Section 4 of 7 - Perinatal post-mortem examination

SECTION 4 PERINATAL POST-MORTEM EXAMINATION

4.1 Introduction

The perinatal autopsy remains the gold standard in diagnostic evaluation of the causes of perinatal death[1, 2]. Information gained from an autopsy can assist in the understanding of events surrounding the death and in future pregnancy planning by enabling consideration of the recurrence risk and different management strategies. Despite this, perinatal autopsy rates have declined over the last decade to a concerning low level and the quality of many perinatal autopsies may be inadequate. The PSANZ perinatal Mortality Group in collaboration with the member organisations of the Australian and New Zealand Stillbirth Alliance are working closely to improve the standards for perinatal post-mortem examinations[3][68].

The purpose of this section is to assist clinicians in improving standards for perinatal post-mortem investigation including communication with the parents. For further information regarding communication with parents, please also refer to *Section 3 Psychological and social aspects of perinatal bereavement.*

This section was developed by Adrian Charles, Susan Arbuckle, Diane Payton, Vicki Flenady, Jane Dahlstrom, Jane Zuccolo, Yee Khong and Nick Smith.

The main resource documents used in the development of this section were:

1. The Royal College of Pathologists of Australasia Autopsy Working Party. The decline of the hospital autopsy: a safety and quality issue for healthcare in Australia. Med J Aust 2004;180(6):281-5.
2. The Royal College of Pathologists of Australasia. Autopsies and the use of tissues removed from autopsies. In. Sydney: Royal College of Pathologists of Australasia; 2002.
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4.2 Recommendations and rationale

4.2.1 Autopsy rate

Clinicians should discuss the value of an autopsy with the parents in all cases of a perinatal death and offer the option of the procedure.

To increase the rates of perinatal autopsy:

- *clinicians should collaborate with pathologists and parent groups such as Stillbirth and Neonatal Death Support (SANDS) and SIDS and Kids to raise public awareness of the value of perinatal autopsy and to advocate for high standards in perinatal autopsy at the local and government level.*
- *clinical leaders should promote formal and informal educational opportunities for clinicians on: post-mortem examination procedures; the potential benefits of an autopsy; compassionate counselling and obtaining parental consent; and address specific local barriers to the conduct of perinatal autopsy.*

(i) Purpose of a perinatal autopsy

The purpose of an autopsy examination extends beyond diagnosis of the cause of death, and the clinician needs to address these purposes with parents at the time of the discussion and approach for consent[4-9].

The main purposes of an autopsy are:

- identification of an accurate cause of death[4, 5, 7, 9];
- exclude some causes of death[10];
- identification of disorders with implications for counselling and monitoring for future pregnancies[10-16];
- to assist in the grieving process by enhancing the parents understanding of the events surrounding the death[2, 11, 16, 17];
- for research purposes e.g. recognition of new disease entities and expansion of the body of knowledge on known diseases[14, 15, 18-23];
- to inform clinical audit of perinatal deaths including deaths due to iatrogenic conditions[21] and confirmation of antenatally diagnosed or suspected fetal pathology[22, 23];
- teaching of pathologists and medical students[10, 11, 24]; and
- medicolegal reasons for example in a coronial investigation or providing information in cases of litigation[10, 16].

(ii) Value of an autopsy

The autopsy examination remains the gold standard for identification of the cause of perinatal death[1, 2]. An accurate cause of death assists in the parents grieving process by providing an explanation for the death and other information on the circumstances surrounding the death which may alleviate feelings of guilt[2, 8, 9, 11, 16]. The quality of research and audit activities and subsequent public health policy based on findings may be compromised due to inaccuracies in causes of death data without an autopsy[25-28].

Several studies have demonstrated the value of a perinatal autopsy in providing information resulting in a change of diagnosis or important additional findings[17, 22, 29-34]. A review of 27 studies found that perinatal autopsy revealed a change in diagnosis or additional findings in 22% to 76% of cases[29]. Another review of 53 studies, across a broad range of health care settings, on diagnostic errors detected at autopsy demonstrated a median error rate of 23.5% for major errors (clinically missed diagnoses involving a principal underlying disease or primary cause of death) and 9% for Class 1 errors (major error that, had they been detected during life, “would”, “could”, “possibly” or “might” have affected patient prognosis or outcome). This study also showed that some decrease in error rate had occurred over time however the rate remained sufficiently high, that encouraging ongoing use of the autopsy appeared warranted[35]. The value of adequate numbers of perinatal autopsies in ensuring standards in perinatal pathology has also been suggested[36].

(iii) Declining rates of autopsy

An optimal rate of 75% for perinatal autopsy examination has been recommended by the Working Party of the Royal College of Pathologists[5]. However, the perinatal autopsy rate has steadily declined over recent years to rates much lower than this recommendation in many regions. A 2.8% per year decline over the last decade (1990-1999) was reported by one tertiary setting in the United Kingdom[17]. Reports of current perinatal autopsy rates range from 33% to 67%[17, 37, 38]. An analysis of perinatal deaths from three states in Australia showed variation in overall perinatal autopsy rates (39%, 48% and 70%) and, for unexplained antepartum deaths, 96% compared with 59% and 62%[39].

(iv) Why the decline?

Consent is the major limiting factor in achieving adequate autopsy rates[16, 40]. Consent for autopsy is difficult for clinicians and parents. Parents are confronted by a process that appears intrusive, and are required to understand detailed consent procedures while in a state of grief[10] and clinicians are reluctant to place further burden on the parents[41].

The adverse publicity generated from the inquiries into autopsy practices in the United Kingdom over retained organs[18, 42, 43] and the enquiry at the NSW Institute of Forensic Pathology[44] are thought to have made a major impact on clinicians willingness to seek consent and parents acceptance of the procedure[45, 46]. Although improvements in practices have resulted from the enquiry, increased complexity in the consent process which followed may be a deterrent to

clinicians[8]. Clinician reluctance to seek consent due to the burden placed on the family may be misplaced as a recent survey of parents indicated that over 80% would agree to a post-mortem examination[46]. The low autopsy rate may also indicate that clinicians are ambivalent about the value of an autopsy[10, 47].

Other factors which may affect a clinician's willingness to approach parents for consent include lower gestation at death[17, 48], and discipline and seniority of clinicians[16, 48]. Khong et al reported, in a recent survey, that while obstetricians and Neonatologist were not averse to seeking consent for perinatal autopsies, midwives and neonatal nurses were influenced by factors which may negatively impact on the consent rate[16]. In this survey, obstetricians and Neonatologist rated nurses and midwives as influential in parents decision about consenting to an autopsy[16].

Provision of educational opportunities for clinicians, both formal (during undergraduate and post graduate training) and informal (through day-to-day positive reinforcement from clinical leaders) is crucial to increasing the rates of perinatal autopsy. Workforce shortages is also a limiting factor in adequate autopsy rates [8].

4.2.2 Placenta, membranes and cord histopathology

Following a stillbirth, neonatal death in the delivery room or birth of a high risk infant, the placenta should be sent for examination by the perinatal/paediatric pathologist regardless of whether consent for an autopsy has been gained.

The placenta is an integral part of the post-mortem examination and, ideally, all placentas should be retained for a few days after birth to allow subsequent retrieval should an infant deteriorate, such as may happen with sepsis, or a metabolic disorder[10]. The placenta, membrane and cord should be sent to the pathologist fresh and unfixed for histopathological examination once samples have been collected for cytogenetics and microbiology. A perinatal/paediatric pathologist should undertake the examination[49]. A recent series of publications in Seminars of Neonatology has highlighted the importance of placental histopathology in identifying causal and associated factors in neonatal morbidity and mortality including: congenital abnormality; fetal growth restriction; pre-eclampsia; infection; conditions as a result of hypoxia such as necrotising enterocolitis and cerebral palsy; and infants who fail to respond to resuscitation[13, 14, 45, 50].

Placental examination by a perinatal/paediatric pathologist should be performed for all high risk neonates including the following:

- infants admitted to neonatal intensive care
- infants failing to respond to resuscitation;
- spontaneous preterm labour and birth
- planned delivery for fetal compromise including growth restriction
- severe cardiorespiratory depression at birth including resuscitated stillborn babies
- signs consistent with congenital infection
- severe growth restriction;
- hydropic infants
- suspected severe anaemia
- suspected or known major congenital abnormalities
- other circumstances where a liveborn infant dies shortly after birth in the delivery room.

4.2.3 Quality and minimum standards

- *The Guidelines on Autopsy Practice produced by the Royal College of Pathologists[5] should be used for guidance on minimum standards until guidelines for Australia and New Zealand are developed.*

- *Specific protocols developed for post-mortem examination in the circumstance of Sudden Unexpected Deaths in Infancy and death with suspected genetic metabolic disorders should be followed.*

- *A perinatal/paediatric pathologist should perform or supervise all perinatal post-mortems. Clinicians should request autopsies from the service providing the highest quality.*

- *Transport to a centre with appropriate expertise should be arranged to ensure that all perinatal post-mortem examinations are of sufficient quality. Transport should be arranged with a registered undertaker.*

- *A comprehensive maternal history should accompany the baby for a post-mortem examination including:*
  - *clinical/obstetric history including relevant previous obstetric history;*
  - *copy of the death certificate;*
  - *copies of all antenatal ultrasound reports; and*
  - *copy of amniocentesis report if available.*

There is limited research on the quality of perinatal autopsies however, the available data suggests that approximately half may not reach minimum standards[47, 51]. The ethics of approaching parents for consent where a quality post-mortem service is not available has been questioned[1].

The post-mortem examination of an infant is very different to that performed on an adult[5, 52-54], and ideally should be performed by a paediatric pathologist. Pathologists with paediatric training find a higher incidence of causes of death in infants[55], provide a much higher proportion of adequate reports[56, 57], and the causes of death based on perinatal/paediatric pathologists reports are infrequently revised by the CESDI review panel[58]. There are currently no guidelines for ANZ on quality and minimum standards for perinatal autopsies. The Royal College of Pathologists Australasia[8] and SIDS and Kids[3] have expressed an intention to support their development. Until the availability of such guidelines, the Guidelines on Autopsy Practice produced by the Royal College of Pathologists should be used for guidance[4].

Specific autopsy protocols for examination for suspected genetic metabolic disorders[59] (*Please see Section 4; Appendix 2 Suspected genetic metabolic disorders: Investigation and autopsy protocol for details on peri-mortem investigations and autopsy for suspected genetic metabolic disease investigations)* and in the circumstance of a Sudden Unexpected Deaths in Infancy[60] have been developed. Please refer to these protocols for full details.

(Please see:
- *Section 4; Appendix 1 RCOP Guidelines for Autopsy Investigation of Fetal and Perinatal Death*
- *Section 4; Appendix 2 Suspected genetic metabolic disorders: Investigation and autopsy protocol for details on peri-mortem investigations and autopsy for suspected genetic metabolic disease investigations*
- *Section 2; Appendix 3 Autopsy clinical summary form.)*

4.2.4 Post-mortem reporting

- *Guidelines for post-mortem reports produced by the Royal College of Pathologists[4] should be used as a guide for reporting of perinatal post-mortem examinations.*

- *Ideally, a preliminary post-mortem report should be forwarded to the referring clinician within 3 working days of the post-mortem. The final report should be forwarded to the referring clinician within 8 weeks of the post-mortem.*

- *The post-mortem report should be made available to the parents at a time when the primary care clinician is present to discuss the findings.*

- *A Plain Language Report (PLR) should be available to parents on request.*

- *A request for the General Practitioner (GP) to receive a copy of the report (including the PLR, if available) should be explicit on the request form, as they are the main care provider on discharge.*

A preliminary report is usually available within 2 days of the examination, and should include a summary of the clinical history, samples taken, and macroscopic findings. The final report may take up to six weeks with more complex genetic or metabolic workups taking up to 6 -12 months. The post-mortem report includes demographic details, a clinical summary, and findings of the external and internal examination including: organ weights; microscopic findings; results of ancillary examinations such as cytogenetics; microbiology; radiology a summary of findings; a commentary to suggest the most likely pathophysiological pathway; and a cause of death if appropriate. Other details ideally recorded are mode of identification, a list of samples taken, a record of X-rays and photographs taken, and details of

the consent and any limitations imposed[10]. A PLR may be helpful to parents[8]. A copy of the PLR, if available, and full autopsy report should also be sent to the GP.

4.2.5 Communication and consent for post-mortem examination

Where possible, a senior clinician who has established a rapport and understanding with the parents should discuss the value of a post-mortem examination and offer the option of the procedure. The clinician should have a high level of communication skills and knowledge of the post-mortem examination, preferably having witnessed several perinatal post-mortem examinations.

The clinician approaching for autopsy consent should discuss the options for a full, limited or stepwise post-mortem examination; the issue of retained tissues; the value of the autopsy and the possibility that the information gained may not benefit them but may be of benefit to others. Parents should be given written information explaining the post-mortem examination.

When consent has been obtained for specific organ/s to be retained for further examination, the parents should be offered the choice of either delaying the funeral until the organs can be returned to the body or specifying their preferred method of organ disposal.

Consent for the autopsy which clearly outlines the extent of the investigation should be recorded on an approved consent form, relevant to the jurisdiction.

The pathologist should be available to discuss the autopsy with the parents before and/or after the procedure and, where possible, the requesting clinician should attend the autopsy and provide the parents with a preliminary report immediately after the examination.

All hospital perinatal autopsy examinations require written consent from the parent following informed discussion[41]. The extent of the examination including retention of organs needs to be clearly explained and documented in the consent form. Options for a full, limited or stepwise autopsy should be explained. Written consent from parents is also required for peri-mortem investigations such as clinical photographs, tissue and blood sampling by cardiac puncture. Written consent is not required for histopathological examination of the placenta, however parents should be informed that this is a part of the routine investigation which may provide valuable information[61].

Parents want to know why their baby has died and consent to an autopsy to find out the reasons. Therefore, parents may be very disappointed and regret their decision about autopsy when a cause of death is not found[3]. Informed discussion with the parents should include the possibility that a cause of death may not be found, however that the information obtained may benefit other babies in the future. Clinicians need to be aware of religious beliefs which may be an influencing factor in a parent's decision[8, 11].

(i) Who should seek consent?

Seeking of parental consent is best done by an experienced clinician who has a rapport and understanding with the parents. While the responsibility for informed consent lies with the primary attending physician[1, 10] and in most cases the consultant clinician will approach the parents, this may be delegated to another attending clinician (e.g. midwife, nurse)[62]. Clinicians seeking consent should be prepared to answer questions about what actually happens to the baby during the procedure and how the baby will look after the examination[62]. Therefore, all clinicians seeking consent should have an in-depth understanding of post-mortem procedures and preferably have witnessed several autopsy examinations. Discussion with parents about consent for post-mortem examination needs to take into account the importance of partnerships in decision making[63].

(Please refer to Section 3 Psychological and social aspects of perinatal bereavement for further discussion and information sheets for parents and professionals)

4.2.6 Costs of a post-mortem examination and transport

Clinicians need to be aware of costs associated with transfer of an infant from non-metropolitan areas to the tertiary centre for post-mortem within their region and to inform parents of any personal cost implications.

Diverse arrangements exist across Australia regarding payment for autopsy[8]. The SIDS Focussing On Stillbirth initiative (SOS)[3] costed the perinatal autopsy at $2,608.25. Currently the post-mortem examination of a stillborn infant is not covered under Medicare and consequently the costs for the post-mortem examination need to be covered either by the institution, requesting clinician or billed to the family.

4.3 Coroner's post-mortem

The purpose of the coroner's post-mortem is to determine the cause of death, and specifically whether it is natural or unnatural. Examples of cases which should be referred to the coroner are:

- babies dead on arrival at hospital, or within 24 hours of admission;
- unattended stillbirth;
- deaths within 24 hours of an operation, anaesthetic or invasive procedure;
- deaths as a result of accident;
- unnatural, criminal or suspicious deaths, e.g. neglect, abuse, poisoning;
- deaths caused by drugs, prescribed or not;
- deaths as a result of medical mishap;
- deaths in which the doctor is uncertain of the cause of death, and unable to confidently complete the death certificate; and
- unexpected death on the ward[10].

If there is any doubt, discussion with an experienced coronial officer or with the coroner is advised. Coroners should ideally arrange for paediatric pathologists rather than general or forensic pathologists to perform the post-mortem[4], and provide results to relevant clinicians.

4.4 Alternative investigations where permission for autopsy is not obtained

If permission for an autopsy is not obtained, other less invasive testing may assist in establishing whether any important abnormalities have been missed. These alternatives permit detailed investigation of the fetus or infant while still respecting the wishes of the parents[64]. However, a Working Group of the Royal College of Paediatrics and Child Health found little evidence for valid alternatives to the paediatric post-mortem[52]. Parents should be informed at the time of consent about the possibility of missing an important finding when a full post-mortem investigation is not undertaken.

4.4.1 External examination by a perinatal/paediatric pathologist, clinical geneticists or paediatrician

An examination by an experienced clinician is of particular importance where an autopsy examination is declined[65]. Clinicians should discuss the importance of this examination with the parents and arrange for an appropriately skilled clinican to undertake the examination.

4.4.2 Babygram

Parents who decline an autopsy should be asked for consent to undertake a full body X-ray (Babygram). A Babygram may detect abnormalities (mainly skeletal) which may not be detected on an external examination. The Wisconsin Stillbirth Service Program has estimated that approximately 20% of unselected stillborns will have abnormalities which are detectable on X-Ray[65].

4.4.3 Ultrasound scan

A detailed ultrasound examination of the infant at the time of confirmation of an intrauterine death or after the birth may identify fetal abnormalities which may not be identified by an external examination[66].

4.4.4 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (if available) may be offered to parents who decline an autopsy investigation. The investigation should be undertaken as soon as possible after a stillbirth. Clinicians should explain to the parents that a full autopsy remains the gold standard as the MRI does supply tissue samples and therefore important information may be missed.

A recent comprehensive overview presented the advantages and disadvantages of the post-mortem MRI[2]. The major advantages of post-mortem MRI included the non-invasive nature of the examination and the detection of pathologies and malformations of the central nervous system. The disadvantages included the lack of tissue sampling; limitations in detection of complex cardiac malformations, and other abnormalities (e.g. tracheo-oesophageal fistula, bowel perforations) which are undetectable by post-mortem MRI; and lack of experience in perinatal post-mortem MRI. The authors concluded that a full autopsy remains the gold standard; however, MRI may play an important role when an autopsy is declined.

4.4.5 Clinical photographs

Following consent from the parents, clinical photographs should be taken for later review, particularly in the circumstance of birth in non tertiary hospital settings. These photos are additional to the bereavement photographs, and should be clearly labelled and filed in the medical record. The use of digital imaging for this purpose is optimal, however issues regarding storage and patient confidentiality should be considered.

4.4.6 Other alternatives to a full post-mortem

Post-mortem needle biopsy; laparoscopic autopsy and small incision access are other alternatives to a full post-mortem for focussed investigation of suspected abnomalities.

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Section 4; Appendix 1 RCOP Guidelines for Autopsy Investigation of Fetal and Perinatal Death[67]

All hospital post-mortem procedures are subject to parental consent that must not be exceeded. The following guidelines apply to an unrestricted post-mortem examination.

1. External examination

- Body weight (to nearest gram, if less than 5kg)
- Head circumference
- Crown-heel and crown-rump lengths
- Foot length
- Apparent gestation
- Maceration (if baby is born dead)
- Meconium staining
- Full description to include, e.g. Fontanelles, eyes, ears, nose, mouth and palate, digits, palmar creases, umbilicus and state of cord, genitalia, anus etc.
- Dysmorphic features, congenital malformations and deformities
- Other abnormalities.

2. Internal examination

- Comment on cranial, thoracic and abdominal cavities
- Retention and fixation of the brain where practicable, subject to informed consent
- Systematic description of major organs and tissues
- Specific reference to ductus arteriosus and umbilical vessels
- Weights of all major organs in digital balance (to 0.1g)
- Comment on muscle and skeleton.

3. Placenta

Placenta to be examined in all cases. A convenient method of ensuring the placenta is available in each case may be to send all placentas from babies admitted to the special care baby unit/neonatal intensive care unit to the pathology department. Whilst these need not be examined unless the baby dies, many departments would, in any case, consider it good practise to examine them.

- Dimensions
- Trimmed weight
- Umbilical cord (length, vessels, abnormalities)
- Membranes (complete, incomplete, colour, abnormalities)
- Fetal, maternal and cut surfaces.

4. Histology

- At least one block of all major thoracic and abdominal organs (right and left lungs, heart, liver, kidney, thymus, adrenals and pancreas)
- Costochondral junction (over 24 weeks' gestation)
- Adequate sampling of brain (varies with case: minimum of one block from hind brain and one from cerebral hemispheres)
- Adequate sampling of placenta (cord, membranes, focal lesions, grossly normal parenchyma to include amnion and decidua).

5. Special procedures and investigations

- X-ray mandatory for suspected skeletal dysplasia and multiple malformations
- Photography mandatory for dysmorphic fetuses and babies without ante-mortem diagnosis; advised for other gross abnormalities
- Bacteriology (blood/spleen/lung/CSF), if clinically indicated
- Virology, if clinically indicated
- Karyotype, if clinically indicated
- Storage of fibroblasts/frozen tissue/DNA, if clinically indicated
- Biochemistry, if clinically indicated
- Haematology, if clinically indicated
- Neuropathology, if clinical or radiological evidence of CNS pathology or the brain appears abnormal on external examination.

6. Autopsy reports

- Demographic details
- Date of autopsy
- Details of consent and any restrictions
- Availability of clinical records at time of post-mortem, including anomaly scans if relevant
- Attendance of clinician
- Clinical history
- Systematic description of external, internal and placental examination and results of X-rays and other ancillary investigations
- Summary of major findings including sex and apparent gestation, estimated timing of death in babies born dead, adequacy of growth and nutrition, presence/absence of congenital abnormalities, major pathological lesions, evidence of chronic stress or disease prior to death, placental examination
- Commentary addressing the clinical questions and significance of pathological findings
- Mode/cause of death
- Record of photographs and any samples retained
- Record of disposal of any tissues or samples
- A provisional report on the macroscopic findings should be issued within 24-48 hours of the autopsy, with histology and further investigations incorporated into a final report when available
- Timely dispatch to clinicians with particular reference to the timing of postnatal appointments.

Section 4; Appendix 2 Suspected genetic metabolic disorders: Investigation and autopsy protocol

Recommendations

To ensure a precise diagnosis, peri-mortem evaluation of infants suspected of having genetic metabolic disorders is required. Parental consent is required for a post-mortem examination and for tissue and blood samples to be taken prior to the death. Clinicians need to counsel parents sensitively about the importance of an accurate diagnosis for future genetic risks in this very distressing time.

Due to the complexity and number of different possible diseases, it is strongly recommended that clinicians discuss each individual case with the State Laboratory to identify the optimum tests to request. Should more expert guidance be required a clinical metabolic specialist should be consulted.

All tissue samples should be stored and transported to a Specialist Metabolic Laboratory for investigation as convenient.

Peri-mortem investigation by the clinician should include the following:

- *Prior to death:*
  - Seek consent from the parents for a metabolic autopsy;
  - Consult metabolic physician or histopathologist before collection of samples;
  - Blood sample (0.8ml) in a lithium heparin tube and refrigerate;
  - Urine sample (5-10 ml);
  - Skin biopsy (3 x 2 mm punch biopsies): It is not necessary for the baby to be taken from the nursery for this procedure. The process, which can be undertaken by a registrar, should only take 15-20 minutes, is minimally invasive, with the sites being covered by a small dressing. *See Section 4; Appendix 2a Screening for genetic metabolic disorders* for futher details of collection.

- *Immediately following the death:*
  - Obtain blood sample by cardiac puncture if blood sample not already taken and only if parental consent has been obtained.
  - Liver and muscle biopsies (for electron microscopy, histopathology and enzymology (for the latter wrap in aluminium foil, snap freeze and store at -70 ºC). Collect within 4 h (preferably 2 h) of death.
  - Contact the laboratory to request that all unused portions of blood or urine specimens are retained. If neonatal screening test has been performed, any unused portions of the blood spots can be requested from the state laboratory. Tandem mass spectrometry can identify selected disorders of fatty acid oxidation and amino acid metabolism in dried blood samples.

A recent publication by Christodoulou and Wilcken in Seminars in Neonatology[59] highlighted the need for an increased index of suspicion for genetic metabolic disorders (inborn errors of metabolism) in neonatal care. The authors describe predominant clinical or biochemical presentations of genetic metabolic disorders in the neonatal period and recommend a protocol for screening for these disorders and also for a genetic autopsy. *Please see Section 4; Appendix 2b, Components of the Genetic Autopsy* for details of a genetic autopsy.

The predominant clinical or biochemical presentations of genetic metabolic disorders are as follows: Acute encephalopathy: hypoglycaemia, hyperammonemia, ketosis, disorders of acid-base balance, seizures as an early predominant feature; Acute hepatocellular disease; sudden death; severe hypotonia; non-immune hydrops fetalis; facial dysmorphism, with or without congenital malformations[59].

Section 4; Appendix 2 a Screening for genetic metabolic disorders

Extract from: Christodoulou J, Wilcken B. Perimortem laboratory investigation of genetic metabolic disorders. Seminars in Neonatology 2004;9(4):275-280[59].

Screening investigations that should be performed in an acutely ill neonate suspected of having a genetic metabolic disorder

Urine

- Odour
- Dipstick tests for ketones, pH, sulphite (a)
- Reducing substances (testing for both glucose and non-glucose reducing substances)
- Amino, organic acid screens (including acylglycines)

Blood

- Full blood count/film
- Urea, electrolytes, anion gap, creatinine
- Glucose
- Calcium
- Blood gases
- Liver enzymes
- Uric acid
- Ammonium
- Lactate and pyruvate
- Amino acids (b)
- Carnitine and acylcarnitines (b)

Cerebrospinal Fluid

- Lactate and pyruvate
- Glucose
- Amino acids (b)

In the case of hypoglycaemia collect blood for the following when the child is hypoglycaemic

- Growth hormone
- Cortisol
- Insulin
- Free fatty acids
- ß – Hydroxybutyrate
- Acylcarnitine profile
- Urine should always be collected at the time of hypoglycaemia

(a) Sulphite is very labile. A negative test result does not exclude sulphite oxidase deficiency or the molybdenum cofactor defect.

(b) These tests should only be ordered after consultation with a biomedical geneticist or metabolic physician.

Section 4; Appendix 2 b Components of the genetic autopsy for investigation of metabolic disorders

Extract from: Christodoulou J, Wilcken B. Perimortem laboratory investigation of genetic metabolic disorders. Seminars in Neonatology 2004;9(4):275-280[59].

Components of the Genetic Autopsy
▪ Careful family history, including three generation pedigree ▪ Invite a clinical geneticist with expertise in dysmorphic syndromes to inspect the infant ▪ Clinical photographs ▪ Full skeletal survey ▪ Parental investigations for a haemoglobinopathy ▪ Maternal investigations for a thrombophilic disorder Samples to collect from the baby Blood ▪ Dried blood spots on filter paper (newborn screening cards, at least two to three cards stored at room temperature but NOT in a plastic bag (for acylcarnitine profile analysis and is a source of DNA)) ▪ Whole blood (5ml in lithium heparin tube (for carnitine, quantitative amino acids, very long chain fatty acids; separated within 20 mins of collection and stored at -70 ºC); AND 5ml in EDTA tube (for DNA extraction; can be stored at 4 ºC for 48 h) AND 5ml in lithium heparin tube (for chromosome analysis; must be commenced within 4 h of sample collection)) Urine ▪ Freeze and store (5ml or more if possible, stored at -70 ºC; (for amino acid and organic acid profiles, acylglycines, orotic acid)) Cerebrospinal Fluid ▪ Freeze and store (1ml stored at -70 ºC (for amino acid profile)) Skin ▪ Biopsy (3x2mm full thickness collected under sterile conditions (DO NOT use iodine-containing preparations) into culture or viral transport, or saline soaked gauze. Store at 4 ºC. Best collected within 12 h of death. Cartilage may be taken for culture if there has been a prolonged period after death before biopsies can be taken. Send as soon as possible to a cytogenetics laboratory. To be cultured for archiving in liquid nitrogen) Other biopsies ▪ Liver and muscle biopsies (for electron microscopy, histopathology and enzymology (for the latter wrap in aluminium foil, snap freeze and store at -70 ºC). Collect within 4 h (preferably 2 h) of death. Consult metabolic physician or histopathologist before collection of samples) ▪ Other tissue biopsies if specific diagnoses are under consideration.