Pineal cysts – a benign consequence of mild hypoxia in a near-term brain?

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Abstract

BACKGROUND: Pineal cysts are benign glial uniloculated or multiloculated fluid-filled sacs located in the pineal gland region. Small pineal cysts are often found incidentally in healthy adults in 1.5–10.8%. Large cysts may cause neurological problems due to pressure exertion on adjacent structures.

METHODS: We have used prospective, observational study of an inception cohort of 16 adolescents of mean age 21.69 years (SD=±0.87) with mild (68.7%) to moderate (31.3%) HIE: 7 girls (43.8%) and 9 (56.3%) boys, born with mean gestational age of 35.75 weeks (SD=±3.80) and mean birthweight of 2 644 g (SD=±815). HIE was confirmed by presence of abnormal CTG and/or meconium and/or Apgar scores less than 7 at 5 minutes and/or need for resuscitation and/or cord pH less than 7.2 and /or BE more than –15. The clinical assessment of HIE was done according to the Sarnat-Sarnat scoring. Neonatal data, including EEG and imaging data, were collected. Adolescents were scanned with 3T Magnetom Trio Tim, Siemens, head coil 12 channels, regular sequences and sagittal 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with voxel size 1 mm^3. Neurological outcome was determined.

RESULTS: In 1 patient we found cortical dysplasia and 1 had a panic attack hence their data were omitted. In the group of 14 we have incidentally found in 5 patients a larger, asymptomatic pineal cysts with the overall incidence of 36%. Other MR findings in the group were in 50% white matter injury, in 50% thinner corpus callosum. No statistically significant difference between neonatal cUS and late follow-up MRI (p=0.881) was found. Correlation was not significant with Spearman correlation koefficient 0.201. Presence of pineal cysts was linked to thinner corpus callosum (p=0.005).

CONCLUSIONS: We propose that larger pineal cyst, in the absence of other imaging findings except for thinner corpus callosum, is a benign consequence of mild hypoxia in a near-term brain. Our findings warrant a larger study.

ORIGINAL ARTICLE

INTRODUCTION

Pineal cysts are benign glial uniloculated or multiloculated fluid-filled sacs located in the pineal gland region. Small pineal cysts of diameter less than 5 mm are common occurrences, often found incidentally in healthy adults in 1.5–10.8% (Mamourian & Towfighi 1986) or found on autopsies in between 25% and 40% (Tapp & Huxley 1972; Hasegawa *et al.* 1987). The size of pineal gland increases until 2 years of age and remains stable between 2 and 20 years (Sumida *et al.* 1996).With aging, the pineal glands develop calcification almost logarithmically with age (Zimmerman & Bilaniuk 1982); the weight of the pineal gland increases gradually from adolescent period to old age (Tapp & Huxley 1971).

Small pineal cysts rarely cause symptoms (Pu *et al.* 2007). Larger pineal cysts are rare to find and may cause a variety of symptoms, including headache, vertigo, hydrocephalus, and vision abnormalities, mainly due to aqueductal compression and compression of superior colliculi.

Asymptomatic, small pineal cysts in healthy adults are considered as normal variants, no surgical intervention or imaging follow-up is warranted. Follow-up studies showed that cysts remain stable in size, rarely they enlarge or or regress (Pu *et al.* 2007). The differential diagnosis of cysts and cystic tumours is crucial, though with no reliable imaging diagnostic criteria (Sumida *et al.* 1996).

The exact cause of pineal cysts is unknown. The cysts is composed of an inner layer of gliotic tissue, an intermediate layer of pineal parenchymal tissue and an outer layer of connective tissue. The pineal gland itself develops from the most caudal portion of the roof of the third ventricle, from an area of ependymal thickening which evaginates during the seventh week of gestation. The gland is at that time a patent cavity connected to the third ventricle, lined by thickened ependyma. Later the pineal parenchyma tubules gradually transform into solid cell masse, separated by connective tissue and nerve twigs until the middle of the first life decade when the structure resembles a mature gland, consisting of pinocytes, arranged into lobules separated with connective tissue septa and thin-walled vessels (Langman 1975).

Hypoxia-ischaemia occurs in 1–6/1000 live full term birth and carries a high risk for neurodevelopmental dissabilities (Volpe 2008). In hypoxic-ischaemic encephalopathy the patterns on MRI give an insight into timing, pattern and severity of the insult and also help to predict the outcome. Two main patterns are described: a basal-ganglia-thalamus pattern seen afer an acute, near total aspyxia with a severe deficit outcome and a water-shed predominant pattern of injury, seen after prolonged, partial asphyxia with a more favourable outcome (de Vries & Jongmans 2010). Despite the general well being these children seem to grow into their deficits.

Abnormal myelination represents a major pathological sequellae of chronic white matter injury. White matter lesions are more vulnarable to hypoxia-ischaemia if preoligodedrocytes are arrested in their maturation and their degeneration is delayed (Segovia *et al.* 2008). Melatonin, produced endogeneously from pineal gland or given exogeneously to rodents shows a neuroprotective effect by promoting oligodendroglial maturation and decreasing microglial activation (Olivier *et al.* 2009). It stimulates proliferation of neural stem cells during hypoxia (Fu *et al.* 2011). It is also a potent free radical scavenger and indirect antioxidant (Signorini *et al.* 2009).

By discovering so many pineal cysts in the group of mild HIE we suggest that this might not be a coincidence. Perinatal hypoxic injury is involved in abnormal myelination where melatonin can play a scavenger role. We suggest that the near-term brain has it own repair mechanism for HIE of endogenous melatonin production which when no longer needed, is followed by filling the hyperproductive pineal gland with fluid which is later seen as pineal gland cyst.

METHODS

Young adults, average age 21.69 years, (SD=±0.87), were selected among the Slovenian infants who were admitted to the NICU due to mild and moderate HIE in 1988–1990. They were born at the mean GA 35.75 weeks (SD=±3.80) and mean birthweight of 2 644 g (SD=±815).

Neonatal data, neonatal EEG and imaging data, mainly cUS, were collected. HIE was confirmed by presence of abnormal CTG and/or meconium and/or Apgar scores less than 7 at 5 minutes and/or need for resuscitation and/or cord pH less than 7.2 and /or BE more than –15. The clinical assessment of HIE was done according to the Sarnat-Sarnat scoring. 31 families were contacted both via the phone and by post-inquiry. 16 yong adults agreed to participate in the late follow-up. Two participants were later excluded: one due to unsuccessful MRI; in the other extensive subcortical heterotopia (congenital malformation) was found on MRI.

Adolescents were scanned with 3T Magnetom Trio Tim, Siemens, head coil 12 channels, regular sequences and sagittal 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with voxel size 1 × 1 × 1 mm. MPRAGE sequence consisted of TR=2 300 ms; TE=3 ms; flip angle 9 °; matrix: 256 × 256. Neurological outcome was determined. The data were analysed by SPSS 19.0 statistical package (SPSS Inc., Chicago, Illinois). We calculated descriptive statistics (mean-M, standard deviation-SD, frequencies) and used the $\chi 2$ test for categorical data and Mann-Whitney U test for ordinal data; *p*-values and correlation Spearman coefficient were calculated.

The study was approved by the Ethical Committee of Medical faculty Ljubljana and University Clinical

centre Ljubljana. The participants were introduced to the procedure and signed the informed consent. They were also advised upon their MRI findings.

RESULTS

Neonatal and late follow-up imaging findings are sumarized in Table 1.

On neonatal cUS examination we have found three normal exams. In four infants diffuse billateral ischaemic changes in the vascular water-shed zones were observed. In six infants billateral hypoxic areas were localized predominantly periventricularly. Three infants had diffuse hyperechogenicity in WM. CT scan was done in six infants: one was normal, one revealed severe generalized brain edema, one subarachnoid haemmorhage, two had intracranial haemorrhage occipitally and around the falx, one had hipodense white matter. In ten children CT scan was not done. None of infants had MRI at that time.

On follow-up, in one MRI was omitted due to a panic attack. In one we found cortical dysplasia – congenital malformation, hence she was excluded from HIE group. In three young adults gross MRI findings were completely normal. No lesions in the basal ganglia and thalami were observed. Seven young adults had thinner corpus callosum as seen on mediosaggital sections at T1. Two had generalized thinner corpus callosum, one had thinner anterior, one posterior, while two had much thinner middle part. One had generally thinner and balooned anterior part.

Seven young adults had white matter gliosis. Multicystic lesions were absent. In one we have found lipoma on velum medullare and hypoplastic vermis in otherwise normal brain MRI, in one neuroglial cyst, one had partial agenesia of anterior part of septum pelucidi. None of the young adults presented with any clinical signs or symptoms.

In five adults we have found pineal cysts. Two were multilocular, three were unilocular. They did not exert compression on the surrounding tissue. All young adults with pineal cyst had thinner corpus callosum. Two young adults with thinner corpus callosum and prominent white matter changes with a severe

Tab. 1. Neonatal and late follow-up imaging findings.

Subject No.	HIE Grade	Neonatal cUS	Neonatal CT	Gross MRI findings at 21 years	Pineal cyst in mm
1	1	1a	ICH, o + f	PC, NC, tCC	Unilocular 16×14×14
2	1	2a	–	Cortical dysplasia, tCC	–
3	1	3	SAH	Normal	–
4	1	Normal	–	Normal	–
5	1	1a	–	Normal	–
6	1	Normal	–	EV, fG, tCC, PC	Unilocular 9×4×8
7	1	2a	Hipodense WM	fG	–
8	2	3	GBE, unenhanced scan	gG, post PVL, EV, tCC, aWM	–
9	2	2b	–	gG, aWM	–
10	2	3	ICH, o + f, GBE	gG, aWM, HS, tCC	–
11	1	1b	–	gG, post PVL, EV, tCC, PC	Multilocular 10×6×5
12	1	Normal	–	PC, tCC	Multilocular 10×5×5
13	1	2b	–	PC, tCC, EV	Unilocular 10×10×10
14	2	1b	–	fG	–
15	2	2a	Normal	L	–
16	1	2a	–	–	–

Patterns of injury seen on cUS: 1 - Bilateral ischaemic changes, in the vascular water-shed zones; 2 - Bilateral periventricular hypoxic areas; 3 - Diffuse hyperechogenicity in WM; changes are graded as a – mild; b - moderate; PVL – periventicular leucomalacia - we use the description of post-PVL changes, despite we are aware, that this is the pattern of hypoperfusion seen earlier in gestation; ICH – intracranial haemorrhage, o – occipitally, f – falx; SAH – subarachnoid haemorrhage; GBE – generalized brain oedema; PC – pineal cyst; NC – neuroglial cyst; L - lipoma; tCC – thinner corpus callosum; EV – enlarged ventricles; G – gliosis; g – general; f – frontal; aWM – atrophy of white matter, HS – hippocampal sclerosis

developmental outcome of epilepsy and cerebral palsy, did not have pineal cyst.

We did not find statistically significant difference between findings on neonatal cUS and late follow-up MRI (p=0.881). With grading system of cUS findings the correlation was not significant with Spearman correlation koefficient 0.201. We did not find statistically significant difference between white matter gliotic changes seen on MRI and presence of pineal cyst (p=0.577). Presence of pineal cysts was linked to thinner corpus callosum (p=0.005).

DISCUSSION

We have found larger pineal cysts in young adults where HIE was mild. Consequences, as seen on MRI and also developmentally, were not severe, however not entirely absent. Statistically significant interaction was observed with pineal cyst presence and thinner corpus callosum. So we speculate that mild hypoxia-ischaemia in near-term brain can trigger the pineal gland excretion of melatonin acting as a powerful anti-hypoxia-ischaemia agent. When inactive, the pineal gland cavity fills with fluid and after years we only observe a benign pineal gland cyst. Thinner corpus callosum means that the pericallosal space is larger hence enabling the pineal gland cyst to enlarge without exerting significant pressure on adjacent structures.

As young adults with pineal cysts had a mild form of HIE with a good developmental outcome and mild gliosis seen on their late-follow-up MRI, it is possible, that this mechanism is efficient only in mild hypoxia-ischemia. In more severe form of HIE which also carries higher risk for not favourable outcome, this mechanism is not sufficient. In more severe forms of HIE the blood flow is more compromised. Vascularisation of the pineal gland commences towards the middle of intrauterine life (Duvernoy *et al.* 2000). The arterial supply is obtained through groups of pineal arteries stemming mainly from the medial posterior choroidal arteries. Venous drainage is provided by the lateral pineal veins draining mostly into the cerebral vein of Galen. The central part of the gland is highly vascularized by large sinusoid capillaries and its peripheral part poorly vascularized by small and fine blood vessels (Vinas *et al.* 1995). So it would be possible, that in more severe HIE the pineal gland is so deprived of blood flow, that it can not respond sufficiently and this is why the pineal gland cysts are not observed.

CONCLUSION

From the observation we propose that pineal cyst can be a benign consequence of mild hypoxia in a preterm brain. Our findings warrant a larger study.

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