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Brain pathology in patients with congenital heart disease

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Abstract

Introduction: *Brain pathology in patients with congenital heart disease (CHD) is associated with neuro-developmental delay. Imaging studies support vascular etiology for both white and gray matter lesions. In this retrospective study, we described the pathological changes in the brains of patients with CHD.*

Material and methods: *Last twenty autopsy cases in pediatric patients with CHD at our institution were retrieved and autopsy reports were reviewed. Available hematoxylin-eosin, special, and immunostains were evaluated, and at least one section from each case was stained with anti-glial fibrillary acidic protein (GFAP), anti-amyloid precursor protein (APP), and anti-HLA-DR antibody. Staining pattern of these immunostains was compared to staining pattern in five control cases. Control cases comprised of 2 cases with no significant pathological changes, and 3 cases with telencephalic leukoencephalopathy. The following histological features were assessed: necrotic cells in cortex, hippocampus, and cerebellum, APP and GFAP staining pattern, and the presence of focal lesions and amphophilic globules. Twenty patients (10 males, 10 females) were identified, with age range between 2 weeks and 19 years.*

Results: *The pathological findings were as follows: 10 cases had changes consistent with acute global hypoperfusion, 8 cases showed features consistent with chronic global hypoperfusion, 4 cases presented focal white matter necrosis (2 with intra-vascular emboli), and 16 cases showed diffuse moderate to severe gliosis, including 7 cases with amphophilic globules. Subarachnoid hemorrhages were present in 5 cases, subdural hemorrhage in 4 cases, intra-ventricular hemorrhage in 2 cases, and germinal matrix hemorrhage in 1 case.*

Conclusions: *In conclusion, diffuse gliosis is the prominent pathological feature in CHD cases. Most of the pathological changes are known to occur in cerebral hypoperfusion regardless of primary cause. Better techniques to improve cerebral perfusion are warranted in the management of these patients.*

Key words: *congenital heart disease, cerebral hypoperfusion, diffuse gliosis, brain pathology, autopsy.*

Introduction

Congenital heart disease (CHD) is the most common birth defect, involving approximately 1% of infants born in the United States [6,14]. Brain pathology in patients with CHD is associated with neuro-developmental delay, but advances in medical and surgical management have improved survival in CHD patients [13]. Neurological deficits, especially cognitive impairment, have become the major challenge in these survivors [13]. To face this challenge, the changes in the brain pathology in the present era need to be understood.

Earlier neuro-pathological studies found that cerebral white matter injury constitutes classic pattern of pathology in addition to sequelae of hypoperfusion in vulnerable gray matter structures, including the hippocampus, thalamus, and brainstem [4,5,9]. Cerebral white matter injury ranges from diffuse gliosis to periventricular leukomalacia (PVL) [9]. Prevalence of PVL varies in different studies, as it was observed in 10/50 (20%) cases of hypoplastic left heart (HLH) syndrome [4], in 32/296 (10.9%) cases of isolated CHD and in 13/92 (14.4%) patients with CHD with anomalies [11], and

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as acute PVL in 14/38 (34%) infants dying after cardiac surgery [9].

Recent pathological studies for assessment of these lesions are scarce [15]. In this study, our aim was to describe the pathological changes in the brains of patients with congenital heart diseases, and evaluate the pattern of injury in these cases.

Material and methods

We evaluated brain pathology from the last twenty autopsy cases in pediatric patients with CHD (types are provided in Table I), over 3 years period, starting from 2017. The autopsy reports were reviewed. All the brains were fixed in 20% formalin. The cerebrum was cut in coronal planes, the brainstem in axial plane, and the cerebellum in either coronal/axial or parasagittal planes. Sections were taken from standard areas and stained with hematoxylin-eosin (H&E), some were stained with H&E-Luxol fast blue, special stains, and immunostains, as required. The available stains, special stains, and immunostains were evaluated, and at least one section from the frontal cortex and adjacent white matter from each case was stained with anti-glial fibrillary acidic protein (GFAP), anti-amyloid precursor protein (APP), and anti-HLA-DR antibody. Staining patterns of these immunostains were compared to 5 control cases. Control cases were selected to compare staining pattern of these immunostains in cases diagnosed with no significant pathological changes (2 cases),

Table I. Clinical information

No.	CA Age – GA	Sex	CHD	Cy	Associated conditions	Surgical intervention (time)	ECMO (duration)
1	29 W 14 D – 27 W	F	TGA, TA	Yes	No	Extended left hemicolectomy for necrotizing enterocolitis (13^{th} D)	No
2	36 W 8 W – 28W	M	TA	Yes	Sepsis and pneumonia	No	No
3	37 W 4 D 4 D – 37 W	M	TRA-TYPE III	Yes	No	No	No
4	38 W 5 D 5 D – 38 W	F	HLH	Yes	Possible MURCS association	No	No
5	39 W 7 D 7 D – 39 W	M	HLH	Yes	No	No	No
6	39 W 3 D 10 D – 38 W	F	DORV	Yes	Tracheoesophageal fistula and esophageal atresia	Surgical repair of tracheoesophageal fistula (1^{st} D)	No
7	3 W 4 W – 39 W	F	HLH	Yes	No	Atrial septectomy (2^{nd} D), hybrid Norwood procedure with pulmonary artery banding (9^{th} D)	No
8	5W 6 W – 39 W	M	Single ventricle	Yes	No	Pulmonary arthroplasty and modified systemic pulmonary shunt (3^{rd} D)	No
9	8 W 9 W – 39 W	M	DORV	Yes	Trisomy 18	No	No
10	3 Mo – T	M	TAPVR	Yes	No	Vertical vein clip at innominate vein anastomosis and ASD pleating (2^{nd} D)	Yes (2 D before death)
11	3 Mo – T	F	PA & dysplastic TV	Yes	No	BT shunt, RVOT patch, fenestrated ASD patch, and PDA ligation at one month	Yes (6 D before death)
12	3.5 Mo 4 Mo – 38 W	M	Shone complex	No	Infantile hepatic hemangioma, sepsis	VSD patch closure with mitral valve repair, fenestrated ASD creation, aortic arch augmentation (50^{th} D)	Yes: 2 weeks (2^{nd}-3^{rd} W)

Table I. Cont.

No.	CA Age – GA	Sex	CHD	Cy	Associated conditions	Surgical intervention (time)	ECMO (duration)
13	5 Mo – T	F	HLH, PA	Yes	No	Reparation a l'Etage Ventriculaire (REV), atrial septectomy, and ligation of AP collateral (time of operation not available)	No
14	3.5 Mo 5 Mo – 34 W	F	TRA-TYPE I	Yes	No	First operation: closure of two VSD (10th D). Second operation: pulmonary artery reconstruction, placement of a new aortic homograft from the right ventricle to the reconstructed pulmonary arteries, and placement of a homograft interposition graft in the ascending order to increase the length of the aorta (3rd month)	N.A.
15	6 Mo – T	F	TA	Yes	No	BT shunt and PA band placement (16th day)	No
16	7 Mo – T	F	DORV	Yes	Antiphospholipid antibody syndrome	Norwood procedure with BT shunt (1st month), central shunt and augmentation of pulmonary arteries (5th month)	Yes (11 D before death)
17	13 Mo – N.A.	F	Cardiac posterior malalignment	No	No	VSD, interrupted aortic arch, sub-valvular aortic membrane resection (2nd week), modified Konno procedure, aortic stent (8th month)	No
18	7 Y – N.A.	M	AS	No	No	Balloon aortic valvuloplasty (6th day), Ross procedure (1st month), aortic homograft (7th year)	Yes (3 D before death)
19	16 Y – N.A.	M	DORV	Yes	No	Staged Fontan, 3 different surgeries in the last 2 years of life	No
20	19 Y – N.A.	M	DORV	Yes	No	Fontan procedure, cardiac transplant on the day of death	Yes (same day of death)
Co1	33 W 1 D 1 D – 33 W		NO	N.A.	Renal agenesis	N.A.	No
Co2	18 Y – N.A.	M	NO	N.A.	Renal medullary carcinoma	N.A.	No
Co3	2 D – T	M	NO	N.A.	TLE	N.A.	No
Co4	4 W 9 W – 35 W	F	NO	N.A.	TLE	N.A.	No
Co5	10 W – T	F	NO	N.A.	TLE	N.A.	No

AS – aortic stenosis, BT – Blalock-Taussig, CA – corrected age if applicable, CHD – congenital heart disease, Co – control case number, Cy – cyanosis, D – days; DORV – double outlet right ventricle, F – female, M – male, G – grade, GA – gestational age, HLH – hypoplastic left heart syndrome, Mo – months, MURCS – Mullerian renal cervico-thoracic and somite abnormalities, N.A. – not available, No. – number, PA – pulmonary atresia, SI – surgical intervention, T – term, TA – tricuspid atresia, TAPVR – total anomalous pulmonary venous return, TGA – transposition of great arteries, TLE – telencephalic leukoencephalopathy, TRA – truncus arteriosus, TV – tricuspid valve, W – weeks, Y – years

where staining pattern for these antibodies was considered as acceptable normal staining. Three cases of telencephalic leukoencephalopathy, which were known to be associated with positive staining as GFAP, should highlight gliosis, APP should highlight axonal swellings, and HLA-DR should highlight microglial proliferation. Scoring (0 – negative, 1 – mild, 2 – moderate, 3 – severe) of gliosis by GFAP and micro-glial reaction by HLA-DR (see Supplemental Fig. 1) was performed by MA (neuropathologist), blinded to clinical information.

The following histological features were assessed in these cases: necrotic neurons in cortical, hippocampal, and Purkinje cells, APP and GFAP staining in white matter, and focal lesions in gray and white matter. Pathological features were then grouped into different patterns of injury. These included: 1) Acute global hypoperfusion, where red eosinophilic ischemic neurons with pyknotic or karyorrhectic nuclei were present in gray matter vulnerable areas, such as the hippocampus, subiculum, border-zone cortical areas if sampled specifically, thalamus, cerebellar Purkinje cells,

Table II. Pathological features

No.	Brain weight (g) (normal range)	HC	AGH	CGH	FWML	AG	DG*	Mi**	ICH
1	122.3 (143-203)	No	Yes	No	No	No	0	1	SAH
2	262.3 (212-302)	No	No	Yes	Yes (sepsis)	Yes	2-3	N.A.	GMH-G1
3	325.9 (228-366)	No	Yes	No	No	Yes	2-3	0	No
4	347 (306-404)	No	Yes	No	No	No	2-3	1	No
5	345.2 (317-419)	No	No	No	No	No	2	1	No
6	308 (376-490)	Mild	No	Yes	Yes (PVL)	Yes	2	1	SAH, IVH
7	458.6 (461.8-595.6)	Mild	Yes	No	No	No	3	1	SAH, IVH
8	474.6 (431.8-517.2)	No	No	Yes	No	No	2-3	1	No
9	393.6 (439-573)	Mild	No	No	No	No	2-3	N.A.	No
10	644.5 (543.7-647.0)	No	Yes	No	No	No	0-1	2	SAH, SDH
11	561 (512.4-643.4)	No	Yes	Yes	No	Yes	3	0	No
12	670.6 (587.8-742.7)	No	No	No	No	No	2-3	1	No
13	526 (571.2-657.0)	No	No	No	Yes***	Yes	2	2	No
14	431 (652.1-775.5)	Moderate	Yes	No	No	Yes	2	1	SDH
15	497 (580.4-773.5)	Mild	Yes	Yes	Yes (PVL)	Yes	2	2-3	No
16	437 (504.7-639.1)	Mild	No	Yes	No	No	2-3	2	No
17	915.6 (655.1-918.5)	No	Yes	No	No	No	1	1	SAH, SDH
18	1,474 (1,381.4-1,568.5)	No	Yes	No	No	No	0	1	No
19	1,384.5 (1292.7-1506.9)	No	No	Yes – dentate gyrus	No	No	2	2	SDH
20	1,153 (1395.2-1498)	No	No	Yes – dentate gyrus	No	No	2	2	No
Co1	237 (168-266)	No	No	No	No	No	1	0	IVH
Co2	1,550 (1,391.3-1,500.7)	No	No	No	No	No	1	0	No
Co3	415.6 (228-368)	No	Yes	No	No	No	2-3	1	No
Co4	363 (431.8-517.1)	No	No	No	No	Yes	2-3	1	No
Co5	424.2 (543.7-647.0)	No	No	No	No	Yes	3	1	No

*AG – amphophilic globules, AGH – acute global hypoperfusion, CGH – chronic global hypoperfusion, Co – control case number, DG – diffuse gliosis, FWML – focal white matter lesions, G – grams, GMH – germinal matrix hemorrhage, HC – hydrocephalus, ICH – intra-cerebral hemorrhage, IVH – intra-ventricular hemorrhage, Mi – micro-glia reaction score, N.A. – not available, No. – number, PVL – periventricular leukomalacia, SAH – subarachnoid hemorrhage, SDH – subdural hemorrhage, * Diffuse gliosis scored as: 0 – negative, 1 – mild, 2 – moderate, 3 – severe. Only grades 2 and 3 were considered positive; ** Micro-glial reaction scored as: 0 – negative, 1 – mild, 2 – moderate, 3 – severe; *** Intra-vascular foreign materials most likely related to previous surgical intervention*

and brainstem, especially pontine nuclei; 2) Chronic global hypoperfusion, when similar areas in (1) showed neuronal loss and gliosis; 3) Focal white matter lesions, when relatively well-circumscribed region showed ischemic changes in white matter; 4) Diffuse gliosis, when widespread moderate (score 2) to severe (score 3) gliosis were apparent by GFAP immunostains. Scattered and mild (score 1) white matter gliosis were not considered under this category, as they were present in control cases with no pathological abnormality; 5) PVL was restricted to cases with focal white matter necrosis around lateral ventricles, but with no identifiable cause for necrosis, such as intra-vascular emboli; 6) Different forms of intra-cerebral hemorrhages according to their location, such as subarachnoid hemorrhage (SAH), germinal matrix hemorrhage (GMH), and subdural hemorrhage (SDH).

Results

We examined 20 cases (10 males, 10 females), with age ranging between 2 weeks and 19 years. Summary of clinical information are presented in Table I and pathological findings in Table II. The predominant CHD was double-outlet right ventricle (DORV) in 5 cases, followed by hypoplastic left heart syndrome (HLHS) in 4 cases. Thirteen cases had various surgical interventions before death.

The pathological findings were as followed: 10 cases had changes consistent with acute global hypoperfusion, 8 cases showed features consistent with chronic global hypoperfusion, 2 cases presented focal white matter lesions (2 were secondary to intra-vascular emboli and 2 were considered PVL), and 16 cases showed diffuse moderate to severe gliosis, including 7 cases with amphophilic globules. Subarachnoid hemorrhages were present in 5 cases, subdural hemorrhage in 4 cases, intra-ventricular hemorrhage in 2 cases, and germinal matrix hemorrhage in 1 case.

Acute global hypoperfusion was present in 10 cases, and it was characterized by ischemic red neurons and karyorrhectic nuclei in CA1 region of the hippocampus (Fig. 1A), dentate gyrus (Fig. 1B), pontine nuclei (Fig. 1C), and cortical area (Fig. 1D). This pattern was also accompanied by chronic global hypoperfusion in 2 cases and diffuse gliosis in 6 cases. Chronic global hypoperfusion was present in 8 patients (4 males and 4 females), which affected similar areas, and was characterized by neuronal loss and gliosis in hippocampal and subicular areas (Fig. 2A, B), cortical laminar neuro-

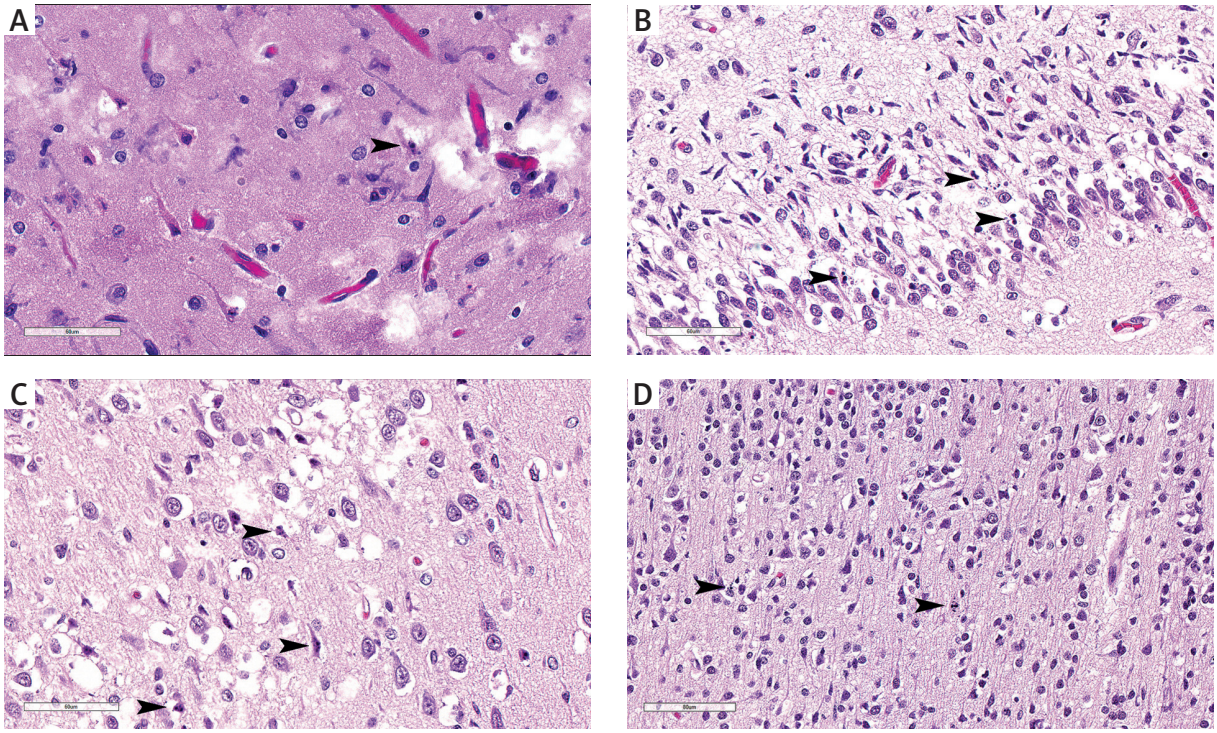

Fig. 1. Acute global hypoperfusion. **A**) CA1 of the hippocampus shows many eosinophilic necrotic neurons and karyorrhectic nuclei (arrowhead) (Case No. 11; HE 400×); **B**) Dentate gyrus shows many karyorrhectic nuclei (arrowheads); **C**) Pontine nuclei with karyorrhectic nuclei (arrowheads); **D**) Temporal lobe cortex with scattered karyorrhectic nuclei (arrowheads) (Case No. 1; HE (B-D) 400×).

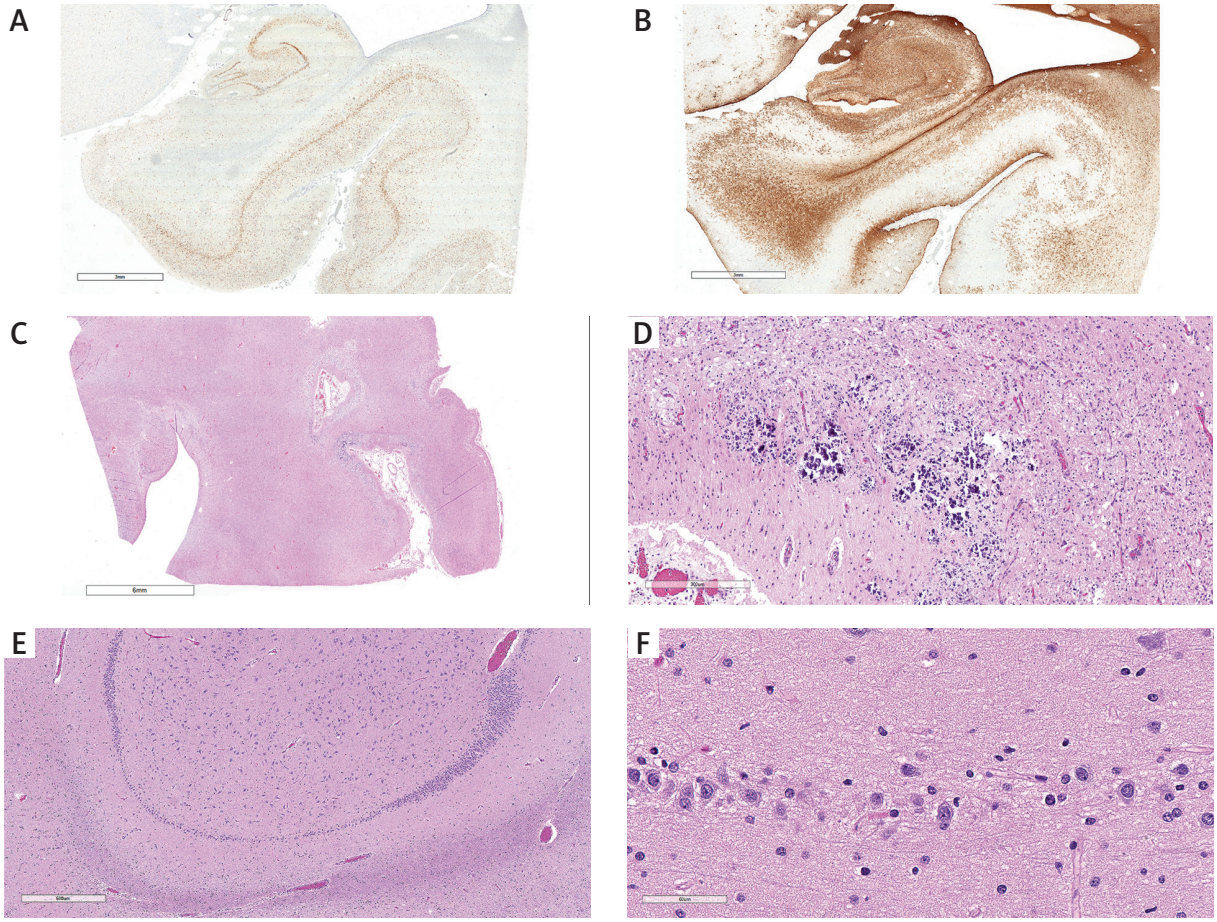

Fig. 2. Chronic global hypoperfusion. **A**) Neuronal loss in CA1 of hippocampus and subicular region; **B**) Moderate to severe gliosis in similar regions (Case No. 11, A) NeuN 10×; B) GFAP 10×); **C, D**) Laminar neuronal loss and calcification (Case No. 16, H&E: C) 5×, D) 200×); **E, F**) Focal selective neuronal loss in the dentate gyrus and no apparent neuronal loss in other areas (Case No. 20, H&E: E) 100×, F) 400×).

nal loss, and gliosis with neo-vascularization and calcification (Fig. 2C, D). The 2 oldest patients had selective neuronal loss in the dentate gyrus (Fig. 2E, F) and no apparent neuronal loss in other areas. All cases with this pattern showed also diffuse gliosis.

Focal white matter lesions were present in 4 cases, and were characterized as relatively circumscribed areas of white matter necrosis (Fig. 3A). The cause of these focal lesions was identified in 2 cases. Case No. 2 had intra-vascular fibrin (Fig. 3B) secondary to sepsis, and case No. 13 presented intra-vascular foreign materials, most likely as complication of previous cardiac surgery. We could not identify the causes of white matter necrosis in the other 2 cases, and thus were considered as PVL. The necrosis in these 2 cases were associated with calcifications indicating older lesions and different from classic necrotic foci in PVL control case (Fig. 3C, D).

Diffuse gliosis was the most common pathology observed in 16/20 cases and negative in 4 cases (2 males and 2 females). This diffuse gliosis could be associated with hypertrophic astrocytes (Fig. 4A), or with no hypertrophic astrocytes (Fig. 4B). The latter is very difficult to distinguish from myelinating glia without GFAP immunostains, which can highlight the widespread reactive astrocytes (Fig. 4C). 7/16 cases were associated with amphophilic globules/ calcifications in the white matter (Fig. 4D, E).

Discussion

Brain injuries in patients with CHD could result from different risk factors at different times, a consequence of CHD or some form of intervention, such as balloon atrioseptostomy in pre-operative period, other risk factors related to anesthesia and surgical operation, and complications, including sepsis [12]. Cerebral hypoper-

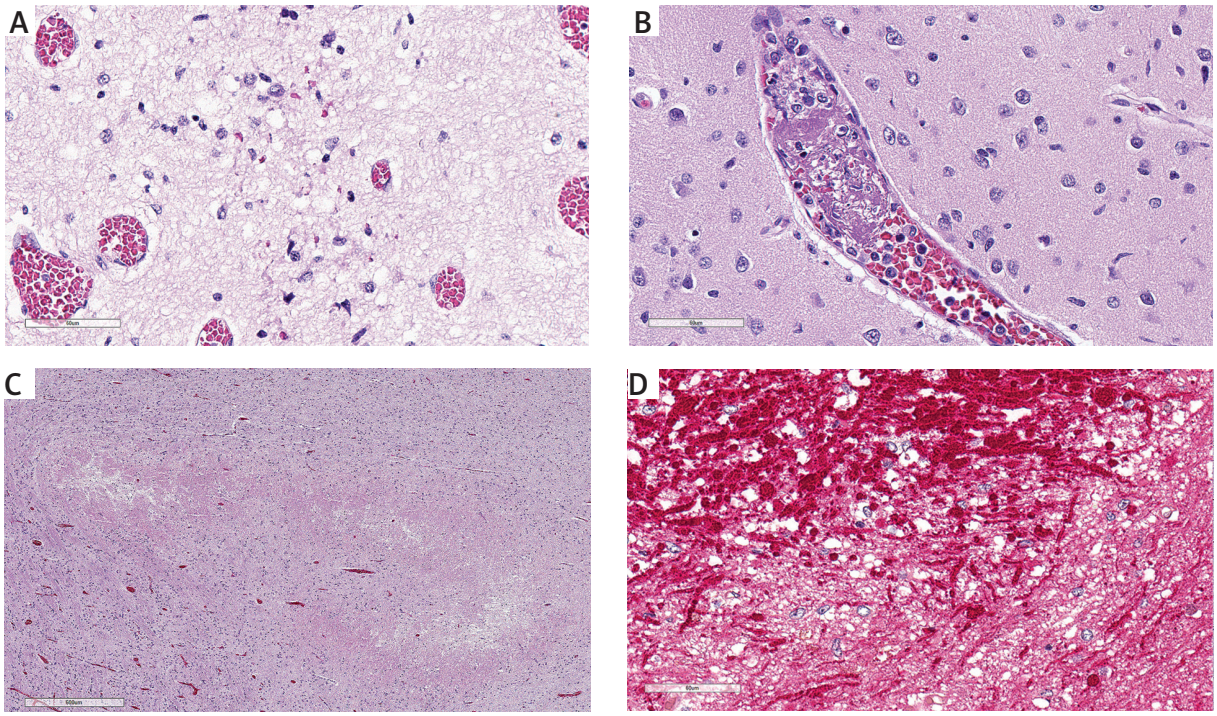

Fig. 3. Focal white matter lesions. **A**) Small focus of white matter necrosis; **B**) Intra-vascular fibrin secondary to sepsis (Case No. 2; A, B) H&E: 400×); **C**) Necrosis in PVL anterior and lateral to the anterior horn of lateral ventricle; **D**) Prominent axonal spheroids in the necrotic zone highlighted by APP immunostains in red (PVL control case; C) H&E 40×; D) Double immunostain APP (red) & HLA-DR (brown) 400×).

fusion is a shared complication in these different settings and often results in comparable brain injuries. Frequently, it is not possible to determine the etiology of cerebral injury during postmortem examination.

Neuro-imaging studies are essential to distinguish between the cause of different brain pathology by comparing pre-operative and post-operative images. New acquired white matter injuries after surgical operation are clearly related to the surgery or its' complications and not to CHD. The etiology of these white matter injuries could also be suggested from the pattern of the white matter injury by imaging. Claessens *et al*. did such a study, and classified the white matter injury into multifocal white matter injury and focal ischemic injury. They found that multifocal white matter injury and hypoxic-ischemic 'border-zone' injury showed diffuse patterns of ischemia most likely related to global hypoperfusion, while focal white matter injury were more related to stroke [2].

In this study, we grouped the brain pathology in patients with CHD into different pathological groups that should reflect probable etiology for the observed brain pathology. The first two groups reflected the expected brain pathology secondary to global hypoperfusion, and differed in the timing of injury in relation to the time of death. The affected areas were similar in both the groups, and included the hippocampus, deeper layer of the cortex, Purkinje cells, brainstem, and thalamic nuclei. In acute global hypoperfusion, shorter time between the time of injury and death is confirmed by the presence of eosinophilic red ischemic neurons and pyknotic or karyorrhectic nuclei. This pattern is indicative of terminal events and not necessarily associated with CHD. In chronic global hypoperfusion, longer duration between the hypoperfusion event and death is confirmed by neuronal loss and gliosis in these areas. This pattern of injury indicates previous or recurrent episodes of cerebral hypoperfusion. This most likely is a consequence of CHD or complication related to CHD in this age group.

Periventricular leukomalacia is considered as a characteristic feature for encephalopathy of prematurity, and is defined as focal periventricular white matter necrosis associated with diffuse gliosis in the surrounding white matter [17]. The underlying mechanism is debated between hypoxic ischemia [17] and fetal inflammatory response [3]. As the term 'encephalopathy of prematurity' implies, this encephalopathy is predominant in preterm infants, with the highest risk period occurring in 23-32 weeks post-conceptional

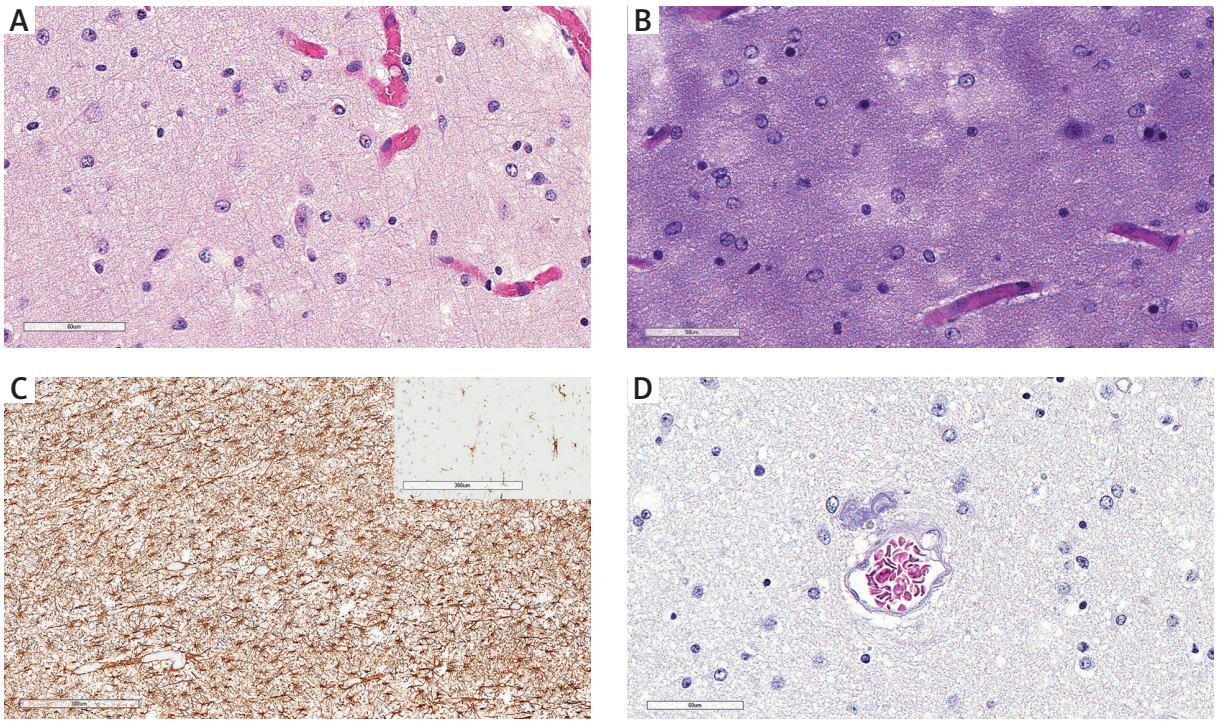

Fig. 4. Diffuse gliosis. **A**) Hypertrophic astrocytes with large eosinophilic cytoplasm (Case No. 13, H&E 400×); **B**) Diffuse gliosis with no apparent hypertrophic astrocytes; **C**) GFAP immunostains highlights moderate to severe gliosis. Inset: GFAP from control case with similar magnification showing score 1 for comparison (Case No. 8; B) HE 400×, C) GFAP 100×); **D**) Amphophilic globules/calcifications in the white matter (Case No. 6; HE 400×).

age [1]. This period reflects the vulnerable period for pre-myelinating oligodendrocyte precursor cells. Cases in term infants with CHD are thought to represent an *in utero* insult that occur in the high-risk period [1], or because of brain immaturity, which may enhance susceptibility of the white matter in these term infants [10]. In this study, we found 4 cases fulfilling the definition of PVL. However, as white matter necrosis is the expected pathology in cases with intra-vascular emboli, we excluded the 2 cases, which showed these findings, leaving 2/20 (10%) of PVL pattern in this cohort. Our result is in agreement with a recent pathological study, where the authors examined 50 cases from two different hospitals and found only 3 PVL cases [15]. The reduction of PVL incidence in CHD patients may be linked to better antenatal management [1].

Imaging studies found that the causes of white mater necrosis in CHD are more attributed to interventions, such as balloon atrioseptostomy [2,8], and post-operative complications of surgical procedures for congenital heart defects, especially when performed on newborns younger than 2 months of age [16]. Kinney *et al.* used the term 'acute PVL' for white matter lesions that developed after surgical intervention in neonates [9]. However, we excluded such cases as PVL, as we did not consider these to represent the same etiology as encephalopathy of prematurity.

We found diffuse gliosis as the most common pathology (16/20) in CHD cases. Four negative cases have possible explanation. Case No. 1, a patient born at 27 weeks gestation and at this gestational age, the astrocytic reaction is not well-developed. Cases No. 10 and 17 had CHD that may not have caused profound cerebral hypoperfusion, and the mild reactive astrocytosis present was considered as negative because similar reaction was present in the control cases with no pathological diagnosis. In case No. 18, astrocytes were lost due to more severe ischemic effect.

We concluded that diffuse gliosis is the classic feature of CHD in the current era. This contrasts with Rettenmair et al. study, where diffuse white matter gliosis was found only in 8/50 cases. This difference could be explained by different method used, as they documented pathological features by going through autopsy reports, and it was not clear if GFAP immunostain was performed on these cases or not [15]. In case it was not, diffuse gliosis with no apparent hypertrophic

astrocyte could be easily missed on H&E-stained sections.

Different forms of intra-cerebral hemorrhages are also associated with congenital heart diseases. In this study, subarachnoid hemorrhages were present in 5 cases, subdural hemorrhage in 4 cases, intra-ventricular hemorrhage in two cases, and germinal matrix hemorrhage in one case. This result agrees with many other studies, which described different forms of cerebral hemorrhages in patients with CHD [2,8,15].

The major limitation of this study was its' retrospective design, and we could not specifically investigate the reduction of white matter volume (well-described in imaging study). The type and timing of surgical intervention in some of these cases, the presence of other comorbidities, such as genetic alteration, sepsis, and anti-phospholipid syndrome as well as the complicated clinical background in these children could contribute to the brain pathology. Therefore, the distinction between the effects of these comorbidities and CHD could not be possible in some of the cases. Also, the use of extra-corporeal membrane (ECMO) in some of the cases can contribute to the pathology, which resemble the pathology in hypoxic ischemic insults [7]. These limitations are common in these types of studies on human tissue and reflect on the unsolved debate regarding the pathogenesis of PVL, whether it is hypoxic-ischemic or inflammatory. We used the known pathological background in our study to reach the conclusion, but given this limitation, better prospective study that account for these different variables are needed.

In conclusion, we found that cerebral white matter injury is still the most common lesion in patients with congenital heart diseases, and most likely results from cerebral hypoperfusion. The cause for the hypoperfusion was not restricted to congenital heart disease, but may also be related to peri-operative and post-operative factors. As diffuse gliosis is the most common pathology, we recommend that GFAP immunostain be performed in all cases with congenital heart disease to identify cases with no hypertrophic astrocytosis that can be easily missed on routine stains.

Disclosure

The authors report no conflict of interest.

The supplemental figure is available on journal's website.

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