Gaia Young (deceased): memorandum by Dorit Young (mother)
Born: 4 March 1996 Died: 21 July 2021

Revised version (amendments marked in red)

Introduction

This note provides a summary of my review of the medical history from my own observations and review of the medical documentation. It is intended to record my understanding of the medical evidence and to identify possible areas of further inquiry.

This note is intended to be shared with: (1) the coroner; and (2) Gaia's previous medical attendants so they can understand my concerns and assist me in the direction for further inquiry. It is intended as a discussion document prepared by an interested, informed lay person - the mother of a much-loved deceased daughter - to ask further directed questions rather than to provide answers. It is not the expression of opinion.

This note has been prepared after consideration of the following materials:

1. Medical records.

2. Post mortem report for the coroner prepared by Professor Michael Sheaff histopathologist, dated 19 October 2021.

3. Autopsy report for the coroner prepared by Professor S Al-Sarraj neuropathologist, dated 7 October 2021.

4. "Unexpected deterioration of a young woman on the Acute Medical Unit": Serious Incident Report prepared by University College London Hospital NHS Foundation Trust (Dr Daniel Wallis, Dr Christine Gregson) dated 9 December 2021.

The toxicology report (reference 1948/21) has not been provided; however, it is referred to in Professor Sheaff's report and the contents summarized there (see below).

An inquest has been opened (presumably in accordance with Coroners and Justice Act 2009, section 1(2)(b)).

This memorandum is directed at consideration of the aetiology of Gaia's death; it is not primarily concerned with issues concerning her medical management. However, I reserve my position in respect of her medical management.

The presentation of Gaia's death does not appear to conform to any recognized disease; however, it may be possible to identify in its pathogenesis, mechanisms of disease. In her case these mechanisms were somehow catastrophically deranged beyond the usual presentation of disease with fatal consequence.

In summary, my review of the evidence indicates that it is incomplete in that it does not provide a cause of death. However, there appear to be areas suitable for further investigation. I ask for further appropriate inquiry.

This memorandum has been revised following consideration of the following:

1. UCHL updated investigation report.

2. The inquest.

3. Attendance at Moorfields Eye Hospital on 4 December 2019, and review of attendance by Moorfields Eye Hospital.

4. My further reading; in particular, urea cycle disorders.

This revised memorandum will be passed to the General Medical Council, the Care Quality Commission, the Healthcare Safety Investigation Board, and the Parliamentary and Health Service Ombudsman.

Brief summary of clinical presentation

Gaia Young was previously well. She was not on regular medication; she was not on hormonal contraception. ~~There was no relevant medical history.~~

On 4 December 2019 Gaia Young attended Moorfields Eye Hospital following referral by her optometrist because of her long history of headaches and the appearance of her optic discs. The diagnosis was "no abnormality". Moorfields have recently reviewed this consultation and confirmed the diagnosis but did not consider Gaia's history of headaches.

On 17 July 2021 at about 18.00 she presented with sudden severe headache and vomiting; she was admitted to hospital. She had been cycling; it was a hot day. Her Glasgow coma score was 15/15. She was noted to be confused and behaving oddly. She repeatedly denied the use of any recreational drugs.

There were no focal neurological signs; there was bilateral mydriasis noted. The fundi were apparently not examined.

She received intravenous fluid infusion (Hartmann's) one litre at 01.00 on 18 July 2021 one hour, one litre at 02.20 two hours, one litre at 04.28 six hours. The intravenous infusion prescription timings are difficult to interpret.

At 03.28 on 18 July 2021 it was noted "assisted minimally to the toilet…passed urine freely"; the Glasgow score was 15/15. It appears that a fluid output chart was not maintained.

She underwent CT head scan at 13.07; the finding was unremarkable.

On the afternoon of 18 July 2021 there was a second attempt at lumbar puncture (the first was not successful); just before this took place, she received a small dose of intravenous morphine. She experienced respiratory arrest and her pulse was tachycardic 180bpm (ECG apparently showed widened complexes). She required intubation and total support; there was an acute drop in her Glasgow coma score.

There was a striking temporal relationship between the attempted lumbar puncture and the sudden deterioration in her neurological status. A second CT head scan after her acute deterioration showed low-lying cerebellar tonsils.

Her condition deteriorated and was considered irreversible. She died on 21 July 2021. Various organs were donated.

The sudden deterioration (due to coning) conveniently and simply divides her illness into two phases: a pre-catastrophic event phase, and a post-catastrophic event phase. The cause of Gaia's catastrophic deterioration was the cause of her death.

Gaia's condition appears to have been an isolated, specific, and exclusive neuropathic process: an encephalopathy characterized by marked raised intracranial pressure and/or cerebral oedema. It was confined to the brain. It is striking that other body systems do not appear to have been involved. The severity of her brain pathology in the context of seemingly normal body function (various organs were not available for pathological examination – they were donated and so were presum~~ably~~ed healthy) seems difficult to explain.

The clinical course can be described as catastrophic, fulminant, overwhelming. The central inquiry is: how can such a fatal condition occur with such rapidity, confined only to the brain and yet have an unknown aetiology?

Review of the post-mortem reports

Dr Sheaff's report has provided the cause of death as follows:

1a. Tonsillar herniation
1b. Raised intracranial pressure
1c. Cerebral oedema

This does not provide any aetiology of Gaia's cerebral oedema; it is a mechanism of death. It is not a cause of death. Professor Sheaff's report includes:

> Neurological system
>
> There was no macroscopic abnormality externally except for the loss of the normal sulci/gyri undulations suggesting generalized oedema…
>
> Toxicology

> The ante-mortem blood samples contained no ethanol, amphetamines, morphine or other drug in a general screen…
>
> Neuropathology
>
> Please refer to full report of Professor Al-Sarraj dated 7 October 2021… No primary neuropathology is identified.
>
> Comment
>
> …Although the ultimate cause of death was apparent (raised intracranial pressure) the underlying cause of the brain injury was not clear…
>
> Ultimately, unfortunately the autopsy cannot establish the underlying cause of the brain oedema and raised intracranial pressure in this case. The brain injury was irreversible and catastrophic but it appears to be a secondary event as no primary pathology was identified within the brain on specialist examination. There are several potential possibilities including hyperthermia (such as heatstroke), toxicity (by an agent not identified on the screen available), a metabolic disorder or a pathological process, which clears soon after provoking the initial insult - such a thrombosed vessel that resolves. This list of potential differentials is not exhaustive.

Accordingly, the inquiry must be directed at investigating the "primary pathology" of which the brain injury was the secondary event. The report states, "This list of potential differentials is not exhaustive" but does not mention idiopathic intracranial hypertension; this condition concerns deranged function rather than abnormal structure (see below). It did not specifically mention hyperammonaemia due to urea cycle disorder, which is associated with non-hepatic metabolic encephalopathy.

Professor Al-Sarraj's report is detailed and descriptive of the brain injury as a secondary event; it does not provide an explanation of a primary event. It provides a description of the pathology of tissue at the time of death; it does not necessarily provide an explanatory pathogenesis in time but rather the description of an end point. Accordingly, the cause of death remains unknown.

The neuropathology report does not provide a description of the choroid plexus. It states also: "There is no evidence of uncal or tonsillar herniation."

At post mortem her height was 164cm, her weight was 54kg, and her BMI was 20.

The post-mortem reports do not provide a cause of death. However, the reports provide information as to what factors were not causes of death:

1. An intracranial vascular event.
2. An inflammatory process due to an infection such as meningitis or encephalitis.
3. Trauma.

4. Non-traumatic injury; acceleration/deceleration; shaken head.
5. A space-occupying lesion giving rise to mass effect.
6. An obstructive lesion giving rise to hydrocephalus.

The remaining possibilities that caused her death include:

1. Non-encephalitic (metabolic) encephalopathy, causing raised intracranial pressure and/or non-inflammatory cerebral oedema.
2. Exposure to drug or toxin.
3. Anatomical malformation (such as Chiari).
4. Idiopathic intracranial hypertension (so called "benign").

There is an apparent contradiction between the two post-mortem reports. Professor Sheaff's report gives the cause of death as "tonsillar herniation". Professor Al-Sarraj's report states that there is "no evidence of uncal or tonsillar herniation". This apparent contradiction requires explanation.

The post-mortem reports describe the state of her tissues at the time of death. They reflect the state of the brain several days after coning (when its blood supply had been interrupted). They do not provide a cause for the coning; accordingly, they do not really provide a cause of death, only a mechanism of death. Indeed, the causal sequence of "1a", "1b", and "1c" appears to be unclear.

Review of hospital investigation report

The report has been prepared from materials including electronic healthcare records and "recollections of clinicians" (presumably in the form of statements). ~~I have not been provided with copies of such statements.~~ The authors also consulted with a variety of experts within the UCL Trust - like the NHNN - on a casual basis via email and phone. I have not been provided with those consultations.

The summary of the report includes the following:

> This serious incident investigation concerns the initial hospital care of a previously healthy 25 year old woman who tragically died with rapidly progressive cerebral oedema (brain swelling)…
>
> This investigation highlights aspects of the patient's care, which could have been improved. What the impact of such improvements would have been on the patient's outcome is not currently certain. The underlying cause of the patient's illness is not known at present, but may become clearer when the results of post-mortem examination are available. This investigation acknowledges there is a range of medical opinion regarding some aspects of the patient's care – in particular the interpretation of the first CT scan, and management of the patient's hyponatremia.

The report is concerned with the "initial hospital care"; it does not consider the possibilities of the "underlying cause of the patient's illness". The report has explicitly been prepared without review of the post-mortem examinations.

The report states (in respect of the initial clinical assessment):

> …ideally the patient's optic discs (at the back of the eye) should also have been examined… It seems likely this would not have been possible because of the patient's inability to co-operate… (page 9)

The significance of fundoscopy is considered later in this note.

The detailed narrative of the report ends abruptly in the afternoon on 18 July 2021. It does not describe the metabolism of water and sodium ion subsequently (page 27). It does not describe the management of salt and water balance.

The reports overview includes:

> The cause of the patient's rapidly progressive brain swelling is not known (the result of post-mortem examination is not currently known to us). The serious incident investigation, with the benefit of hindsight, has identified learning from some shortcomings in the patient's care; but whether her tragic death could have been prevented is not clear.

The evidence of the pathological endpoint was not reviewed in the report. However, the pathogenesis (as opposed to pathology) of Gaia's condition from clinically available information does not appear to have been considered in any detail.

Post-mortem examination provides information as to the end stage pathology; it may not necessarily provide information as to the disease process itself. Clinical information may provide such insights.

There were striking ante mortem clinical findings: the lack of response to salt replacement; the sodium level at its lowest was 122mmol/L (the report describes this as "profound" hyponatraemia but does not provide an indication as to what levels are dangerous); the lack of correlation between the clinical picture and the first CT scan. These may provide some insights (see below) of her disease process.

The focus of the report is on management of hyponatraemia *per se*. However there is a view that hyponatraemia may have been a marker of an underlying condition which eventually proved fatal.

Consideration of this published paper was helpful in interpreting the hospital report:

> Mortality and Serum Sodium: Do Patients Die from or with Hyponatremia?
>
> Clin J Am Soc Nephrol. 2011 May; 6(5): 960–965. A Chawla and others
>
> Conclusions
>
> The nature of underlying illness rather than the severity of hyponatremia best explains mortality associated with hyponatremia. Neurologic complications from hyponatremia are uncommon among patients who die with hyponatremia.

The text of this paper indicated that cerebral oedema did not feature markedly:

> Over the 12-year span of this study, we found only one patient with sNa <120 mEq/L who died of cerebral oedema, and this patient had coexistent intracranial pathology. (at page 8/11)

The broad conclusion of this paper is that hyponatraemia may not be of itself a lethal condition. This paper accords with a view that hyponatremia was a marker for Gaia's underlying illness: she may have died with hyponatremia, not of hyponatremia. It may have been the effect of her underlying illness but not the cause of her death. She may have died of an underlying condition (see below).

The updated investigation report remained unsatisfactory; it disregarded my comments. The clinical reasoning was unsound, the diagnostic analysis was chaotic. It was misconceived: cause of coning and cause of death were not distinguished; pathogenesis and pathology were conflated; mechanism of death and cause of death were not separated; epiphenomena were treated as causal evidence; cause and effect were reversed.

There was little systematic attempt to consider the "primary pathology" postulated by Professor Sheaff (see above). Consideration of the clinical information and pathological findings suggested a primary encephalopathic disease with the following characteristics:

> It originated in the brain.
> It was confined to the brain.
> It was lethal.
> It did not leave any trace of itself.

However, the updated investigation report continued to be preoccupied with salt and water metabolism, and cerebral oedema – this approach did not provide a satisfactory or convincing explanation. There was little consideration as to whether these were primary or secondary effects. It did not set out any conceptual framework to provide the basis of a differential diagnosis. There was little attempt to reconstruct the sequence of findings prior to coning. There was hardly any fresh thinking.

Review of investigations in the medical records

The medical records indicate extensive investigations in real time. It is quite striking that the investigations were generally unremarkable in someone who was shortly to die of a fatal condition. Some results are abnormal. However, such abnormalities are not sufficient to denote conclusively and completely a cause of death.

The investigation results are reviewed in the context of the post-mortem results to see if they may suggest further direction of investigation.

The significance of an abnormality must be assessed to consider if it is aetiologically relevant or epiphenomenal. Likewise, abnormality should not be over-interpreted in the context of this case.

Normal ranges are not provided in the medical records for many investigations; where such ranges are provided they are set out in in this note.

Deranged electrolytes and chemistry

The initial blood results include:
pH 7.514
carbon dioxide partial pressure 3.33kPa
oxygen partial pressure, 10.9kPa
potassium 3.4mmol/L
sodium 129mmol/L
ionized calcium 1.10mmol/L
chloride 97mmol/L
glucose 6.3mmol/L
lactate 2.7mmol/L
urea 3.5mmol/l
standard bicarbonate 23.2mmol/L

The glucose at 02.03 on 18 July 2021 was 6.3mmol/L.
The glucose at 03.53 on 18 July 2021 was 7.5mmol/L.

These results demonstrate several minor abnormalities. They appear to be consistent with the history of vomiting. The normal urea provides evidence of absence of significant dehydration. The eGFR was normal and remained normal. Her kidneys were considered suitable for organ donation.

There was no measurement of ammonia.

Low sodium level

The initial sodium level was 129mmol/L; the following day it was 122mmol/L (despite electrolyte infusion replacement, three litres in 9 hours). Thereafter the sodium level rose, and she subsequently became hypernatremic. Such low sodium levels are abnormal but do not seem very abnormally low.

Lactate ion

The admission (17 July 2021, 23.19) lactate level was 2.7mmol/L (raised). The pH was 7.514, carbon dioxide partial pressure 3.33kPa, oxygen partial pressure, 10.9kPa; the oxygen saturation was 100%. Her observations were unremarkable.

Later, at 01.00 18 July 2021 Hartmann's solution was administered.

On 18 July 2021at 02.00 the lactate level was 2.3mmol/L.

On 18 July 2021 at 18.28 the lactate was 1.8mmol/L.

On18 July 2021 at 19.45 the lactate was 1.3mmol/L.

Thereafter the lactate level was normal.

The initially raised lactate level preceded the infusion of sodium lactate.

What is the significance of elevated lactate (with concomitant mildly elevated glucose)? There is no suggestion of hypoxia or acidosis (alkalosis possibly from history of vomiting and low carbon dioxide).

Her observations were normal. The elevated lactate cannot be related to her cardiopulmonary status.

The elevated lactate cannot be related to infusion of sodium lactate as it was raised before fluid infusion

Lymphocytopaenia

The absolute lymphocyte count was initially low (0.68 x10^9/L; reference range 1.2 to 3.65) then became normal. There was no suggestion of an inflammatory process or immune disorder. There was no infectious process. It seems unlikely to be clinically significant.

Raised D-dimer

The D-dimer 18 July 2021 23.30 was raised (1,050ug/L; reference range 0 – 550). The scans and post-mortem indicate that thrombotic disease was not involved. The raised D-dimer does not appear to be significant.

CT scans of head

The CT head scan at 13.07 on 18 July 2021 was reported as follows:

> No previous neuroimaging available for comparison.
>
> …The ventricles and basal cisterns are patent…
>
> Impression
> No acute intracranial finding.

The CT head scan at 16.53 on 18 July 2021 was reported as follows:

> Comparison to the CT head performed 3 hours prior the same day.

> There is poor grey-white matter differentiation and loss of defined sulcal spaces. Findings are suspicious for generalized brain oedema. The cerebellar tonsils are at 1cm below the foramen magnum. The ventricular system and basal cisterns are slightly effaced due to the generalised oedema…
>
> Impression
>
> Slight degradation of grey-white matter differentiation as well as loss of sulcal spaces. Low lying tonsils. In combination with the drop in GCS these findings are suspicious for generalized brain oedema…

The striking feature of the first scan is the absence of reported acute abnormality in a patient who would shortly experience tonsillar herniation.

The striking feature of the second scan is the apparent lack of correlation between the low-lying cerebellar tonsils, the acute change in neurological status and the seeming lack of description of marked cerebral oedema (merely "suspicious for generalized brain oedema").

There was no description of any abnormality of the choroid plexus.

Drug and toxin screen

There was an extensive though not exhaustive toxicology screen. No substances were found. There was absence of evidence of toxic agents; there was evidence (necessarily incomplete) of absence of toxic agents.

Consideration of possible aetiologies for ~~cerebral oedema~~ encephalopathy

The brain does not regulate its environment; the homeostasis of the brain is generally maintained by factors outside the brain; the normal function of the brain is dependent on the stability of the function of the body. The development of encephalopathy and/or cerebral oedema appears to have occurred without disturbance of any bodily system. This suggests (using Dr Sheaff's reasoning) that the primary pathology was itself confined to the brain – a primary intrinsic neuropathic process to have caused the secondary event of the brain injury. Moreover, it could have been a transient event.

Non-encephalitic encephalopathy

The underlying pathology is a non-inflammatory cerebral oedema. There are at least two possible mechanisms: (1) abnormality of the extracellular fluid: derangement of water metabolism causing hyponatremia; (2) abnormality of the tissue: metabolic encephalopathy.

(1) Deranged water metabolism

The sodium level was 122mmol/L at the measured lowest at the time of the acute deterioration (18 July 2021 at 15.59). This level is not generally associated with dangerous morbidity (though acute onset hyponatremia may have more marked effect on the brain of a young woman).

A mechanism of hyponatremia by salt depletion by vomiting and dehydration with replacement by fluid appears not to accord with the evidence. Fluid replacement was three litres of Hartmann in 9 hours. Gaia had healthy organ systems, which ought to have been able to correct the electrolyte imbalance; she was able to "pass urine freely" and there was no clinical suggestion of fluid overload. Moreover, the sodium level continued to fall despite infusion of sodium solution. What was the cause of the low sodium level?

A plausible mechanism is derangement of water metabolism by inappropriate ADH secretion causing water retention and sodium dilution. Inappropriate ADH secretion syndromes are recognized in intracranial pathology.

The subsequent rise in sodium level (which required to be treated by desmopressin and dextrose solution) may reflect progression of more serious brain damage causing failure of ADH secretion (diabetes insipidus).

The evidence tends to suggest the hyponatremia was an effect of a primary encephalopathy rather than being the cause of a secondary encephalopathy.

So the question remains: what was the primary encephalopathy?

(2) Metabolic encephalopathy

Could there have been an abnormality of the function of the cell membranes themselves? Another postulated mechanism is metabolic encephalopathy: a primary failure of metabolism by some disease as denoted by the abnormal and persistently elevated blood lactate level, and a mildly elevated blood glucose. The CSF chemistry usually reflects blood chemistry; is it possible in case this that the elevated blood lactate and blood glucose levels reflect elevated CSF levels? There does not appear to be a ready explanation for the isolated raised blood lactate and raised blood glucose level.

A metabolic disease could lead to failure of energy production and loss of cellular membrane integrity of the brain cells. At molecular, subcellular, and cellular level this postulated pathogenesis appears to correlate with the clinical picture and the biochemistry. This conforms with Dr Sheaff's postulation "a metabolic disorder or a pathological process which clears soon after provoking the initial insult" – the elevated lactate later became normal.

It is accepted that there is unlikely to be a described disease, which conforms to this mechanism. However, our understanding of the molecular basis of disease is in its early stages and is incomplete. Cellular components, which are common to almost all

cells, may at molecular level be specific for a particular tissue. It explains why some diseases are organ specific. Such molecular specificity could have a specific genetic basis. There are known existent disorders whose mechanism of disease affect a subcellular component common to most cells but affecting only the element in a particular tissue. This analogy could provide a possible model for Gaia's underlying disorder.

Could Gaia have had a specific susceptibility that affected the function of her brain cell membranes, which was deranged by a non-specific minor insult, which resulted in a catastrophic metabolic disturbance? A situation where the susceptibility is specific, the trigger may not be.

Inborn errors of metabolism can cause encephalopathy; there are the urea cycle disorders which can be associated with endogenous hyperammonaemia (most commonly ornithine transcarbamylase deficiency, an x-linked recessive gene; there are others associated with autosomal recessive genes). It is a form of non-hepatic metabolic encephalopathy (although the defect is in the hepatocyte mitochondria, there is no liver disease in the usual sense). The central nervous system is particularly sensitive to the toxic effect of ammonia compared to the rest of the body (selective chemical toxicity).

(Note: I have recently met with the mother of a previously well teenage boy who died after a brief catastrophic encephalopathic illness like Gaia's; his liver was donated. The cause of death was unascertained initially. A few months later the recipient of the liver suffered neurological symptoms. The matter was investigated; the deceased boy had suffered from ornithine transcarbamylase deficiency. The cause of death was amended accordingly. This case was reported in The Daily Telegraph, 13 August 2022.)

An expert review of metabolic encephalopathy may assist in describing mechanisms of disease, and known diseases in the context of this case.

Neurotoxin or drug effect

Gaia's bodily fluids have been subjected to screening analysis for drugs and toxins. There is absence of evidence of toxin; there is evidence of absence (necessarily incomplete) of toxin. Accordingly, there is the possibility of drug or neurotoxin.

Drugs and toxins generally exert their effects specifically by affecting existent pharmacological receptor, hormonal, or enzyme systems and so altering the homeostasis of the body. This is achieved by molecular specificity and amplification – action on tissue is not generally caused directly by the extrinsic agent but by its effects on a body system, which can cause secondary effect.

Neurotoxins and neurotropic drugs act on nervous tissue: this describes the site of action not necessarily the tissue of effect. Their damaging effects are generally not

confined to the nervous system by direct neuropathic action but generally mediated by disturbance of bodily function.

In this case the mechanism of brain damage was confined to the brain; the body functions appeared to be intact and stable. It is difficult to see what drug or toxin could have such a mode of action, to cause cerebral oedema directly by a specific, exclusive action and in isolation – without disturbing other body systems. The notion of an unidentified neural agent acting in this way appears to be a theoretical construct.

The brain is sensitive to endogenous ammonia compared to the rest of the body; accordingly, ammonia can be considered a selective neurotoxin: there is specificity and exclusivity for the brain presumably through a direct chemical effect rather than by any receptor mechanism. See:

> Non-hepatic hyperammonaemia: an important, potentially reversible cause of encephalopathy. Postgrad Med J 2001; 77: 717-722. ND Hawkes and others.
>
> What is the utility of measuring the serum ammonia level in patients with altered mental status? H Elgouhari and R O'Shea; Cleveland Clinic Journal of Medicine, volume 76, number 4 April 2009.
>
> Hyperammonemia due to urea cycle disorders: a potentially fatal condition in the intensive care setting. Journal of Intensive Care 2014, 2:22. Machado and Pinheiro da Silva.
>
> Urea cycle disorders: a life-threatening yet treatable cause of metabolic encephalopathy in adults. Blair NF, et al. Pract Neurol 2015;15:45–48.

The learning from these publications is that measurement of blood ammonia should be part of the investigation of acute encephalopathy.

An expert review of neurotoxicology may assist in reviewing known toxins and the mode of action in the context of this case

<u>Abnormal form of the brain</u>

The striking features of the two CT head scans of 18 July 2021 concern the lack of correlation of the report of cerebral oedema and the clinical events. The description of cerebral oedema was not marked considering the clinical events. The first scan was initially reported as ~~did~~ not describ~~e~~ing cerebral oedema at all. The second scan noted suspicion of cerebral oedema in the context of low-lying cerebellar tonsils. It raises at least three questions:

> (1) were the scans adequately reported?
> (2) was there raised intracranial pressure absent cerebral oedema (first scan)?

(3) was there a primary anatomical anomaly of low-lying cerebellar tonsils? If so, was this a case of previously occult asymptomatic malformation such as Chiari?

An expert review of radiology may assist in explaining the lack of correlation in the report of the scans and the clinical events.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension is believed to be due to over production of cerebral spinal fluid; the mechanism of disease is partly understood but the aetiology is not – hence the description "idiopathic" (apparently previously so called "benign" because it is not fatal). It tends to affect women of childbearing age. There are generally not extracranial features, usually no focal neurological features, no tissue damage. It is usually of gradual onset and self-limiting. It is a cause of raised intracranial pressure without cerebral oedema. The brain imaging may be unremarkable. There may be papilloedema with apparently normal brain scan.

Gaia's first CT scan did not show cerebral oedema or other acute pathology. There was no extracranial pathology.

Is it possible that Gaia suffered a primary acutely catastrophic derangement of the pathophysiology of idiopathic intracranial hypertension causing brain herniation? A non benign (or malignant) idiopathic intracranial hypertension that reached a critical point. There was no primary tissue damage. Was the cerebral oedema a secondary event (see Dr Sheaff's postulation) – the effect rather than the cause of the raised intracranial hypertension?

It is recognized that idiopathic intracranial hypertension can exist in fulminant form:

> Fulminant idiopathic intracranial hypertension. M Thambisetty and others; Neurology 2007; 68 229 – 232.

If it can exist in a "fulminant" form then the question arises whether it can exist in a supra-fulminant form.

Gaia's fundi were not examined. The hospital report states that the fundi should "ideally" have been examined. The question arises as to whether fundoscopy (was it attempted on admission?) ought to be part of the basic clinical assessment of any patient in the circumstances of Gaia's case: a matter of routine rather than "ideal".

Gaia's case resembles a publicised case (see *Rose v R (Rev 1)* [2017] EWCA Crim 1168; attached): a previously well child suffered a sudden catastrophic illness over a few hours with fatal outcome due to raised intracranial pressure without any neurological indicators.

The *Rose* case is factually different to Gaia's case. However, it may be worth a review to see if it can provide any insight into the pathogenesis of Gaia's death (see paragraphs 6 to 10). In Gaia's case it was not obstructive hydrocephalus due to a structural abnormality of the brain but possibly overproduction of CSF by an apparently structurally normal brain. The pathology may be different, but the pathogenesis may have been similar.

Could Gaia have suffered from a comparable process of acute decompensation of critical intracranial hypertension?

The *Rose* case concerned the medical and legal consequences of failure to perform fundoscopy.

Change in posture

There was a striking temporal relationship between the second attempted lumbar puncture and the catastrophic decline in neurological status. Could the abrupt and enforced change in posture (flexion of the spine and ventral compression of the head and neck area) have precipitated the brain herniation in a state of critical intracranial hypertension?

Formulation

The process of collecting primary medical information is probably now concluded; the evidence is incomplete in that it does not provide a conclusive cause of death. My review of the existent evidence leads to the formulation of the following propositions:

1. Gaia experienced a metabolic non-hepatic encephalopathy as the primary pathology causing intracranial hypertension and/or non-inflammatory cerebral oedema such as hyperammonaemia due to urea cycle disorder.
2. Gaia had an occult anatomical formation of the brain making her vulnerable to raised intracranial pressure.
3. Gaia's cerebral oedema was a secondary event due to herniation following primary acute catastrophic supra-fulminant idiopathic intracranial hypertension.
4. A combination of some of these factors and the postural change at the time of the second lumbar puncture initiated the process of tonsillar herniation.

These are recognized disease mechanisms which individually or more likely in some combination may have caused Gaia's death. Gaia's death does not readily conform to a recognized disease; however, its pathogenesis does conform to recognized patterns disease development which may have become catastrophically deranged beyond the usual pattern of disease presentation.

My favoured "best fit" postulation concerns catastrophic idiopathic intracranial hypertension, or hyperammonaemic metabolic non-hepatic encephalopathy: it accords with existent evidence, and conforms with recognized disease processes, and does not involve construction of any novel mechanism. It is not inconsistent with the existent evidence. Whilst it is not supported by positive evidence, there is absence of evidence and evidence of absence of an alternative known cause. It accords with Occam's principle (entia non sunt multiplicanda praeter necessitatem).

This is my formulation, and I would be grateful for the inquest process and Gaia's former medical attendants to consider it.

Conclusion

There is a large amount of medical information. The cause of Gaia's death remains unknown. However, review of the evidence has been informative. It has identified areas which are unlikely to reward further investigation. However, it has identified areas where the evidence is incomplete are which are worthy of further investigation; these include:

1. Neuroradiology expert review of the CT scans: in particular (1) consider the extent of cerebral oedema in first and second CT scans; (2) to review the choroid plexus; (3) was there any underlying abnormality of the brain (low lying tonsils in second scan: any evidence of Chiari in first scan?).
2. Neurotoxicology expert review to comment on mechanisms of brain damage injury of known neurotoxins in the context of this case; role of endogenous hyperammonaemia.
3. Neurologist expert review of: (1) metabolic encephalopathy mechanisms of disease in the context of this case; (2) mechanism of raised acute catastrophic idiopathic intracranial hypertension; (3) the role of fundoscopy in the context of this case; (4) the role of measuring ammonia in the context of this case.
4. Genetic studies: to investigate if there was any genetic basis for Gaia's condition.

There is a requirement for a neuropathology review. There is an apparent contradiction between the two post-mortem reports. Professor Sheaff's report gives the cause of death as "tonsillar herniation". Professsor Al-Sarraj's report states that there is "no evidence of uncal or tonsillar herniation". Inquiry could also be made of Professor Al-Sarraj as to the choroid plexus.

Gaia's death is the subject of a coroner's inquest. The Coroners and Justice Act 2009 provides at section 5(1)(b): The purpose of an investigation… into a person's death is to ascertain… how… the deceased came by his or her death.

According to the present state of the evidence I do not consider that this inquiry can be adequately addressed.

Accordingly, I respectfully ask the coroner in accordance with the statutory duty to make further inquiry to address how Gaia came by her death.

I ask the court to obtain expert reports in neuroradiology, neurotoxicology, and neurology as indicated above (please see: *Nguyen v HM Assistant Coroner for Inner West London* [2021] EWHC 3354 (Admin) (10 December 2021) attached). This case provides some indication from the High Court as the approach of the coroner's court to submissions of relatives in respect of expert evidence.

I ask for an explanation of the apparent contradiction on the face of the two post-mortem reports.

I am grateful for your consideration of this note.

First postscript: coroner's inquest 14 February 2022

The inquest took place on 14 February 2022.

There were no independent experts giving evidence other than the two pathologists; there were no independent clinicians to give evidence on the care provided. The hospital was permitted to investigate itself in an independent judicial process; there was no external scrutiny.

The coroner and UCLH opposed my request for a neurologist and other experts to attend. The coroner returned a narrative conclusion and concluded that the cause of death was "unclear".

Second postscript: implications for the recipient of Gaia's liver

This note has been concerned with Gaia. However, there may be wider patient safety issues - implications for the recipient of Gaia's liver. It may be that she died from an inherited urea cycle disorder. The following publication is referred to:

> Ornithine Transcarbamylase Deficiency (OTC) in the Donor Liver, the Importance of Ascertaining the Cause of Death in the Brain Dead Donor. M George and others; Am J Transplant. 2017; 17 (suppl 3).

This publication contains the following statements in its Abstract:

> The importance of ascertaining the cause of brain death in the donor is vital… The lesson that we learnt was education and awareness of OTC deficiency in adult patients and the importance of having a clear cause of brain death in the donor.

The following publication is referred to:

> Case 252: Acute Hyperammonemic Encephalopathy Resulting from Late-Onset Ornithine Transcarbamylase Deficiency. M Hershman and others. Radiology 2018; 287:353–359.

This publication contains the following statements in its history:

> The patient's condition deteriorated, with increasing cerebral edema over the next week, and she was declared brain dead. Her liver was transplanted into an adult recipient, who subsequently developed cerebral edema and elevated plasma ammonia levels, resulting in death in the immediate postoperative period.

The UCLH letter dated (Catherine Mooney) 20 January 2022 included the following:

> The purpose of the serious incident investigation is primarily to review the care of your daughter and to identify any learning. We do not have the same purpose as the Coroner who needs to determine the cause of death.

This denotes an astonishing lack of medical curiosity for a leading clinical and research institution. It is crass. I am surprised that UCLH consider that it does not need "to determine the cause of death"; this position conflicts with the papers which considers the risk for the recipient of a liver from brain dead donors.

In any event the care cannot be assessed without some consideration of the differential diagnosis of the cause of the encephalopathy. How can the failure to perform fundoscopy be assessed without some index of suspicion of raised intracranial pressure; how can the failure to measure ammonia be assessed without some index of suspicion of urea cycle disorder. I consider UCLH's statement to be fundamentally illogical and it is asked to explain itself.

Dorit Young

13 December 2021

29 August 2022