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Post-mortem magnetic resonance (PMMR) imaging of the brain in foetuses and children with histopathological correlation

--Manuscript Draft--

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Abstract:	Post-mortem magnetic resonance (PMMR) imaging is rapidly emerging as an alternative 'less invasive' and more widely accepted investigative approach for perinatal deaths in the UK. PMMR has a high diagnostic accuracy for congenital and acquired foetal neuropathological anomalies compared to conventional autopsy, and is particularly useful when autopsy is non-diagnostic. The main objectives of this review are to describe and illustrate the range of common normal and abnormal central nervous system (CNS) findings encountered during PMMR investigation. This article covers the standard PMMR sequences used at our institution, normal physiological postmortem findings and a range of abnormal developmental and acquired conditions. The abnormal findings include pathologies ranging from neural tube defects, posterior fossa malformations, those of forebrain and commisural development as well as neoplastic, haemorrhagic and infectious aetiologies. Neuropathological findings at conventional autopsy accompany many of the conditions we describe, allowing readers to better understand the underlying disease processes and imaging appearances.

Post-mortem magnetic resonance (PMMR) imaging of the brain in foetuses and children with histopathological correlation.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Post mortem magnetic resonance (PMMR) imaging of the brain in foetuses and children with histopathological correlation

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1. Guarantor of integrity of the entire study – OJA
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19th June 2017

Dear Dr Grant Baxter,

Thank you for your review of our paper entitled 'Post mortem magnetic resonance (PMMR) imaging of the brain in fetuses and children with histopathological correlation'. Manuscript ID: CRAD-D-17-00125.

We have reviewed your comments and have altered our original manuscript in response to these. The issues raised have been directly addressed below in red text.

Editor/ Deputy Editor:
Whilst there is no absolute necessity to include an Ethical or consent statement for an article as this my feeling is that some comment would probably be justified give the sensitive nature of this work. I think one or two sentences to address this as a routine service?, previously discussed ethically at point of establishing service, discussion/counselling with parents re nature of work, findings and freedom to publish work etc. would be helpful.

Thank you for your suggestion. We have included a paragraph and subheading entitled 'PMMR within a clinical service' in our article that covers ethics and consent. This appears near the start of the paper after the introduction. An additional three references have been added.

Reviewer #1:
5. Key words: fetal is repeated
The word fetal has now been replaced with foetal throughout the written article. 'Fetal' within the references have been left alone, as this is how they have been published and found on PubMed.

63. Subsequent axial: a space is missing
This has been corrected.

149-151: Question: Which ones are difficult to identify at PMMR in small foetuses? All above? Just the optic nerve? Can you clarify the sentence? Suggestion for the sentence: Ofactory bulbs, cavum septum pellucidum and interhemispheric fissure are all absent although the optic nerves may have a more variable presence…
Thank you – your suggestion has been implemented.

149-154: although is used 3 times. Maybe a synonym?
This has been corrected.

265 – reference to Figure 7, 425 – correct hemimegaencepahly
This has been corrected.

Once again we thank the reviewers for their invaluable input. We believe that as a result of these suggestions, our manuscript has now been greatly enhanced and we do sincerely hope that you will find it publishable in the updated state.

Post-mortem magnetic resonance (PMMR) imaging of the brain in foetuses and children with histopathological correlation.

INTRODUCTION

Congenital brain malformations account for nearly 20% of all fatal congenital abnormalities[1], and developmental disorders of the central nervous system are the commonest indications for late terminations of pregnancy (ranging from 29%[2] – 78%[3]). Conventional autopsy can help to confirm or establish the cause of death, as well as provide additional clinical information with which to aid future pregnancy management or in genetic screening of family members[4]. Nevertheless, declining rates of parental acceptance[5,6] has meant that less invasive autopsy is becoming more important[7], with post-mortem magnetic resonance (PMMR) imaging the most widely accepted investigative approach in this population.

Several studies have demonstrated PMMR to have a high diagnostic accuracy for congenital and acquired foetal abnormalities when compared to standard autopsy[8,9] with a high negative predictive value of over 90%, particularly for the brain[9] and concordance with autopsy for spinal imaging in 98% cases[10]. It may also provide important diagnostic information in foetuses where conventional brain autopsy is non-diagnostic (such as in cases of severe autolysis or massive haemorrhage)[9], and that if clinical history and imaging do not suggest a brain abnormality, then opening the skull at autopsy is unlikely to detect a significant neurological abnormality or cause of death[8]. In certain cases, where a brain abnormality is identified (such as an intracranial or neck mass), PMMR may also play a role in image-guided targeted biopsy in order to obtain a diagnostic tissue sample for histological analysis without the need for a larger incision and brain extraction[11].

The main objectives of this pictorial review are therefore to describe and illustrate the range of common normal and abnormal neuropathological findings encountered during PMMR investigation from our experience of over one thousand cases at a specialist children's hospital.

PM MR within clinical service

Post mortem MRI is becoming increasingly offered to parents, and integrated into clinical perinatal autopsy services worldwide, with significant advances in practice originating from the UK[12,13]. The majority of perinatal autopsies are performed due to parental consent rather than for medicolegal purposes, and thus parental consent for imaging, and subsequent use of imaging for teaching and research must be made clear and transparent during the autopsy referral procedure. A detailed review of parental consent in the setting of less-invasive autopsy is available elsewhere[14], but radiologists working in this field should be aware of the over-riding legislative framework.

Imaging sequences

The detailed protocols (with sequence parameters) for brain PMMR imaging in foetuses and children are published elsewhere[9,15]. Sequences and protocols are defined for a 1.5T Siemens Avanto machine (Siemens Medical Solutions, Erlangen, Germany), with a dedicated head coil, spine and neck matrix coil, but can be easily adapted for other machine manufacturers **(Table 1).**

In brief, high resolution isotropic 3D T1-weighted imaging (multi-slice gradient-echo FLASH (Fast low angle shot)) is used, which allows excellent 3D visualisation of the brain structures, and isotropic acquisition, which allows reformatting in any plane. This sequence allows for assessment of cerebral anatomy, maturation of brain parenchyma, but with relatively low signal combined with low contrast. Subsequent axial and coronal DESTIR (dual-echo short-tau inversion recovery) sequences in both axial and coronal planes provide greater contrast and fluid sensitivity. Short TE STIR (short tau inversion recovery) sequences facilitate a more proton density weighted image, and the longer TE STIR more T2-weighted images. Susceptibility-weighted imaging (SWI) for haemoglobin breakdown products, and Diffusion Weighted imaging (DWI) to detect water movement in the brain following death may also be indicated[15].

NORMAL POST MORTEM FINDINGS

Foetal brain development follows a recognised pattern, a familiarity with which can aid in accurate detection of cerebral malformations, and also in recognising delayed brain development when combined with the clinical history **(Figure 1).**

The gestational ages of development for various neural structures is a topic of much debate and variation within the medical literature. It is generally accepted however that by early pregnancy (within the first trimester), the neural tube has formed and closed and the connecting commissures, diencephalon, telencephalon and hindbrain have formed, containing the ventricular system[16]. As a general rule of thumb, on MR imaging the Sylvian fissure begins to appear at 16 weeks, parieto-occipital at 22 weeks, central sulcus at 26 weeks, and is almost complete by 34 weeks[17]. As well as cortical changes, myelination of the white matter, which generally progresses from caudal to rostral, will continue through the first few years of infancy[18]. A knowledge of expected signal changes seen on T1-weighted images during transient foetal lamination (occurring between 15-26 weeks gestation) has been shown on PMMR to have a high sensitivity (96.2%) and specificity (89.7%)[19]. After 26 weeks gestation, the lamination patterns in the cerebral wall gradually disappear and are no longer reliable indicators[20].

Head moulding and Brain disruption

Sudden changes in pressure applied to the foetal head through the birth canal may cause tears in the cerebral cortex. Forceps or assisted delivery procedures in larger infants, particularly in the context of a known antenatal death, may exaggerate these findings. Although this is a relatively frequent finding in post-mortem cases, it is seldom encountered in live neonates and postulated to occur from a lack of elasticity within the intracranial structures after foetal death has already occurred in-utero prior to delivery. Sunken globes may also be seen as an incidental finding, however care should be exerted when interpreting cases where extensive skull deformation has occurred as this can be 'normal' following perinatal death and may markedly distort the normal neuroanatomy mimicking underlying pathology **(Figure 2).**

Ischaemia, cerebral oedema and grey-white matter differentiation.

Accurate diagnosis of ante-mortem ischaemic injury is particularly difficult to detect using post-mortem MR imaging[2]. Although loss of grey and white matter differentiation, loss of normal high signal intensity in posterior limb of internal capsule and white matter T_2 prolongation are recognised imaging features of ante-mortem ischaemic injury, they can also represent normal postmortem changes[21]. Other features such as diffuse cerebral oedema, and abnormal increase in signal intensity of deep

grey matter structures (basal ganglia, thalami) and cerebellum are markers of global brain ischaemia in life, but are also frequently seen at PMMR, making their clinical significance unclear.

Furthermore, we have noted that apparent tonsillar descent is a relatively frequent “normal” post mortem findings even in the absence of neural tube defects, which may be due to cerebral oedema or soft tissue. At present it is not possible to differentiate the timing of brain ischaemia with any confidence on PMMR in children, and this is an area for further research.

Cortical venous stasis

Venous stasis is a normal finding following death, but can equally also be mis-intepreted as antemortem venous thrombus. It is likely that stasis without venous dilatation is a normal physiological post mortem finding, whereas the venous dilatation may imply antemortem thrombus. More accurate characterisation of the rate at which these changes occur, together with knowledge of the antemortem state, body preservation techniques and time interval from death to imaging may help to discriminate these postmortem changes from antemortem or perimortem pathology. T1-weighted imaging may be used to highlight haemorrhagic parenchymal changes, and more advanced MR techniques such as gradient-echo susceptibility weighted imaging (SWI) need to be evaluated in this context. Similarly, small apparent intraventricular haemorrhages in foetuses may be interpreted as “normal“ spontaneous events[1].

ABNORMAL POST MORTEM CHANGES

For simplicity, neuropathological abnormalities have been divided here into those which are congenital (referring to abnormalities of normal neurological embryological development) and ‘acquired’ (either idiopathic, sporadic or secondary to known causes). In reality, there is some overlap between the two categories, such that one ‘congenital/developmental’ abnormality may consequently result in an ‘acquired’ condition (e.g. Chiari or craniofacial malformations leading to ventriculomegaly) and vice versa (e.g. an *in utero* infection resulting in abnormalities of neuronal migration abnormalities).

Congenital Abnormalities

Forebrain Malformations

Holoprosencephaly is a term representing a spectrum of malformations with widely variable outcomes resulting from nonseparation of the prosencephalon by the 5th gestational week[22]. It is considered the most common significant malformation of the brain and face in humans[23] affecting an estimated 50 per 10,000 terminated pregnancies[24], and can also be associated with other non-craniofacial anomalies the commonest of which include genital defects, polydactyly and vertebral defects[24]. The severity is related to the degree of midline separation with four generally accepted subtypes – alobar, semilobar, lobar and middle interhemispheric (MIH) forms[25],[26]. The aetiology is broad, encompassing both inherited and non-inherited forms, teratogens and environmental factors (e.g. maternal diabetes). Around 24-45% of all cases will have a chromosomal abnormality (typically trisomy 13)[25] and half of patients with this condition will have a recognised syndrome[27].

In alobar holoprosencephaly **(Figure 3),** macroscopically there is a univentricular brain without lobar division. External features reflect the severity of the internal malformation and may include cyclopsia, proboscis, hypotelorism, agnathia and cleft lip and palate, all of which may be more apparent at PMMR using volume rendering reconstruction techniques. Olfactory bulbs, cavum septum pellucidum, interhemispheric fissure are all absent although the optic nerves may have a more variable presence[28]. The deep grey matter nuclei are fused in the midline and there is an absent third ventricle. At post mortem imaging, the diagnosis can be confused with severe hydrocephalus or hydranencephaly[28], while these conditions display normal thalamic cleavage.

The craniofacial features of semi-lobar holoprosencephaly are generally less severe or absent **(Figure 4)**. Intracranially, separation can be seen in some portions of the posterior hemispheres although the thalami and hypothalamus may remain ‘fused’ and there may be a dorsal cyst[22]. In lobar holoprosencephaly there is near complete separation of the thalami and the third ventricle is fully formed, with both these structures best elicited on the coronal plane on PMMR imaging. The posterior aspect of the corpus callosum may be normal but the cavum septum pellucidum is never present[28]. Given the continuum of the holoprosencephaly spectrum, the differentiation between lobar and semilobar subtypes can be difficult and may be immaterial.

MIH subtype of holoprosencephaly appears radiologically different from the previous three subtypes described, where the most severely non-separated region of the forebrain include the parietal and frontal lobes rather than the basal forebrain. The callosal body is usually absent and the caudate nuclei and thalami appear incompletely separated[29]. Two thirds of patients have subcortical heterotopic grey matter or cortical dysplasia which, if present, are best appreciated on the T1 3D imaging and inversion recovery sequences.

Posterior Fossa Malformations

The classification of posterior fossa malformations can be a complex and controversial topic. In the medical literature, they have been classified by their presumed embryological[30], aetiological[31] origins or anatomical appearances[32] with variations in each type of classification system between authors. Of the variety of classifications available, one focussing on anatomical appearances is the most practical for radiologists to follow and also take into account the reality that current knowledge of embryological or aetiological origins of many of these malformations is incomplete.

On imaging, consideration should be given to the following areas when attempting to reach a diagnosis – the presence of abnormality of the retrocerebellar fluid space, posterior fossa size, cerebellar size and cerebellar morphology[33]. On 3D isotropic brain sequences, the sagittal reconstruction is particularly sensitive to cerebellar and posterior fossa anomalies **(Figure 5)**.

An abnormally enlarged retrocerebellar fluid space and posterior fossa are seen in cases of Dandy-Walker malformation (DWM) which is the most common posterior fossa malformation[34] and classically comprises of complete or partial cerebellar vermis agenesis, cystic dilatation of the 4th ventricle and enlargement of the posterior fossa with upward displacement of the transverse sinuses, tentorium and torcula**.** Cases without posterior fossa enlargement are generally termed 'Dandy-Walker variant' (DWV), although this term is now avoided in preference of a more anatomical description of any malformation "not conforming to the triad" for DWM[35].

DWMs are commonly associated with hydrocephalus (in up to 80% of cases)[36], and may be associated with other anomalies which can also be identified at whole body PMMR. These include

intracranial anomalies such as corpus callosal agenesis, migration anomalies, schizencephaly, or body abnormalities such as cardiac defects[37] and syndromes (such as Meckel-Gruber, PHACE and cranio-cerebello-cardiac syndromes).

Posterior fossa malformations which present with an enlarged retrocerebellar fluid space, but not an enlarged posterior fossa and with normal cerebellar appearances typically include cystic lesions such as Blake's pouch cyst, mega cisterna magna or an arachnoid cyst. When identified on PMMR, these are likely incidental or a feature relating to termination of the pregnancy unlikely related to the cause of death.

Where there is enlargement of the retrocerebellar fluid space but a small cerebellum, the underlying abnormality is typically due to cerebellar agenesis. This may be complete or partial, and can be due to genetic or acquired factors (such as from *in utero* infections or vascular events). Other associated abnormalities with this entity can include pontine hypoplasia and other cranial anomalies such as hydranencephaly and anencephaly[38]. Where the cerebellar morphology is abnormal, the likely differential diagnoses may include vermian agenesis, rhobmoencephalosynapsis or Chiari II malformation[39].

Chiari Malformations

Four traditional varieties of Chiari malformations exist (types I to IV), representing varying degrees of hindbrain malformation, with all apart from type IV being associated with hindbrain herniation through the foramen magnum. Whilst Chiari I malformations (tonsillar descent through the foramen magnum) are the most common of all types in life, they are rarely the cause of death and, in our experience, can be easily overcalled on PMMR as apparent inferior displacement of the cerebellar tonsils on imaging can be seen but is not normally identified at autopsy.

Chiari II malformations comprise of herniation of the cerebellar vermis with caudal descent of the fourth ventricle and brainstem. It is almost always seen in the presence of a myelomeningocele[40]. At our institution only one case has been seen on PMMR, with the sagittal T2 spinal sequences most helpful in the identification of the myelomenigocoele. Whilst obvious macroscopically, these may be

subtle or compressed when imaging the patient supine and should therefore be sought in cases where the suspicion for hindbrain descent is raised.

Chiari III malformations are exceedingly rare and characterized by a high cervical or low occipital encephalocele and osseous defect with or without spinal cord involvement[41]. To date there have only been approximately 30 cases reported, the majority incompatible with life [42]. Chiari type IV malformations are defined as hypoplasia or aplasia of the cerebellum but may only have mild to moderate neurological deficits despite the perceived severity of malformation on imaging[43].

Abnormalities of Commissural Development

The largest commissural tract connecting the left and right cerebral hemispheres is the corpus callosum (CC) which develops between 8- 20 weeks gestation, in a rostro-caudal direction[16]. Whilst relatively simple to detect in older gestation foetuses, the CC can be difficult to define on PMMR at 1.5T before 18 weeks, and thus the challenge is differentiating physiological development from pathological partial absence. It is unsurprising that in a recently published PMMR series, most of the congenital brain malformations which were both apparently over-called and not detected were related to corpus callosum anomalies in early gestation foetuses (<21 weeks)[9].

Agenesis of the CC may be complete or partial, usually attributed to the stage of arrested development. Callosal abnormalities rarely occur in isolation and can be associated with other malformations such as Dandy Walker malformations, interhemispheric cysts, hydrocephalus, anomalies of neuronal migration and encephalocoeles[16]**.** They have also been reported in the cases where there has been exposure to known toxic insults, such as in foetal alcohol syndrome[44].

Malformations of Cortical Development

Malformations of cortical development (MCD, previously defined as 'neuronal migration disorders'[45]) comprise of a heterogeneous group of abnormalities. The timing and stages at which neurological development *in utero* are disrupted ultimately determine the characteristics of the cortical malformations that ensue[46]. These disorders can be familial or occur sporadically, associated with

genetic disorders or linked with a known insult such as with congenital cytomegalovirus[47] where the presence of polymicrogyria or schizencephaly **(Figure 6)** may be seen.

When assessing for MCDs on imaging, one must entail a detailed and careful evaluation of the cortical surface, cortical thickness and other associated brain malformations as these abnormalities may be subtle. Whilst there is little literature on the imaging seen at post-mortem examination, preliminary experience in one centre using ultra-high field 7 Tesla imaging have reported improved characterisations of these disorders compared to lower field imaging in live patients[48]. In our experience imaging at 1.5T, the malformations are usually best identified on 3D imaging sequences due to the thinner slice thickness, lack of gap between slices and therefore the ability to re-construct the neuroanatomy in a variety of planes and option to surface render the brain making asymmetric gyral patterns more obvious **(Figure 7).**

Abnormalities of Spinal Development (Including Neural Tube Defects)

Neural tube defects (NTDs) rank amongst the commonest cranio-spinal abnormalities for which pregnancy terminations are performed with incidence rates ranging from 10-27% of all neurological foetal malformations[49],[50],[51],[52].

The classification of neural tube defects within the medical literature is inconsistent and occasionally contradictory making the accurate reporting of these defects confusing. For the sake of practicality, abnormal closure of the neural tube during embryonic development can be classified on PMMR into those that are ‘open’ where exposed neural tissue is visualised (these are disorders of primary neurulation, known as ‘open neural tube defects’ – as seen in anencephaly, craniorachischisis, myelomeningocoeles and myeloschisis) or ‘closed’ where there is no exposed neural tissue (these are not typically considered true neural tube defects as their pathogenesis may occur as a result of abnormal gastrulation, secondary neurulation or dysjunction during embryological development – examples include meningocoeles, encephalocoeles, split spinal cord, dermal sinuses, neurenteric cysts)[53].

In a large 16 year retrospective review of nearly two thousand perinatal and foetal autopsies[54], abnormalities of spinal development were present in 4.9% of cases. Of these, 43% were anencephaly, 18% had encephalocoeles and the remaining 39% had isolated spina bifida (with lumbosacral region being the most common location). The aetiology of these disorders may be genetic (known associations occurring with trisomy 18 and triploidy with spina bifida[55,56]), part of a syndrome (such as encephalocele in Meckel Grueber syndrome[57] **(Figure 8)**), environmental (e.g. folate deficiency) or sporadic. As associated anomalies are present in around 50% of cases, particularly the urogenital system[54], careful evaluation of the abdomen is recommended when any disorder of spinal development is identified at PMMR.

‘Acquired’ Abnormalities

Haemorrhage and Ischaemic Lesions

The majority of intracranial haemorrhages are easily detectable on PMMR as the signal abnormalities are typically present across almost all sequences, but can be emphasised on susceptibility weighted imaging (SWI). They are relatively common, and in one perinatal autopsy series, the incidence of ischaemic-haemorrhagic lesions of the foetal brain has been reported as between 3 – 5 per 100 cases[58]. Other secondary effects of haemorrhage may also be apparent on imaging, such as ventriculomegaly, and intraventricular clots[59].

The difficulty at PMMR is to judge when the size of the haemorrhage is “significant”: whilst small isolated intraventricular bleeds in early gestation foetuses may be considered a normal post-mortem imaging finding, large haemorrhages are unusual in older foetuses. In a large prospective study, PMMR was accurate in the detection of major intracranial bleeds (i.e. those considered to be related to cause of death) **(Figure 9),** however small intracranial bleeds formed the majority of apparent false positive findings (42%, 19/45 cases), which were interpreted at autopsy to be normal post-mortem change[9]. Subdural haemorrhages are generally easily recognised, although assessment of their age and timing is controversial.

Ventriculomegaly

Ventriculomegaly (VM) is one of the most common CNS abnormalities seen on antenatal sonography[60] and can result in termination of pregnancy, particularly if it does not resolve on sequential imaging *in utero*[61,62] VM may be associated with other neurological abnormalities (e.g. cortical malformations), genetic anomalies (mostly karyotype anomalies) or in the presence of intracranial infection and haemorrhage[63,64]. Interestingly, VM has been shown to resolve in 50% of cases between the antenatal and post mortem imaging period, although the exact mechanism is unclear, possibly secondary to fluid shifts following death[65]. Nevertheless, it is important to counsel both clinicians and parents prior to post-mortem examination to this fact, as the diagnostic yield may be variable and the purpose of further post-mortem investigation is in determining causes for the VM (and potential predictions for risks of recurrences in future pregnancies) rather than on determining whether VM was present or not[62].

Congenital Infections

Organisms responsible for foetal central nervous system infections gain entry by two main routes, either via the cervix to the amniotic fluid (in the case of bacterial infections) or across the placenta into the foetal circulation (seen in syphilis, toxoplasmosis and viral infections[66]). The neurological abnormalities from intracranial infections will depend on the gestational age at which the insult occurred[67]. Where the infection has persisted, there may be a heterogeneous spectrum of mixed developmental and destructive lesions[68].

Of the 'STORCH' infections (i.e. Syphilis, Toxoplasmosis, Rubella, Cytomegalovirus, Herpes), cytomegalovirus (CMV) is the commonest, with the highest mortality rates. It is estimated that at birth, 10% of infected foetuses will be symptomatic and have neurological manifestations[69] with approximately a third of these succumbing to their infection[70]. Abnormalities of the 'temporal polar regions' (i.e. the anterior aspect of the temporal lobe) are highly suggestive of CMV infection[71] as are a periventricular distribution of calcification[68], malformations of cortical development (such as lissencephaly and polymicrogyria[72]) and ventriculomegaly[73]. Although it is possible to detect the sequelae of intracranial infections with PMMR, it is difficult to be specific and in many cases the post mortem imaging may be macroscopically unremarkable[74], thus histological or molecular investigations (e.g. CMV-DNA[75]) may be required.

Congenital brain tumours

Congenital central nervous system (CNS) tumours are rare but typically a strong indication for termination of pregnancy, and the proportions of their distributions differ from older children as two thirds are supratentorial[76,77]. In comparison to older children, the type of tumour also differs, with over half of all reported cases being intracranial teratomas[78] **(Figure 10).** The remainder comprise of the much rarer histologically types which include astrocytomas, choroid plexus papillomas, CNS embryonal tumours and atypical teratoid/rhabdoid tumours (ATRTs)[76]. Associated congenital anomalies are present in 14-20% of cases, particularly with intracranial teratomas commonly reported to occur with cleft lip or palate[78]. In some cases, intracranial masses can appear 'tumour-like' but may in fact represent vascular anomalies or large areas of haemorrhage, such as an intra-cranial cavernous malformation (**Figure 11)**. Although not routinely performed, post-mortem virtual angiography can be employed to evaluate vascular anomalies in greater detail[79], and may also assist in identifying cerebral sinovenous thromboses (CSVT).

Conclusion

PMMR is key for neuroradiological examination in the perinatal post mortem setting, as an adjunct or alternative to conventional autopsy. PMMR has high diagnostic accuracy, although features associated with infection and corpus callosal abnormalities remain challenging. A clear understanding and greater experience of the range of appearances on post-mortem imaging can assist in cases of perinatal death, especially where normal findings may preclude intracranial tissue extraction.

TABLE LEGENDS

Table 1

Sequence parameters for brain and spine post-mortem MR (PMMR) in a neonate or infant

Sequence	FOV (mm)	Slice thickness (mm)	Matrix	Voxel size (mm)	TR (ms)	TE (ms)	Flip angle (o)	Averages (NEx/ NSA)	Number slices and gap	Approximate length of sequence (min)
Brain Imaging										
3D FLASH T1-w (sag)	256	1	256/256	1.0 x 1.0 x 1.0	11	4.9	15	3	60 per slab	5.44
2D DESTIR T2-w (axial and coronal)	100	2	172/256	0.4 x 0.4 x 2.0	5460	16 and 115	150	6	18 (1mm)	13.46
2D GRE T1 HEME (axial)	100	4	120/256	0.5 x 0.4 x 4.0	800	26	20	4	18 (0mm)	6.26
DWI (axial) (b-values 0, 500, 1000)	230	5	128/128	1.8 x 1.8 x 5.0	2700	96	90	3	19 (0mm)	1.06
Spine Imaging										
3D CISS T2-w (Sag)	150	1.5	128/256	0.6 x 0.6 x 1.5	9.1	4.5	70	8	12 per slab	4.24
3D FLASH T1-w (sag)	150	1.25	128/256	0.6 x 0.6 x 1.3	11	5.3	15	10	16 per slab	3.19

2D, two-dimensional; 3D, three-dimensional; Sag, sagittal acquisition; CISS, constructive interference steady state; DESTIR, dual-echo short-tau inversion recovery; DWI, diffusion weighted imaging; FLASH, fast low angle shot; FOV, field of view; GRE, gradient recalled echo; HEME, T2 weighted gradient recalled echo sequence; NEx, number of excitations; NSA, number of signal averages; T1-w, T1 weighted; T2-w, T2 weighted; TE, echo time; TR, repetition time; TSE, turbo spin echo; VIBE, volumetric interpolated breath-hold examination.

Adapted from Norman W, Jawad N, Jones R, Taylor AM, Arthurs OJ. Perinatal and paediatric post-mortem magnetic resonance imaging (PMMR): sequences and technique. Br J Radiol. 2016; 89: 20151028

FIGURE LEGENDS

Figure 1

Delayed gestational age according to conventional dating (last menstrual period, LMP). Comparison between two different stillborn foetuses at 22 weeks gestation with differing degrees of intracranial development. (a) Axial T2 weighted imaging in a foetus with normal brain development. (b) Axial T2 DESTIR imaging in a foetus with underlying temporo-parietal polymicrogyria at autopsy. Note the delayed formation of the Sylvian fissures bilaterally (white arrows).

Figure 2

Head moulding. (a) Coronal and (b, c) axial T2 DESTIR images of the same stillborn foetus at 39 weeks gestation demonstrate marked head moulding with distortion of underlying normal brain contents, sunken globes (white arrows), intracranial gas locules (yellow arrows) and extrusion of brain parenchyma through the left lamboid suture (red arrow).

Figure 3

Terminated foetus at 20 weeks gestational age for aloboar holoprosencephaly. (a) Coronal T2 DESTIR imaging demonstrates a mono-ventricle with fused midline brain structures. (b) Sagittal T2 weighted and (c) 3D volume rendered imaging reveal abnormal facial features with large protruding proboscis (white arrow). (d) Macroscopic pathological brain specimen at autopsy in coronal section confirm the imaging findings of the monoventricle.

Figure 4

Semilobar holoprosencephaly in a terminated foetus at 24 weeks gestation. (a, b) Axial T2-weighted imaging demonstrates rudimentary frontal horns, fusion of the thalami (white arrow), absent cavum septum pellucidum and division of the occipital lobes (yellow arrow). (c) Coronal T2 weighted imaging confirms fusion of the thalami, with slight indentation in the cortex superiorly in the midline, representing the interhemispheric fissure (red arrow).

Figure 5

Stillborn foetus at 28 weeks gestational age with multiple posterior fossa abnormalities. (a) Sagittal T1, (b) Coronal T2 DESTIR reveal cerebellar vermian hypoplasia and prominent posterior fossa CSF space (white arrow) but without elevation of the torcula. (c) A 3D volume rendered image allows for better identification of micrognathia in the same patient. Unfortunately the pathology in this foetus could not be confirmed with pathology, highlighting the value that PMMR can provide in certain cases where autopsy may be non-diagostic.

Figure 6

Bilateral open-lipped schizencephaly. (a) Axial T1 weighted imaging in a 35 week foetus reveals bilateral clefts (white arrows) in the posterior aspect of the frontal lobes with interposed CSF filling within the clefts. (b) A photograph at autopsy taken from the inferior aspect of the brain in a 26 week gestation foetus with the same pathology demonstrates abnormal orientation of the gyri (white arrow) radiating from the cleft (black arrow).

Figure 7

Left sided hemimeganencephaly in a foetus of 18 weeks gestation. (a) Axial T2 weighted imaging reveals asymmetry in the size of the cerebral hemispheres with overdevelopment of the left occipital and parietal cortex. (b) Macroscopic examination of the brain confirms the asymmetry of the cerebral hemispheres, (c) with the divided right and left cerebral hemisphere sections better highlighting these differences. Histology from the left occipital lobe (d) demonstrates a thickened cortex with poor definition of the cortical ribbon. Although on imaging the right cerebral hemisphere appeared comparatively ‘normal’, on histology (e) the cortex was thick and disorganised with leptomeningeal heterotopias and periventricular heterotopias.

Figure 8

Meckel Gruber syndrome in a terminated 20-week gestation foetus. (a) Sagittal radiograph of the skull from a whole body skeletal survey demonstrates a large posterior soft tissue defect (white arrow). (b) Axial T2 DESTIR image reveals a posterior encephalocoele containing the occipital cortex (white arrow). (c) Coronal T2 weighted imaging of the thorax and abdomen shows bilateral enlarged multicystic kidneys. (d) A photograph obtained at autopsy of the posterior aspect of the foetus’ head

demonstrates the large encephalocoele. (e) The open autopsy performed show bilaterally enlarged kidneys (yellow arrows) occupying the majority of the abdominal cavity, in keeping with the enlarged cystic kidney changes seen on imaging.

Figure 9

Stillborn foetus of 36-weeks gestational age with large right lateral ventricular haemorrhage. (a, b) Coronal T2 weighted images reveal blood products within the right lateral ventricle extending into the white matter with associated mild midline shift to the left. (c) Axial gradient echo sequence demonstrates blooming artifact within the blood products as well as further small foci of haemorrhage within the right occipital and left temporo-parietal cortex. (d) Macroscopic coronal sections of the right cerebral hemisphere at autopsy confirm the presence of intracranial haemorrhage.

Figure 10

Intracranial teratoma with cervical extension in a 27-week gestation foetus. (a) Post mortem photograph of the patient's right side reveals marked macrocephaly with a lobulated mass extending inferior to the right ear. (b) Sagittal and (c) coronal T2 weighted images show a large intracranial mass heterogeneous internal signal and cervical extension (white arrow) displacing the underlying brain (dotted outline) to the left. (d) Histological analysis confirms the diagnosis of teratoma.

Figure 11

Posterior fossa mass in a 29 week gestation foetus terminated for suspected intracranial tumour, found to be a cavernous malformation at autopsy. (a) Coronal T2 DESTIR, (b) axial T1 weighted image both demonstrate a lobulated mass in the brainstem with low T2 signal, and high T1 signal. (c) Axial unenhanced post-mortem CT reveals internal calcification within the mass. (d) Histopathological analysis with Haematoxylin & Eosin stain demonstrates the lesion identified on MRI, comprising of closely packed, dilated, thin-walled vessels containing some thrombi with minimal intervening foci of normal brain. (e) Elastic Van Gieson staining demonstrates a thin layer of collagen within the vessel walls, but no elastin. These appearances are those of a vascular malformation with a cavernous pattern.

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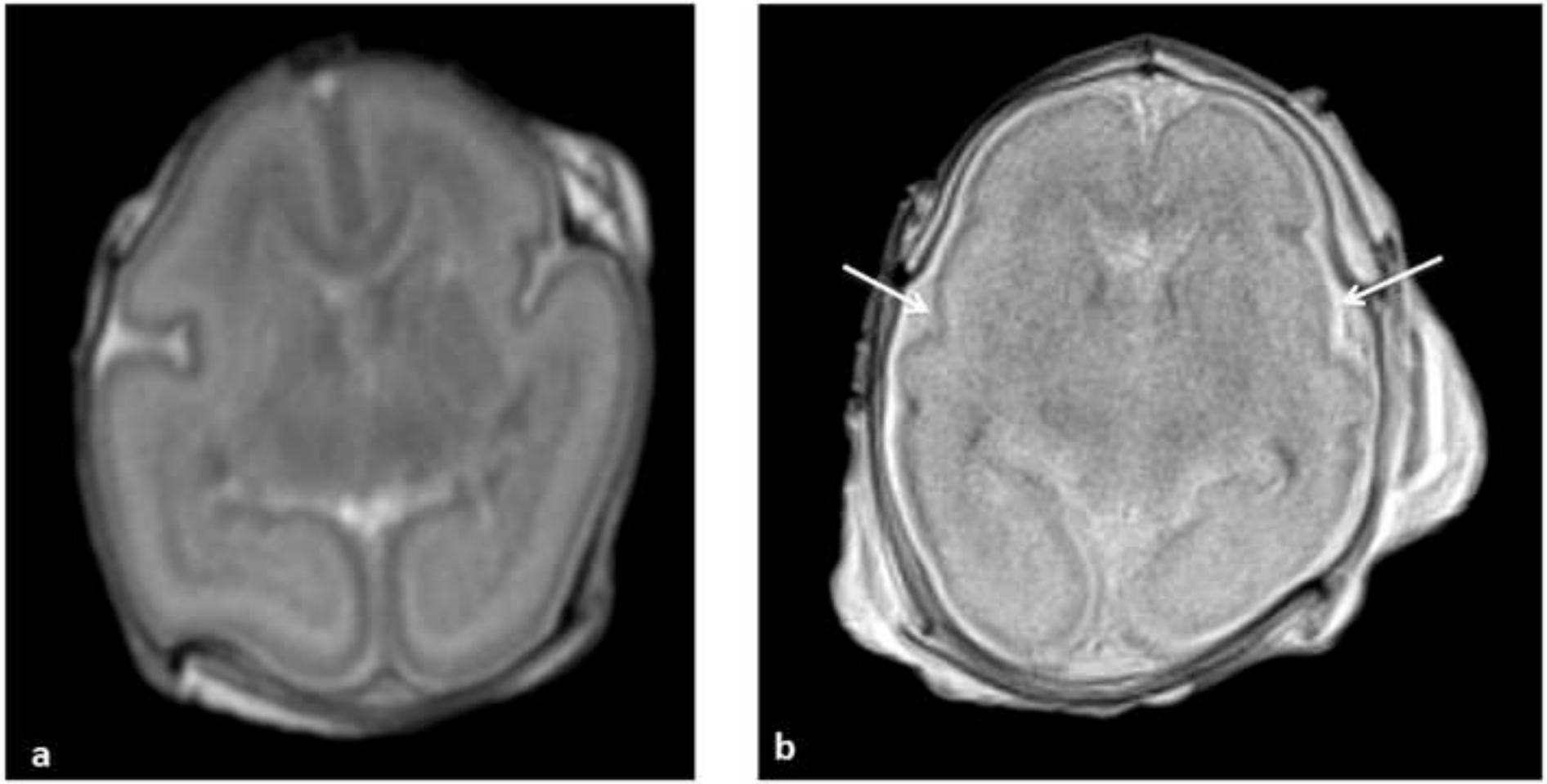

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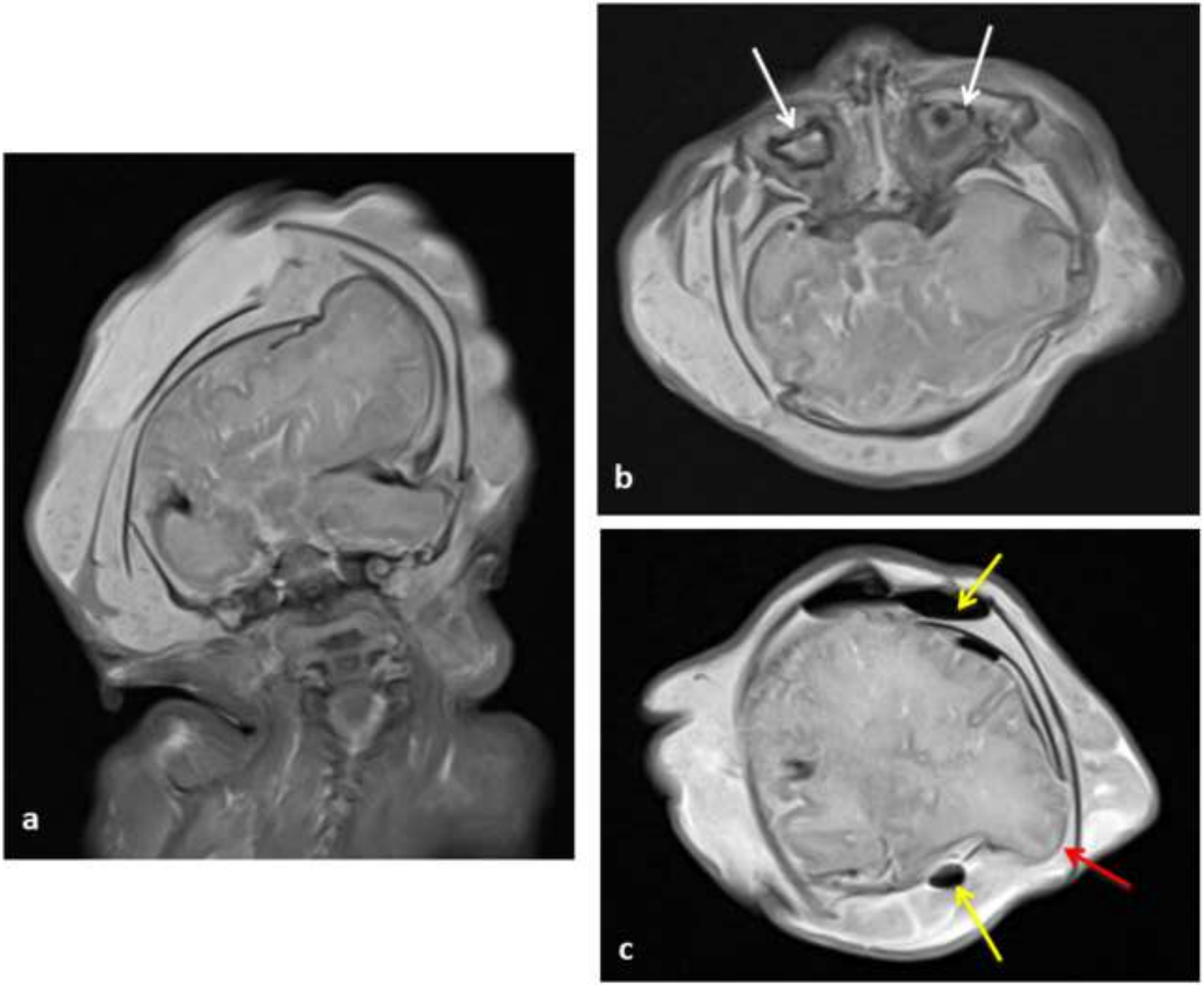

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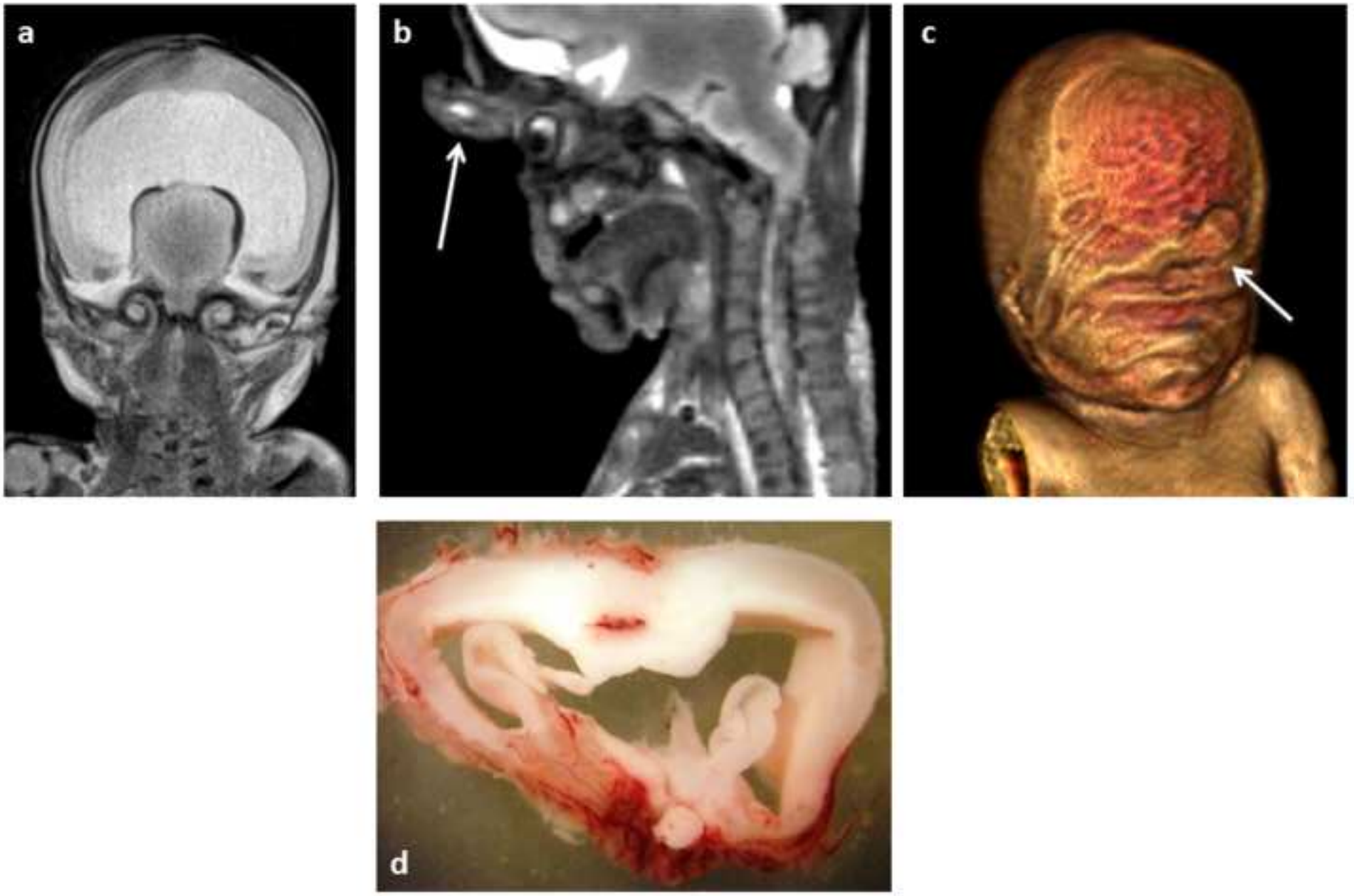

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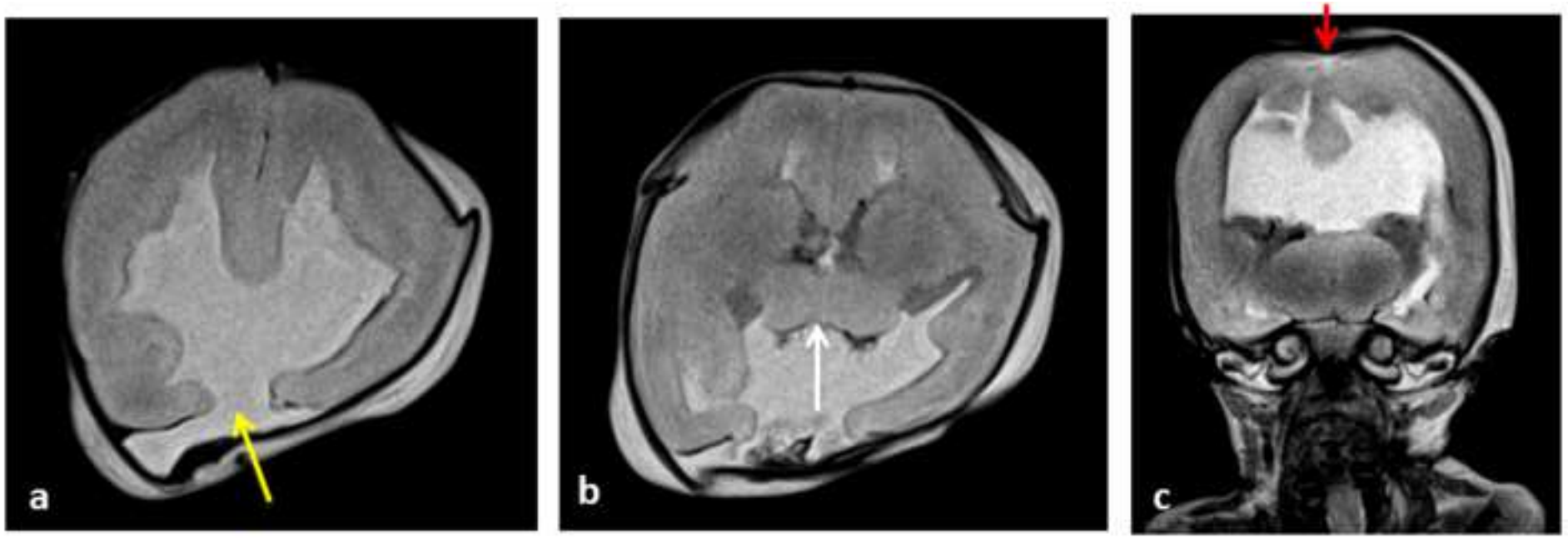

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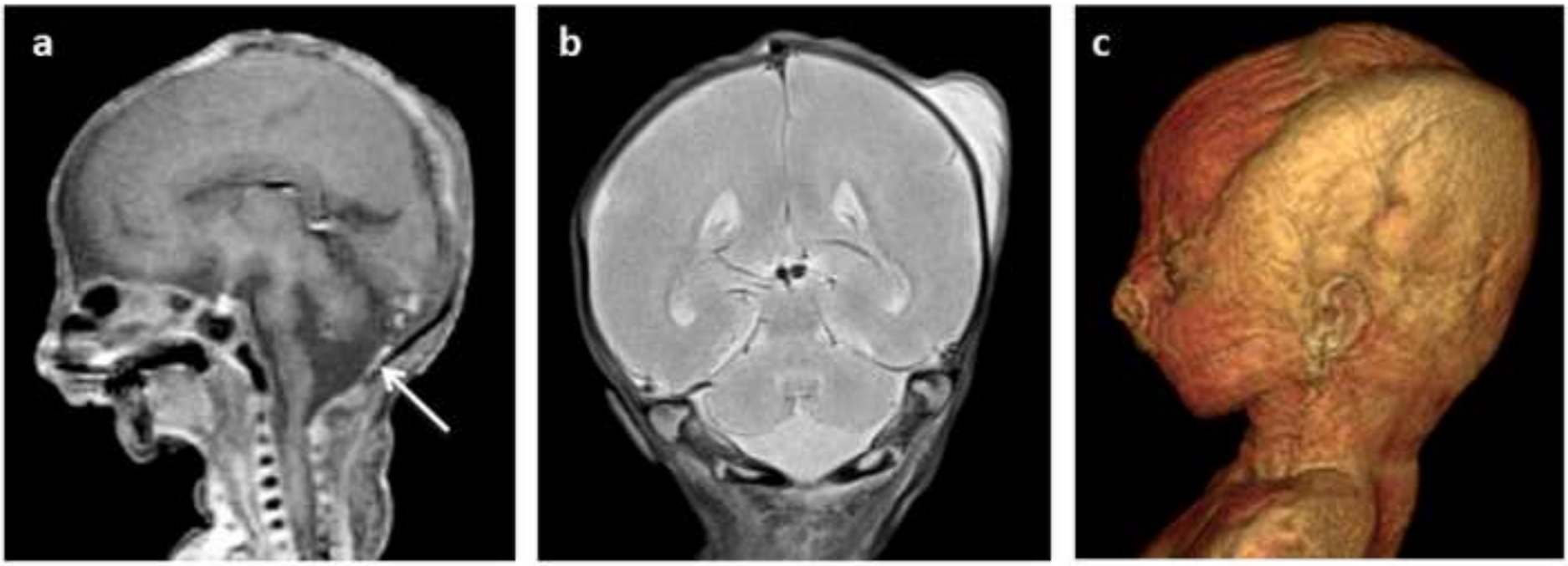

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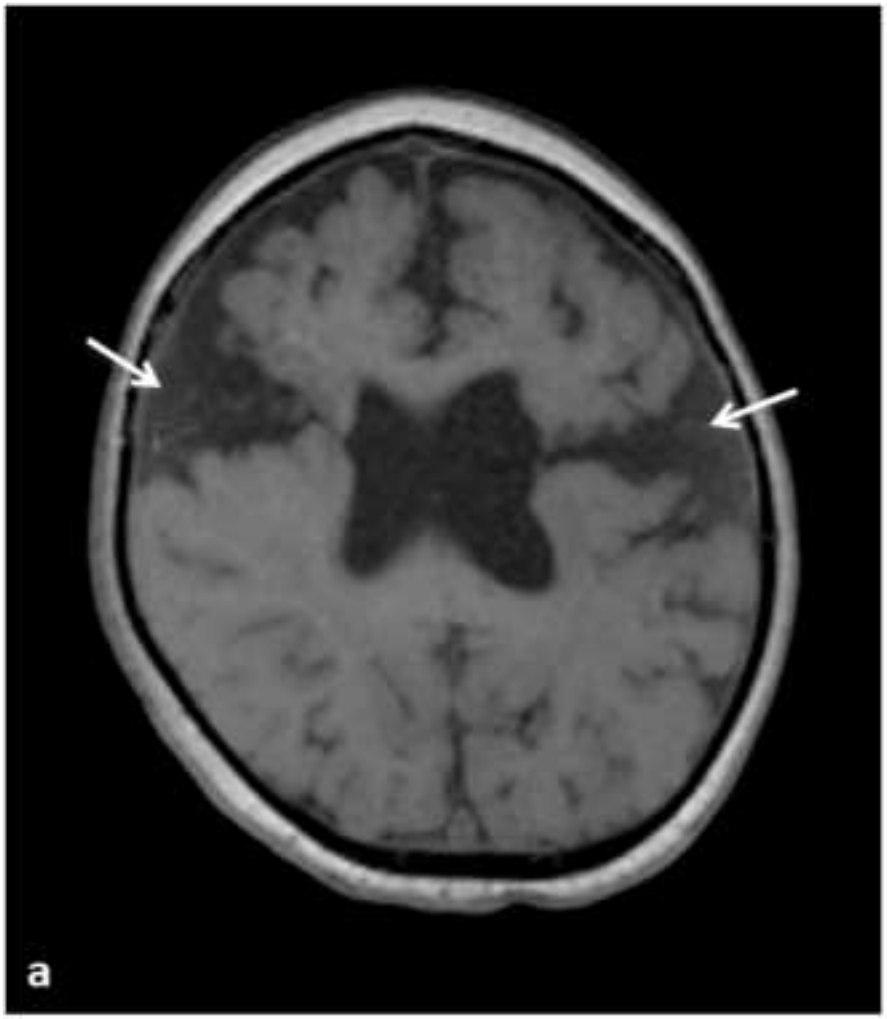

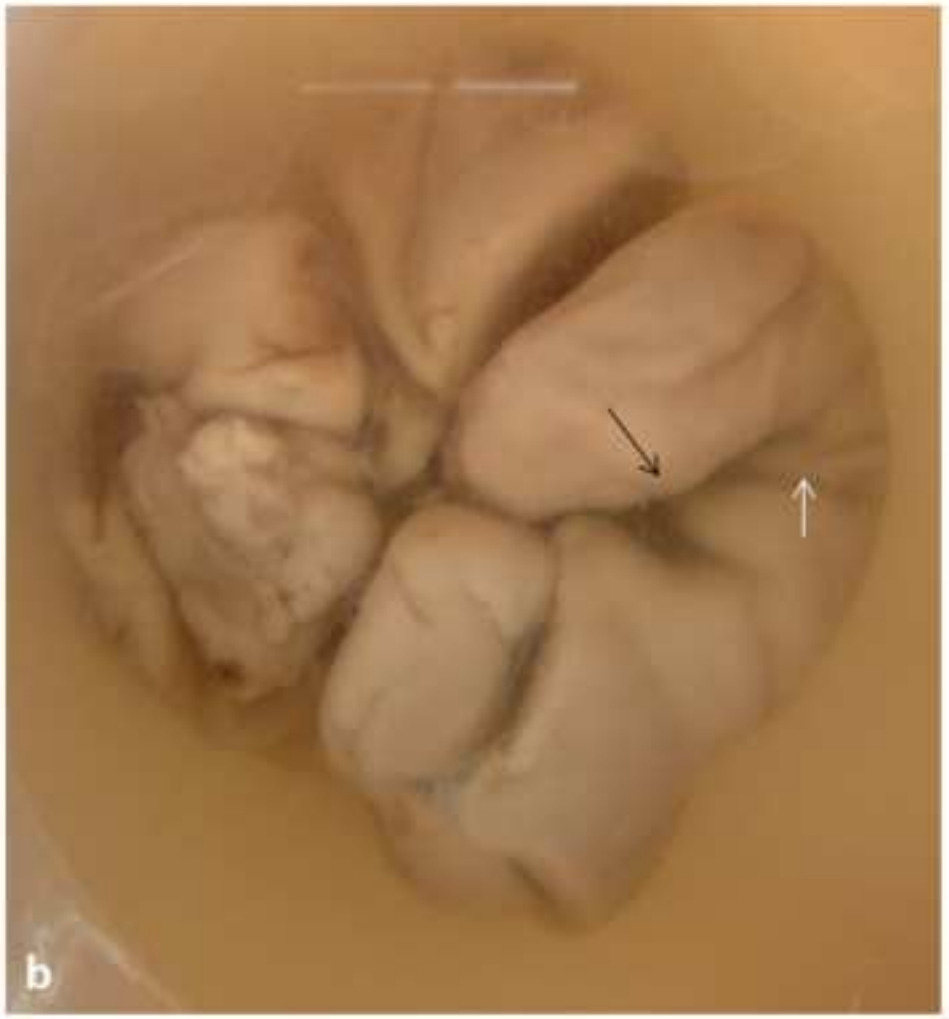

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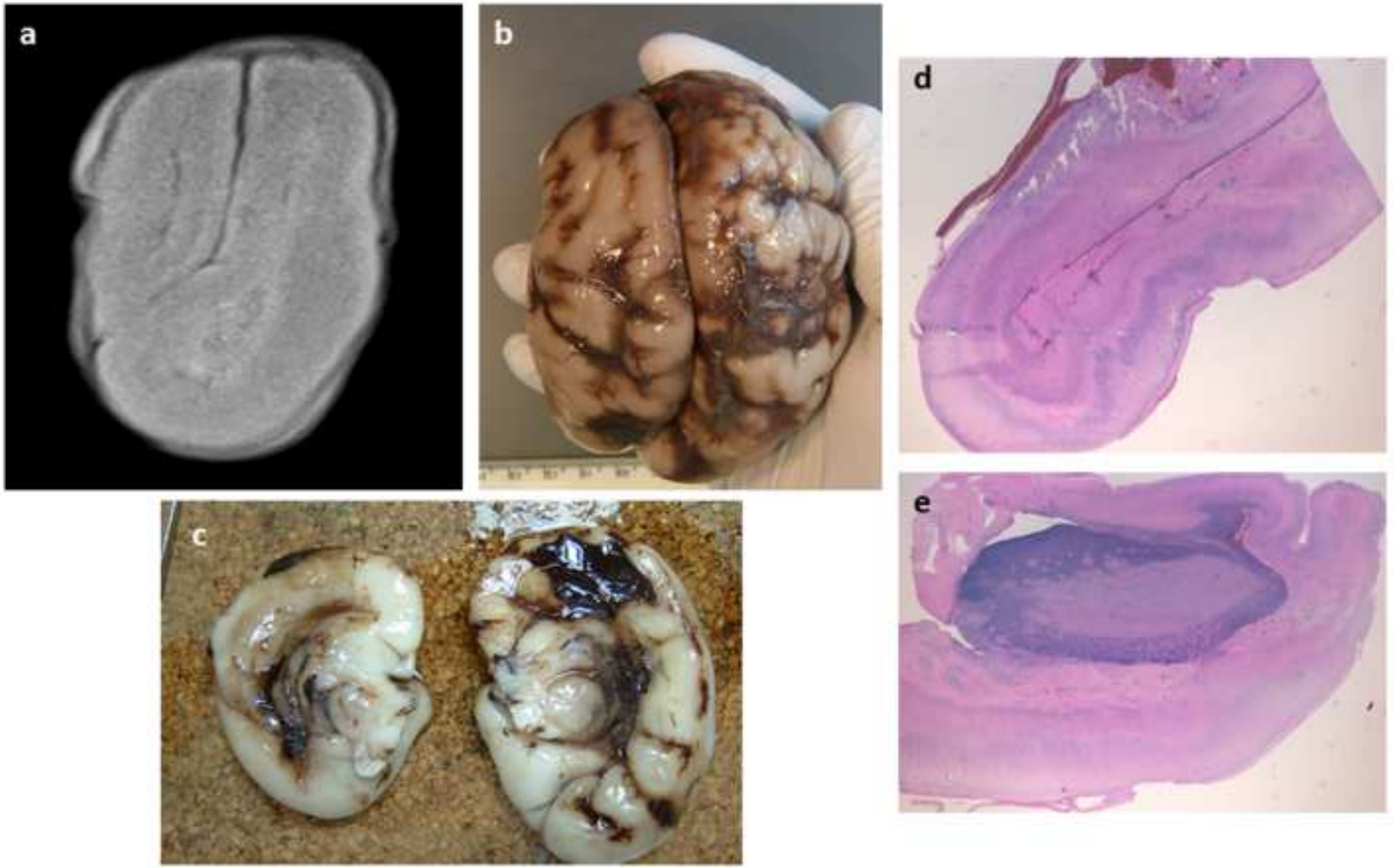

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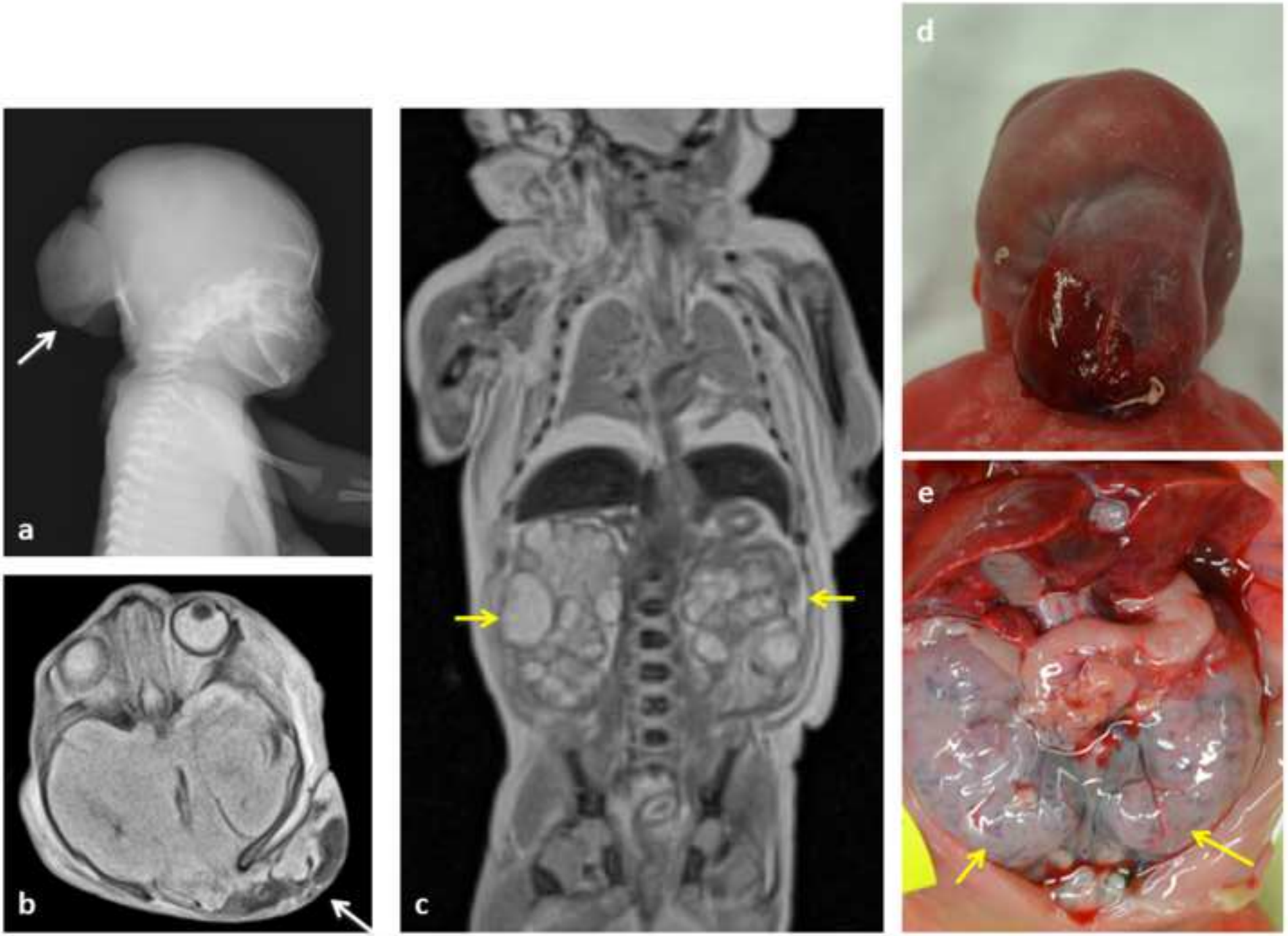

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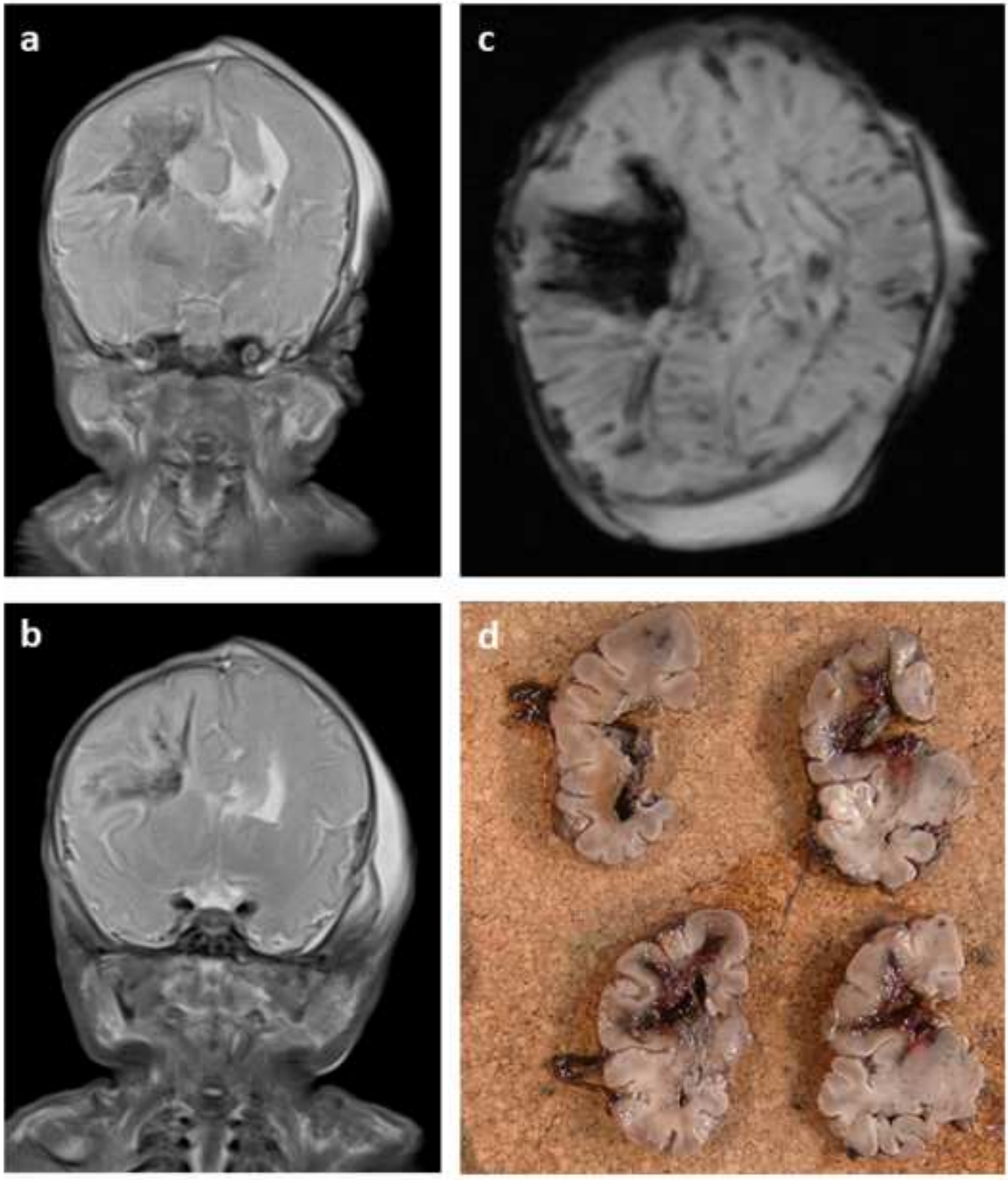

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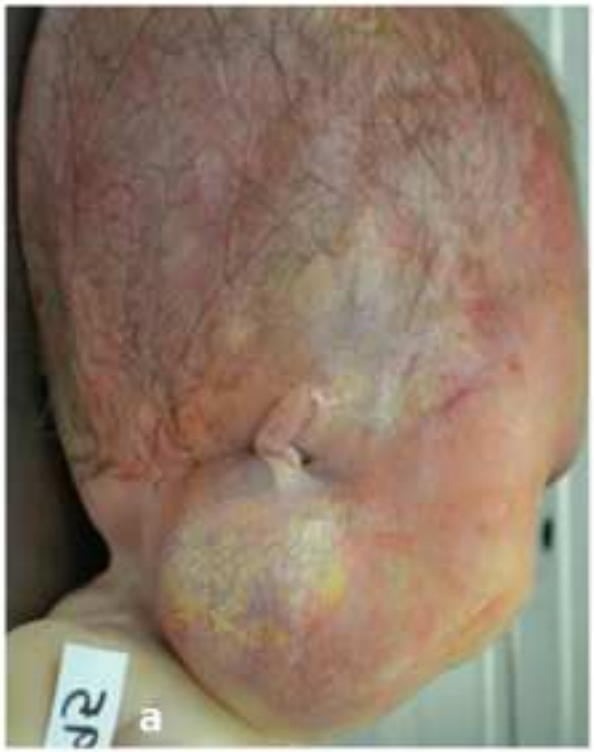

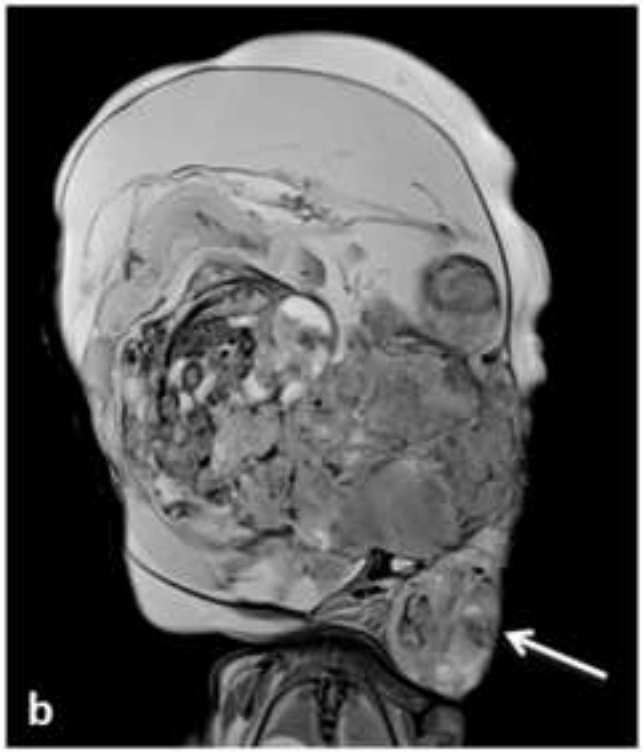

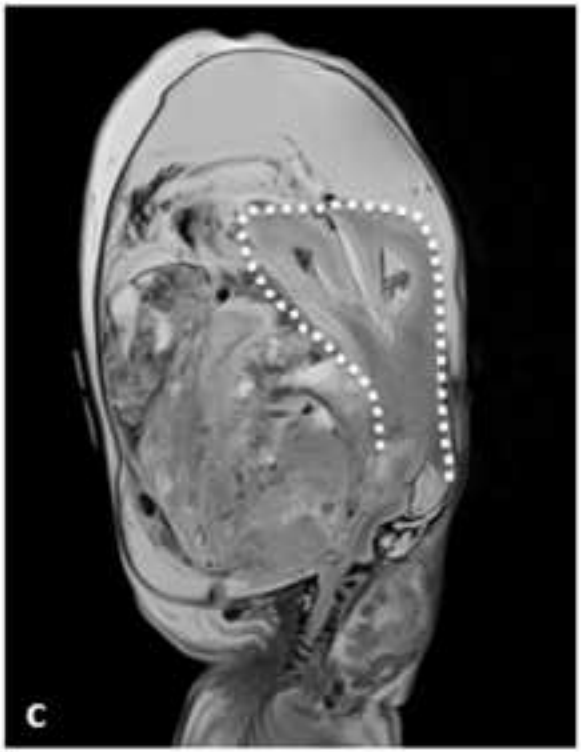

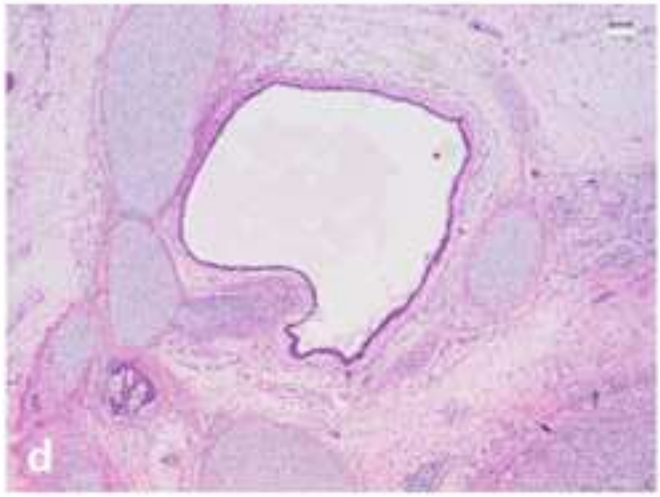

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