cerebral changes characterized by reduced brain volume and altered metabolism have been demonstrated using magnetic resonance imaging (MRI) and spectroscopy as early as the third trimester in fetuses with cyanotic CHD. The exact mechanisms leading to these findings are not precisely characterized but are likely, in part, a consequence of reduced cerebral blood flow (Limperopoulos et al., 2010; Clouchoux et al., 2012). Reduced oxygen saturations have been found to strongly correlate with reduced frontal GM volume in infants (Watanabe et al., 2009). Brain growth is especially rapid in the first 2 years of life; GM reaches its maximum volume around 2 years of age whereas WM has a slower growth process that continues through childhood (Zhang et al., 2005). Thus, cyanosis may have differing neurological effects depending on the developmental stage at which it occurs.

Clinical evidence of brain injury and altered brain structure in children with cyanotic CHD is well described and has been reviewed elsewhere(Owen et al., 2011). In contrast, data are lacking studying the effects of chronic cyanosis in adults with CHD. The only substantive data consists of a qualitative radiological study by Horigome et al. They reported, seven of 15 subjects showed evidence of prior ischemic events. Three subjects also had *qualitatively* "mild diffuse cortical atrophy", however no quantitative brain volumes were measured. Supporting a causative role for the degree of chronic cyanosis, the 8 subjects in that study with a radiologically "normal" MRI had oxygen saturations >85% in contrast to the subjects who had abnormal scans and more severely reduced oxygen saturations (Horigome et al., 2006).

In this study we examine a cohort of adults with cyanotic CHD and no clinical history of stroke or known neurological deficit. Our hypotheses were: (1) that the radiological changes present in the adult population would be dominated by the vascular consequences of cyanosis with increased small vessel disease (WM hyperintensities) and large vessel ischemic disease (lacunar infarcts) and (2) that the quantitative MRI analyses would show decreased overall GM and WM volumes in excess of those expected due to normal aging. Finally, we sought to characterize any potential relationships that might exist between brain volume and several clinical and important laboratory parameters that reflect differing aspects of the pathophysiology of chronic cyanosis such as inflammation, endothelial dysfunction and neurohormonal activation. We chose 3 circulating markers for measurement; ADMA is a potent nitric oxide synthase inhibitor and marker of endothelial dysfunction (Vallance et al., 1992), BNP reflects neurohormonal activation in heart failure (Iwanaga et al., 2006) and hsCRP is an important acute phase reactant and inflammatory marker (Anand et al., 2005). Our study represents the first systematic effort to understand the brain imaging changes occurring in this group.

2. Methods

2.1. Subjects

Ten consecutively consenting adults with cyanotic CHD (3 females, 7 males) were recruited from the CHD database at Royal Prince Alfred Hospital (RPAH), Sydney, Australia. The inclusion criterion was resting transcutaneous oxygen saturations chronically ≤90%. Exclusion criteria were a contraindication to MRI, genetic abnormality or a major physical or intellectual impairment. Subject characteristics are shown in Table 1. Age- and sex-matched controls for brain volumetric analysis were drawn from the Brain Resource International Database, a standardized database combining demographic, psychometric, physiological and anatomical information. Exclusion criteria were any known neurological disorder, previous head injury, mental retardation, DSM-IV Axis 1 diagnosis and history of drug dependence. MRI datasets were acquired at Westmead Hospital (Sydney, Australia) (Grieve et al., 2005; Paul et al., 2005).

Simplified cardiac anatomical characteristics for cyanotic CHD subjects included atrioventricular septal defect with Eisenmenger physiology (n = 3), ventricular septal defect with Eisenmenger physiology (n = 1), ventricular septal defect with severe pulmonary stenosis (n = 2, both with Blalock–Taussig shunt, 1 with Glenn shunt), pulmonary atresia with ventricular septal defect and major aorta to pulmonary artery collaterals (n = 1), pulmonary atresia with intact septum (n = 1, with Glenn shunt), pulmonary atresia with single ventricle (n = 1, with Potts shunt) and pulmonary stenosis with essentially single ventricle (n = 1, with Blalock–Taussig shunt).

Informed written consent was obtained from all subjects and the study was approved by the Sydney Local Health District Ethics Review Committee (RPAH Zone).

2.2. Study design

Study protocol included brain MRI with angiographic and volumetric sequences. In addition, cyanotic CHD subjects also had hematological and biochemical assessments that included a full blood count, NT pro-brain natriuretic peptide (BNP), high-sensitivity C-reactive protein (hsCRP) and asymmetric dimethylarginine (ADMA). Whole blood viscosity was also measured (Brookfield Digital Viscometer, rotational speed of 12 rpm, shear rate 90 s^{-1}). Functional capacity was assessed with 6-minute walk test (6MWT).

2.3. Cerebral MRI

MRI imaging on the CHD cohort was performed using an 8-channel head coil on the 1.5 Tesla Philips Achieva Scanner (Philips Medical Systems, Best, The Netherlands) at Specialist MRI, Sydney, Australia. The imaging parameters were as follows: 3D SPGR — TR 8.3 ms, TE 4.6 ms, Flip 30°, TI 500 ms, NEX 1, resolution 1 mm^2, 1 mm sagittal slices; DWI — TR 10 s, TE 140 ms, Fat Sat ON, NEX 1, resolution 1.72 mm^2, 5 mm axial slices (skip 1.5 mm), 7 orientations, b = 1000; FSE — TR 4700 ms, TE 100 ms, NEX 1, resolution 0.6 mm^2, 5 mm axial slices (skip 1.5 mm); GRE — TR 747 ms, TE 23 ms, NEX 2, resolution 0.9 mm^2, 5 mm coronal slices (skip 2 mm); MRA — TR 23 ms, TE 7 ms, NEX 1, resolution 0.6 mm^2, 1.4 mm axial slices; and FLAIR — TI 2800 ms, TR 10 s, TE 140 ms, NEX 2, resolution 0.4 mm^2, 5 mm slices coronal (skip 2 mm).

Control data was acquired using a 1.5 Tesla Siemens (Erlangen, Germany) Vision Plus system at Westmead Hospital as previously described (Grieve et al., 2011a). MPRAGE sequence — TR 9.7 ms, TE 4 ms, flip angle 12°, TI 200 ms, NEX 1, resolution 1 mm^2, and 1 mm sagittal slices.

Radiological reporting and scoring of WM hyperintensity and lacunar lesions were performed by a neuroradiologist (SMG). No clinical scoring was performed for the control data due to a lack of FLAIR data for these subjects. WM scoring was performed using the Scheltens Scale primarily using the FLAIR data but with reference to the other T1W, T2W and DWI datasets (Brickman et al., 2008; Scheltens et al., 1993). This is a semiquantitative method with good intra- and inter-observer reliability that separates WM hyperintensities into periventricular (lateral bands, frontal horn, occipital horn), lobar (frontal, temporal, parietal, and occipital), infratentorial (cerebellum, medulla, pons, midbrain) and subcortical