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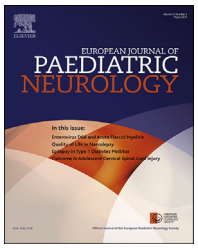

Original article

Punctate white-matter lesions in the full-term newborn: Underlying aetiology and outcome

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ABSTRACT

Background: Punctate white matter lesions (PWMLs) are small focal patches of increased signal intensity (SI) on T1- and decreased SI on T2-weighted magnetic resonance imaging (MRI). To date, there have been few reports of PWMLs in term born infants.
Objective: To identify associated diagnoses and factors predictive of clinical outcome in (near) term infants with PWMLs.
Methods: MRI studies and clinical records of (near) term infants, with PWMLs on MRI scans performed in two institutions in the first 28 postnatal days were reviewed. The PWMLs were classified according to their number, pattern and distribution. The medical records were examined to assess the associated diagnoses and determine the neurodevelopmental outcome at >12 months of age. Infants with congenital heart defect(s), those who had neonatal surgery, or those with perinatal arterial ischemic stroke were not eligible for the study.
Results: Forty-two (near) term infants with PWMLs were included. The major clinical association was perinatal asphyxia, present in 19/42 (45%). Ten (24%) had a history of seizures unrelated to asphyxia or a genetic diagnosis. Eleven (26%) had pathological genetic mutations. Other diagnoses, without seizures were identified in 2 (5%). The lesion load of PWMLs was high (>6) in 30/42 (71%). Evidence of irreversible white matter injury was present in 5 infants who had follow-up MRI performed between 18 and 24 months of age, because of clinical concerns. Five infants died and 37 had follow-up at a median age of 24 months. Neurodevelopmental outcome was poorest amongst 6 infants (16%) whose PWMLs occurred in the setting of a genetic disorder.

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Conclusion: PWMLs in (near) term infants represent white matter injury that may evolve into gliosis and/or white matter loss. Infants with PWMLs in the setting of a genetic disorder appeared at most risk of a poor outcome.

1. Introduction

PWMLs are small focal patches of increased signal intensity (SI) on T1-weighted MRI, and decreased SI on T2-weighted images, most readily seen during the first postnatal week and most frequently occurring in very preterm infants.[1–3] They are often interpreted as punctate haemorrhages, but when the MRI is performed during the first week after birth, most of these lesions show restricted diffusion and no decrease in signal on susceptibility weighted imaging (SWI), suggesting an ischaemic nature.[4,5] Whilst low signal on the ADC map can also be seen in infants with a haemorrhagic lesion, punctate haemorrhages are often associated with a rim of increased signal on DWI, whilst appearing darker and speckled on the ADC map, allowing them to be distinguished from punctate ischemic lesions.

The reported incidence of PWMLs ranges from around 20% to more than 50% in very preterm infants.[2,6–11] They have also been reported in (near) term infants[5,9,11] in a variety of clinical settings including hypoxic-ischaemic encephalopathy,[12] congenital heart disease,[13] following neonatal surgery for non-cardiac congenital anomalies,[11] and in association with genetic disorders.[14] The reported incidence in congenital heart disease varies between 30 and 65% and an incidence of 32% was reported in infants following surgery for non-cardiac congenital anomalies.[11,15]

Different classification systems for PWMLs have been used. These scoring systems are based on the number of PWMLs,[5] the pattern of the lesions[4,9] and the volume of the cerebral hemisphere occupied by PWMLs.[16]

The clinical outcomes reported following PWMLs in preterm infants range from normal[9] to cognitive delay and cerebral palsy.[8] Cerebral palsy is probably related to PWMLs clustered around the corticospinal tracts or an abnormal signal intensity of the posterior limb of the internal capsule (PLIC). Outcome data in term infants with PWMLs is limited. A small cohort of term infants who underwent neonatal surgery for their congenital heart defect who had moderate to severe white matter lesions on their pre-and postoperative MRI had an unfavorable cognitive outcome at school age.[17]

In this study, we retrospectively reviewed the MRI studies and clinical records of (near) term infants identified to have PWMLs on MRI scans performed in the first 28 days after birth at two institutions in the Netherlands to identify the associated diagnoses and factors predictive of clinical outcome.

2. Methods

Review of the MRI databases of two level three neonatal intensive care units in the Netherlands, Wilhelmina Children's Hospital, Utrecht, and Isala Women and Children's Hospital, Zwolle, identified infants whose MRI scans of the brain performed within the first 28 days after birth had been coded as showing evidence of white matter injury (WMI). Infants who had moderate to severe HIE and, since 2008, those who had therapeutic hypothermia, had an MRI. All infants with neonatal seizures and other neurological symptoms, or suspected white matter abnormalities on ultrasound, also had an MRI. Infants with cardiac or non-cardiac congenital anomalies who had surgery in the neonatal period and infants with perinatal arterial stroke were excluded.

The databases spanned the periods from December 2000 to September 2017 at the Wilhelmina Children's Hospital, and January 2014 to September 2017 at Isala Women and Children's Hospital.

The review of the databases identified a total of 91 infants whose MRI scans of the brain showed evidence of WMI.

2.1. *Magnetic resonance imaging (MRI)*

In all cases, MR imaging had been performed as part of routine clinical care in infants admitted with neonatal encephalopathy and/or seizures or other neurological symptoms. The Institutional Review Board (IRB) of both institutions gave approval for use of the clinically acquired data for study purposes. Since clinically obtained anonymized data were used, written informed parental consent for participation in the study was waived by the IRBs.

a MRI protocol

Detailed information regarding the imaging methods utilized has been described previously.[1,13] MRI was performed using a 1.5 T or 3.0 T MR system (Philips Medical Systems, Best, The Netherlands). Vacuum pillows (MedVac, Kohlbrat & Bunz, Radstadt, Austria) were used to prevent infant movement during the examination. Earmuffs were applied for hearing protection (Minimuffs, Natus Medical Inc. San Carlos, CA, USA; Em's 4 kids LLC, Culver City, CA, USA). Infants who did not receive intravenous sedation were sedated with either chloral hydrate (50 mg/kg orally) or an intramuscular injection of a combination of pethidine (2 mg/kg), chlorpromazine (0.5 mg/kg), and promethazine (0.5 mg/kg). Heart rate, respiratory rate and transcutaneous oxygen saturation were monitored. A neonatologist or physician assistant was present throughout the examination and transport. MRI images included T1-or T2-weighted sagittal sequences; T1-and T2-weighted axial sequences, and axial DWI (3 directions) with 3–4 mm thick slice thickness, and b values of 0 and 800 (3T) or 1000 s/mm^2 (1.5T). An ADC map was generated by the Philips

MR system. From 2008 onwards, the susceptibility weighted sequence (SWI) became available and was used at the discretion of the attending neonatologist.

b Review of the MRI's

The MRI's from both institutions were separately reviewed for PWMLs and associated abnormalities by two experienced neonatal neurologists (MH and LSdeV). In addition, the MRI's from Isala Women and Children's Hospital, Zwolle, were reviewed by an experienced neonatologist with more than 10 years' experience in assessing neonatal MRIs (HvS or GvW-M). Consensus was reached as to whether PWMLs were present. Infants were eligible when the PWMLs were the predominant finding. Infants with perinatal arterial stroke with PWMLs were not included.

After review of the 91 MRI scans, 44 infants were excluded from the study because the appearances of the lesions on MRI were not consistent with PWMLs, resulting in a total of 47 infants meeting radiological criteria for inclusion (See Fig. 1). Only those with a follow-up of more than 12 months were eligible for the study.

PWMLs were classified according to their number in each cerebral hemisphere (<3, 3–6, >6), pattern (linear, cluster or mixed) and predominant distribution.[9] Their location was classified as anterior when they were predominantly situated anterior to the frontal horn of the lateral ventricles, posterior when they were predominantly posterior to the occipital horn of the lateral ventricles, parietal when between the two, or multifocal/generalized (Figs. 2 and 3).

2.2. *Neurodevelopmental follow-up*

All infants were followed up post-discharge by an experienced neonatologist, pediatrician or neonatal neurologist.

Five of the 47 infants were excluded from the study because their period of clinical follow-up was less than twelve months and thus considered too short. Of the other 42, five had died. In the remaining 37, the period of neurodevelopmental follow-up ranged from 12 months to 12 years (See Fig. 1).

Neurodevelopmental assessments were performed by a trained neonatologist or psychologist in 30 children, utilizing the Griffiths Mental Development scales (GMDS) and/or

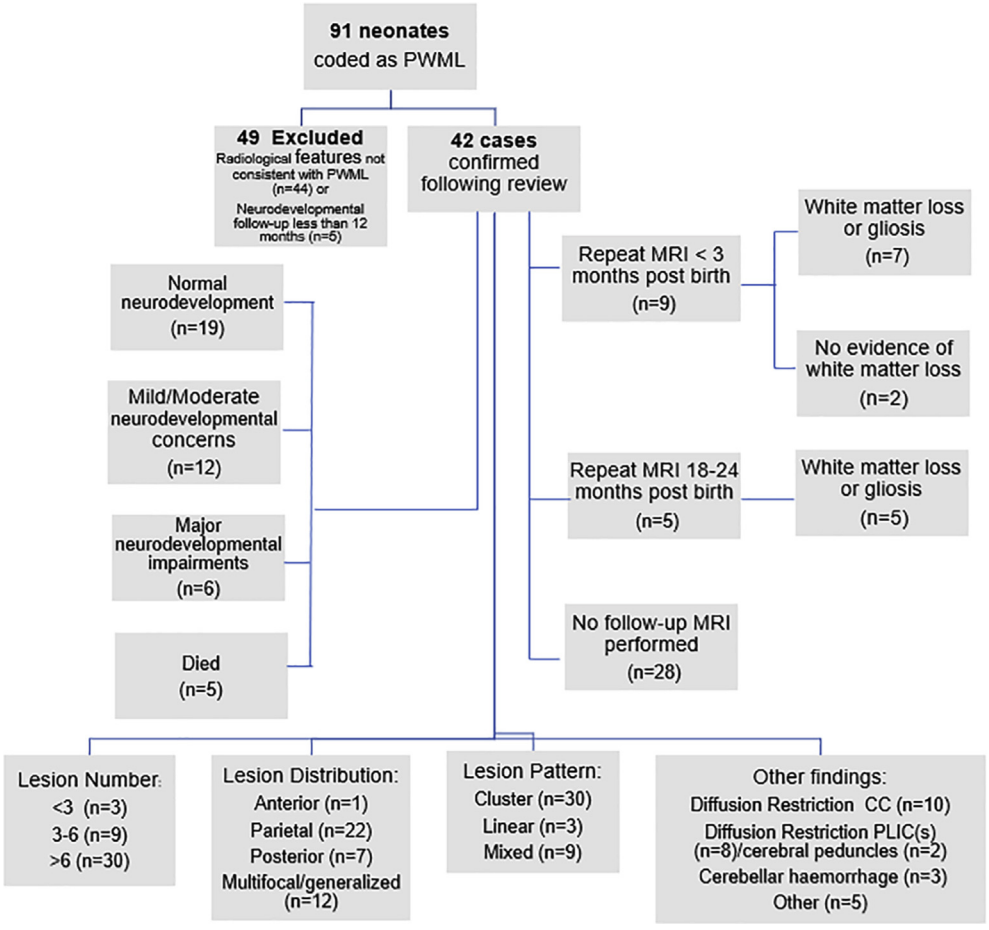

Fig. 1 – MRI findings and neurodevelopmental outcome. This figure summarises the study's results. Along the horizontal axis, along the bottom, the findings on the initial, post-birth MRI scans are shown. Along the vertical axis on the left, the neurodevelopmental outcomes are shown; along the vertical axes, on the right, are the findings on the follow-up MRI scans.

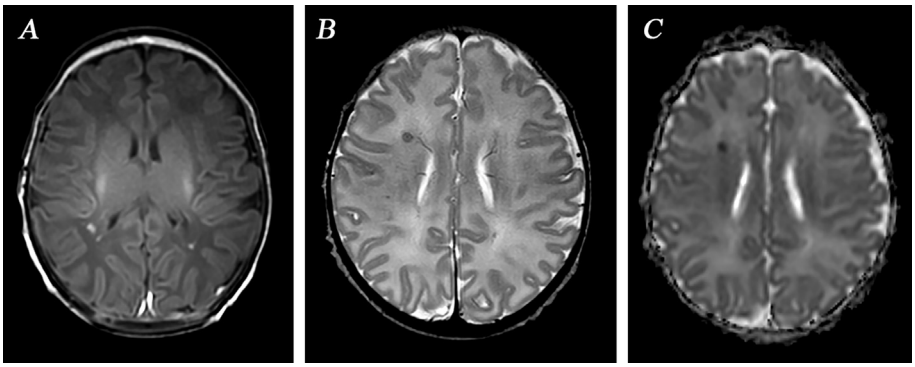

Fig. 2 – Posterior predominant PWMLs in a term infant with Tuberous Sclerosis. Axial MRI, performed on day 8. Several punctate lesions are seen as increased signal on T1 (a), one in the right frontal lobe as decreased signal on T2 (b) as well as on the ADC map (c).

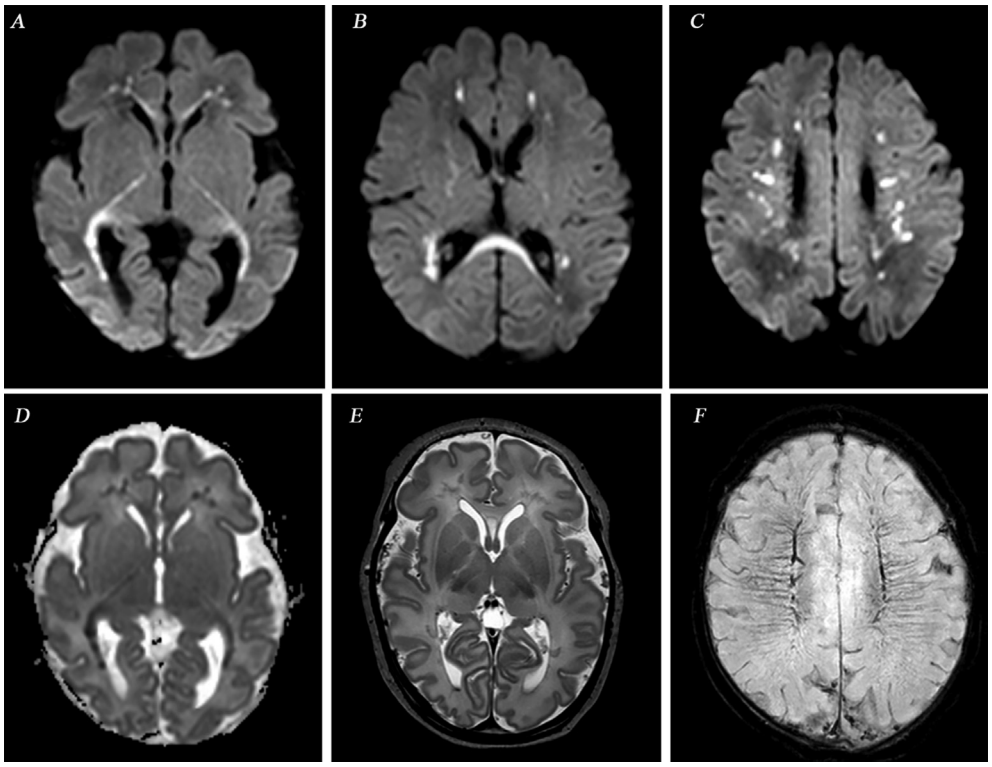

Fig. 3 – Different patterns of PWMLs shown on an axial MRI performed on day 5, using DWI (A,B and C), ADC map (D), T2 weighted sequence (E) and SWI (F). Areas of increased signal intensity are seen on DWI showing a linear pattern in both frontal lobes (B) and cluster pattern at the midventricular level (C), and involvement of the PLIC and optic radiation (A) and corpus callosum (B) On the ADC map the low signal intensity in the optic radiation and PLIC are less evident than on DWI (D). A small amount of blood is seen in the right occipital horn (E). The SWI supports the ischemic nature of the PWMLs (F). The infant's developmental quotient on the GDMS at 42 months was 103.

Bayley Scale of Infant Development-III (BSID-III) assessments in children 12–24 months, and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at 5–6 years and/or Wechsler Intelligence Scale for Children (WISC) in the older children. In five children, the neurodevelopmental assessments had been performed without utilizing a formal assessment scale. Three were too severely affected (all had a genetic disorder) and the other two were seen by the local pediatrician and no neurological or developmental concerns were present. The two remaining infants were still too young

for a standardized developmental assessment and so had informal neurodevelopmental assessments, with formal assessments scheduled for when they reach two years of age.

2.3. *Review of the medical records*

The medical records of the 42 cases were scrutinized. Information was collected to determine the associated diagnoses and the neurodevelopmental status of the infants at follow-up.

3. Results

3.1. *Clinical characteristics*

The clinical characteristics of the 42 infants are presented in Table 1. Fifteen (36%) of the 42 infants had a GA of 36 and 37 weeks.

3.1.1. *Associated diagnoses*

The major clinical association with the presence of PWMLs on the initial MRI was a history of perinatal asphyxia, which was present in 19/42 infants (45%). Five of them received therapeutic hypothermia. Five other infants (12%) had a history of seizures secondary to hypoglycaemia in the absence of perinatal asphyxia, two of whom were infants of a diabetic mother. Five additional infants (12%) presented with seizures without an underlying cause identified.

Eleven infants (26%) had pathological genetic mutations (SLC13A5 in five, 22q11 deletion in two, tuberous sclerosis in two (See Fig. 2), and single cases of Prader–Willi syndrome and of a SMAD6-RNF 213 mutation). One (2%) had an inborn error of metabolism (methylmalonic acidemia) and another (2%) had Parecho virus encephalitis.

Table 1 – Clinical characteristics of study population.

	N = 42
GA (mean, SD)	38.8 (1.5)
GA (range, weeks)	36–41
GA 36 + 37 weeks	15 (36%)
BW (mean, SD)	3414 (646)
Male: Female	24 (57%):18 (43%)
Background diagnosis	
Perinatal asphyxia	19 (45%) (5 HT)
Genetic	11 (26%)
Hypoglycaemia	5 (12%)
Seizures of unknown etiology	5 (12%)
Metabolic disorder	1 (2%)
Viral infection (parechovirus)	1 (2%)
Death	5
Age follow-up (median, months)	37 at median 24 months
GMDS at 18–24 months	10
BSID at 24 months	13
WPPSI at 5–8 years	6
WISC-R at 12 years	1
Neurodevelopmental assessment without formal scales less than 18 months	5
	2
MRI	
Day MRI (median, range)	5 (1–23)
Repeat MRI <3 months	9
Repeat MRI 18–24 months	5

GA = gestational age; SD = standard deviation; MRI = magnetic resonance imaging.
GMDS = Griffiths Mental Development Scale; BSID: Bayley Scales of Infant Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC-R: Wechsler Intelligence Scale for Children–Revised.

3.1.2. *Neuro-imaging findings*

The initial MRI scans were performed at median postnatal day 5 (range 1–23 days). In 31 infants, the initial imaging was performed within the first seven days after birth (74%); in 10 infants in the second week (24%) and in the other infant in the fourth week after birth (2%).

Follow-up MR imaging was performed in 14/42 infants (33%). In 9/42 (21%) infants this was performed by the age of three months because of a large load of PWMLs on the initial MRI and in the other five (12%) a second MRI was performed between 18 months and two years of age because of developmental concerns. Three of the five late scans were in infants with a pathological genetic mutation.

a Neonatal MRI's (see Fig. 1)

The initial MRI scans predominantly showed a cluster pattern of PWMLs (n = 30, 71%). A mixed pattern was evident in nine cases (21%), whilst three cases showed a linear pattern (7%).[4]

In 30 (71%) infants >6 PWMLs were seen in one or both hemispheres, in nine cases (21%) there were 3–6 and in the remaining three cases (7%) < 3 PWMLs.

The distribution of the PWMLs was as follows: anterior (n = 1, 2%), parietal (n = 22, 52%), posterior (n = 7, 17%), multifocal/generalized (n = 12, 29%).

Eight of the eleven genetic cases (73%) had the greatest lesion load (>6 PWML), whilst the remaining three had a low lesion load.

The most common other findings were diffusion restriction in the corpus callosum (n = 10) and/or in one or both posterior limb(s) of the internal capsule (PLIC) (n = 8) and/or in one or both cerebral peduncles (n = 2). The PLIC could not be assessed on the T1 weighted sequence in three infants as they were <38 weeks. One of the other five with diffusion restriction of the PLIC had an abnormal SI of the right PLIC with subsequent development of a left sided hemiparesis. In the other 4 infants the PLIC had a normal SI on the T1 weighted sequence. Cerebellar haemorrhages were present in three cases, large haemorrhages in two and a punctate haemorrhage in the third. The following additional findings were each present in a single case: venous sinovenous thrombosis (Fig. 4), bilateral germinal matrix haemorrhages, bilateral intraventricular haemorrhages, post-haemorrhagic ventricular dilatation and polymicrogyria.

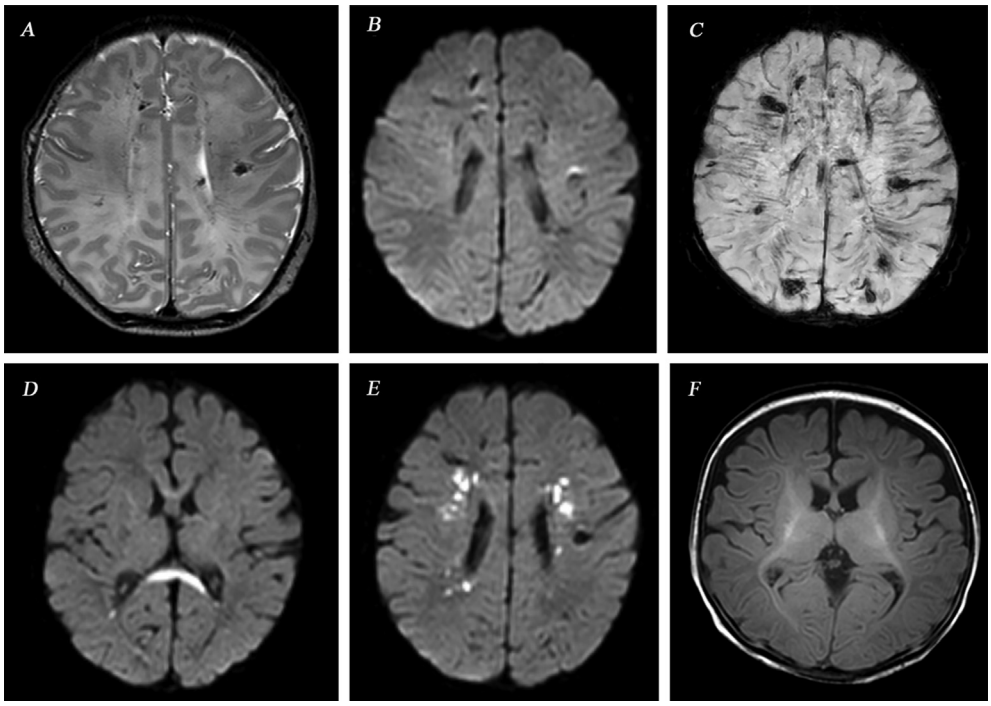

Fig. 4 – Radiological evolution of PWMLs over 3 months in a term infant with sinovenous thrombosis. MRI, axial plane, performed on day 3 (a–c), day 8 (d,e) and at three months (f). On day 3, low signal intensity lesions are seen on T2 (a), no clear increased signal intensity lesions are seen on the DWI (b) but many low signal intensity lesions are seen on SWI (c) suggestive of haemorrhagic PWMLs. By day 8, d) the DWI showed restricted diffusion in the corpus callosum (d) together with e) predominantly ischaemic lesions in a different distribution (e). The follow-up MRI at 3 months of age, f) showed evidence of white matter loss. BSID-III at 24 months was normal (cognitive and motor score both 115).

b Follow-up MRI (see Fig. 1)

Nine of the 37 survivors (24%) had a repeat MRI within three months after birth. In seven (78%) there was evidence of white matter gliosis or of white matter loss (thinning of the corpus callosum, ex-vacuo ventricular dilatation). In the other two cases, the follow up MRI scan appeared normal.

In all five infants (14%) whose follow-up MRI scans took place between 18 months and two years of age, evidence of white matter gliosis and/or white matter loss (thinning of the corpus callosum, ex-vacuo ventricular dilatation) was present.

In the infant with sinovenous thrombosis (Fig. 4), sequential MRI scans showed a temporal progression of the PWMLs, with a change in distribution between the first and the second MRI scan performed five days later, with follow-up MRI performed three months later, showing white matter loss.

No child who had a repeat MRI within 3 months after birth, also had a later MRI.

3.1.3. *Outcome (see Fig. 1)*

The thirty-seven surviving infants were followed up for periods ranging from 12 months to 12 years of age (median age 24 months).

Nineteen of the 37 children (51%) were neurologically and developmentally normal: nine of the 25 with >6 PWMLs, compared with 10/12 with a smaller number of PWMLs (p 0.01) (seven of the nine with 3–6 PWMLs and all three with <3 PWMLs).

Eleven children (34%) had minor abnormalities of tone, movement or development. Of the eleven, nine had >6 PWMLs, whilst 2/12 with a lower number of PWMLs were in this group ($p = 0.28$) (two with 3–6 PWMLs and none with <3 PWMLs). These included in-toeing of the gait, unilateral tightness at the ankle, and concerns regarding mild speech delay and/or reduced coordination.

One infant (3%) with >6 PWMLs and involvement of the PLIC on neonatal MRI had evidence of a mild hemiparesis at 24 months of age.

Six (17%) children, all with >6 PWMLs, developed major cognitive and/or behavioural difficulties, all of whom had an underlying genetic disorder.

Amongst the five infants who died, four had an underlying genetic disorder (SLC13A5 encephalopathy in three, 22q11 deletion syndrome in one), and one had an underlying inborn error of metabolism (methylmalonic acidemia).

4. Discussion

Progress has been made in recent years in determining the nature of PWMLs. Cluster type PWMLs likely represent ischaemic non-haemorrhagic injury to the white matter[4,16], whilst linear type PWMLs tend to follow haemorrhagic injury.[4,18] Some of the haemorrhagic lesions may be related to venous congestion, and may represent small areas of venous infarction with haemorrhage.[18]

Niwa et al. reported post-mortem gliosis in brain areas where non-haemorrhagic PWMLs were present, whilst haemorrhages were seen in brain areas with signal loss on SWI, thus confirming a haemorrhagic origin of the PWML.[18]

Different conditions may be associated with haemorrhagic and non-haemorrhagic PWMLs.[19] In our study, PWMLs occurred in various clinical settings, including HIE, genetic disorders, sinovenous thrombosis, infection, and in the presence of an inborn error of metabolism. None of the infants with PWMLs in the setting of HIE within our series had evidence of basal ganglia-thalamic injury, or of another more extensive pattern of brain injury.

We excluded infants with congenital cardiac and non-cardiac anomalies who had surgery during the neonatal period, since these were reported previously, and infants with perinatal arterial stroke as in these infants the outcome is mainly related to the location and extent of the stroke.[20,21]

Follow-up imaging was performed in a minority of the infants. This was undertaken because of clinical indications and/or a high lesion load. In two of the nine infants with follow-up imaging at or before three months of age no abnormalities were seen. All five infants with later follow-up imaging (at 18–24 months of age), performed because of developmental concerns showed evidence of white matter gliosis and/or white matter loss.

Dyet et al. reported that PWMLs were no longer evident at term in 8 of their 13 preterm born infants in whom PWMLs had been identified in early MRI scans, and that the lesions were less obvious and less numerous in the others.[10] Martinez-Biarge et al.[3] also observed in preterm infants that the course of non-haemorrhagic white matter injury generally follows three stages, including an intermediate stage where there may be no abnormality. Kato et al. reported a late preterm infant with hypoxic-ischaemic encephalopathy and PWMLs at day 8, who then demonstrated a phase of pseudonormalisation on follow-up imaging at 16 days, prior to the emergence of radiological evidence of gliosis on follow-up MR imaging at 18 months.[21] Kersbergen et al. reported that PWMLs were evident in only 55 of 91 preterm infants rescanned at term equivalent age who had demonstrated PWMLs on an early MRI.[4]

In one of the infants in our series (Fig. 4), MRI was performed on postnatal days three and eight in the setting of sinovenous thrombosis and then at 3 months of age. The initial lesions appeared predominantly haemorrhagic on postnatal day three, while by postnatal day eight, ischaemic non-haemorrhagic PWMLs predominated, in a different distribution to the PWMLs present on the initial scan. On the scan at 3 months the most striking feature was loss of white matter, with thinning of the corpus callosum and ex-vacuo dilatation of the lateral ventricles.

Kersbergen et al. reported the presence of additional lesions in nearly half of their preterm infants with PWMLs, including post-haemorrhagic ventricular dilatation, cystic periventricular leukomalacia, periventricular haemorrhagic infarction and cerebellar, mostly punctate, haemorrhages.[4] In our series, the most common associated findings in the initial MRI scans were diffusion restriction in the corpus callosum and/or in one or both PLICs, and cerebellar haemorrhage, which was punctate in one.

Most previous studies have focused on preterm infants. However, Li et al. reported 11 term infants with PWMLs in the setting of neonatal encephalopathy.[5] In the majority, they found associated restriction diffusion on DWI and concluded that the PWMLs were the consequence of ischaemic brain injury.

Reports of the outcome of infants with PWMLs have also focused mainly on preterm infants and have varied significantly. The latter may be due to heterogeneity in inclusion criteria.[4] Cornette et al. reported a favourable neurodevelopmental outcome in preterm infants with isolated punctate lesions, while the presence of other lesions rendered the outcome less favourable.[9] In contrast, de Bruïne et al. found a significant association between PWMLs and cognitive and psychomotor developmental delay, and cerebral palsy.[8]

Lesion load has been considered an important determinant of neurodevelopmental outcome.[2,4,16] However, Guo et al.[16] recently quantitatively assessed white-matter injury volume and location in very preterm infants. They concluded that the total white matter injury volume did not accurately predict neurodevelopmental outcome at 18 months chronological age. Adverse motor and cognitive outcomes were associated with more severe white matter injury in the frontal lobes, indicating that the lesion location contributed to the neurodevelopmental outcome. They acknowledged that independent pathways to adverse outcomes may coexist with those producing the PWMLs, such as severe intraventricular haemorrhage. In our series, the least common pattern of distribution of the PWMLs was anterior predominant (n = 1). Therefore, we are not in a position to assess/confirm the findings of Guo et al. in relation to the effects of frontal lobe PWMLs on development.[16]

In our series, the six (near) term surviving infants with the poorest long-term neurodevelopmental outcome all had an underlying genetic syndrome. Two of these had homozygous or compound heterozygous mutations in SLC13A5 and have been included in a previous report.[14] One had tuberous sclerosis, with associated developmental disability. One had a SMAD6-RNF 213 mutation, resulting in a Moya–Moya like phenotype, with subsequent multiple ischaemic events which occurred in different vascular territories at 6 months of age. One had Prader–Willi syndrome and the sixth had a 22q11 deletion.

Eight of our eleven genetic cases (73%) had the greatest lesion load (>6 PWMLs), whilst the remaining three had a low lesion load, but nevertheless a poor neurodevelopmental outcome.

It is likely that the poor neurodevelopmental outcome in these genetic cases is multifactorial and not the consequence of the presence of the PWMLs alone. Furthermore, the variability in the lesion load amongst our genetic cases, together with the finding of a major lesion load amongst many of our non-genetic cases, suggests that major lesion load, alone, is not predictive of an associated genetic disorder.

Older papers report focal white matter abnormalities amongst infants with tuberous sclerosis and with 22q11 deletions. Mitnick et al.[22] reported the presence of focal signal hyperintensities on T1 weighted imaging amongst a series of infants with 22q11 microdeletions, which likely corresponds to what is now classified as PWMLs. Griffiths et al.[23] reported 20 children with tuberous sclerosis, 4 of whom had white

matter abnormalities not related to cortical tubers. However, the lesions they reported appeared as white matter cysts in three and infarction in the fourth. They did not report any cases of PWMLs within their series.

The infants in our series with the smallest load of PWMLs (<3) were all neurologically and developmentally normal at follow-up. Nevertheless, the lesion load alone does not appear to be a robust predictor of outcome. In our series, there was considerable variability in the outcome amongst infants with the same lesion loads, even in the same clinical settings.

The DWI abnormalities present in the PLICs in the neonatal MRIs of eight of our cases did not translate into a correspondingly high rate of motor impairments. Only one of these eight children developed a hemiparesis. The diffusion change in these infants probably did not evolve into permanent injury, as demonstrated by the absence of structural change in the PLICs in all infants of those eight who underwent follow-up MR imaging after the neonatal period. This serves to highlight the potential pitfalls of attempting to predict the outcome on the basis of a single DWI finding alone.

This study reinforces that PWMLs may arise in a variety of clinical settings. In the absence of perinatal asphyxia, other underlying causes, especially genetic disorders, should be considered. The underlying cause, rather than the lesion load and location, seems important for neurodevelopmental outcome in children with PWMLs on neonatal MRI.

Whilst the number of infants in this series is relatively small, the lessons learned are more broadly applicable and may contribute to a better understanding of the natural history of PWMLs including the long term outcome, especially in (near) term infants.

Conflicts of interest

None.

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