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9 December 2025

Gaia Young (deceased)
Born 4 March 1996
Died 21 July 2021

Dear Dr Gross

Thank you for your letter dated 20 November 2025 in response to my letter dated 6 November 2025 on the aetiology of Gaia's acute fatal brain illness.

I am copying this letter to University College London Hospital NHS Foundation Trust (the "Trust") and various clinicians in a spirit of collaboration.

I repeat the content of previous correspondence which set out my formulation and reasoning as to why Gaia's illness was ornithine transcarbamylase ("OTC") deficiency.

Your letter raises some issues which I address as follows:

Summary: evidence for OTC

The analysis of the evidence leads to the conclusion that Gaia died from OTC deficiency hyperammonaemic encephalopathy.

You state: "The evidence for OTC in an adult lady aged 25 is quite complex." I disagree – it appears simple and robust. The available evidence of clinical and pathological features of fatal OTC deficiency hyperammonaemic encephalopathy is limited: disturbed cerebral function; respiratory alkalosis with hypocapnia; antemortem generalised cerebral oedema; absence of post-mortem abnormality apart from secondary changes in the brain.

Although the evidence is incomplete it is sufficient to enable identification of Gaia's illness. These scant non-specific features in combination provide a clinical pathological diagnostic fingerprint that is specific and exclusive. Gaia had these.

It is difficult to see what other condition Gaia had, if not OTC deficiency.
Your attachment "extensive review"

You state: "…I will attach an extensive review."

1. You have not provided any copy of this document.
2. You have not identified this document.
3. You have not cited any extract from this document.
4. You have not indicated why this document is relevant.
5. You have not indicated how you rely on this document.

Please will you address these matters.

OTC deficiency encephalopathy

You state: "clearly there is a compelling consideration that this could have been a fatal metabolic encephalopathy". I agree. I consider that OTC encephalopathy represents a perfect and unique clinical pathological correlation. I asked: "I appeal to you all to consider OTC hyperammonaemia. If you can find a better fit, then please advise me." There has been no suggestion from you or anyone else of a better fit. It follows therefore that Dr Killingley's proposal (which I adopt) prevails.

Differential diagnosis

You state: "What one has to accept here is that there has to be a differential diagnosis." I agree. In my memorandum (13 December 2021) to the court and the Trust, I set out the wide-ranging differential diagnosis as follows:

1. Metabolic encephalopathy
2. Drug or toxin
3. Anatomical malformation (eg Chiari)
4. Idiopathic intracranial hypertension (based on the erroneously reported first CT scan as essentially normal: applying Dandy Friedman criteria)

Differential diagnosis is an evolving, dynamic process. As my understanding of the medicine, pathology, and evidence developed only metabolic encephalopathy survived. Dr Killingley's letter (7 March 2022) helped refine the differential diagnosis from metabolic encephalopathy to OTC deficiency hyperammonaemic encephalopathy.

Liver impairment and OTC

You state:

> "As I have always understood that the ammonia and glutamine elevations are caused by liver impairment and one might expect under that circumstance that the liver function tests would be abnormal."

And:

> "…this could well have been an isolated example of an adult OTC deficiency encephalopathy with cerebral oedema. There is however a lot of evidence such as the

> normal liver function tests and no other clues that make that diagnosis far more difficult from a scientific perspective."

This is incorrect. You have not provided any peer reviewed published material to support your assertion that liver function tests are deranged in hyperammonaemia due to OTC deficiency. There is little reason why a discrete isolated enzyme deficiency should be associated with deranged liver function tests. Non-hepatic causes of hyperammonaemia are recognised and diverse; see:

> Non-hepatic hyperammonaemia: an important, potentially reversible cause of encephalopathy. Postgrad Med J 2001; 77: 717-722. ND Hawkes and others.
>
> > See case 3 [OTC deficiency]: "Serum alkaline phosphatase was 307IU/l (normal30±115) but liver function was otherwise normal." (page 719)

You refer to valproate induced hyperammonaemia; this primarily occurs by inhibiting the urea cycle. The literature indicates that liver function tests may be normal; see for example:

> Hyperammonemia Due to Valproic Acid in the Psychiatric Setting, RB Carr, K Shrewsbury; American Journal of Psychiatry, vol 164 no 7 July 2007.
>
> > "…there have been several additional case reports and studies within the neurology literature that have established hyperammonemia with otherwise normal hepatic function as a potential side effect of valproic acid, especially in children and adolescents."

There have been reports in the literature of liver donations from fatalities due to proven OTC hyperammonaemia; see:

> Case 252: Acute Hyperammonemic Encephalopathy Resulting from Late-Onset Ornithine Transcarbamylase Deficiency. M Hershman and others. Radiology 2018; 287:353–359.
>
> > "The key to the diagnosis in this case is the patient's age, clinical history (*including a lack of underlying liver disease*), and fate of the organ transplant recipient resulting from elevated plasma ammonia levels from inability to express the ornithine transcarbamylase enzyme." (emphasis added, at page 355)
>
> 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).

It is inconceivable that any liver with deranged liver function tests of unknown cause would be transplanted. Indeed, Gaia's liver was retrieved for transplantation. Your assertion that Gaia's normal liver function excluded OTC is explicitly contradicted by the literature.

You state: "There is however a lot of evidence… that make that diagnosis far more difficult from a scientific perspective." You do not identify such evidence that makes the diagnosis

more difficult; please will you do so. I am not aware of any evidence which refutes the diagnosis.

You refer also to "no other clues" as making diagnostic difficulty. I disagree; it is the lack of clues (evidence of absence of abnormality) that was informative – it excludes the conditions which Gaia could not have had. Gaia's condition must have been whatever was not excluded (see below on autopsy report.).

The autopsy reports

The autopsy reports confirm that there was no primary brain pathology. You state:

> "What it demonstrated was that Gaia had cerebral oedema which generates a raised pressure syndrome and is ultimately the tragic cause of passing. I agree that it is a secondary event that goes without saying, but it does not tell us why the brain should have reacted as it did and in such an acute way."

I agree. However, you do not suggest what the primary event was. OTC deficiency provides a perfect clinical pathological correlation (as previously stated).

The autopsy reports are immensely informative: they say what could *not* have caused Gaia's death. As such they add much to the diagnostic process, contrary to your view.

The Hershman paper

You state: "The Herschman paper which I have now attached, is a true one-off situation, hence the reason for the case report."

This is incorrect. It was not a "one off" situation. It was an example of an albeit rare late presentation of acute fulminant fatal hyperammonaemic OTC deficiency crisis. This is well established in the literature; see:

> Urea cycle disorders: a life-threatening yet treatable cause of metabolic encephalopathy in adults. Blair NF, et al. Pract Neurol 2015;15:45–48.
>
> > "However, the first sign may be an acute life-threatening encephalopathy. We are aware of a similar case at another hospital, where the diagnosis of a urea cycle disorder was not recognised, with a fatal outcome. Indeed, in several reported adult cases the initial presentation was fatal." (at page 47)

Other proven fatal cases include Rohan Godhania and Elliot Peters which were described in the lay press.

There is an established pattern of presentation of fulminant fatal encephalopathy. Gaia's case conformed to that pattern.

Hyponatraemia

In your report you stated:

> "I personally would not have been concerned about a sodium level of 129. Most neurologists are used to dealing with people who have sodium levels as low as 99 or below 110…" (paragraph 41)

In my letter I stated:

> "…hyponatraemia is a well-known non-specific epiphenomenon of any acute brain condition (SIADH) and was not of itself capable of explaining Gaia's death."

Gaia received 3 litres of Hartmann's in 9 hours and was passing urine. Her sodium fell to 122. It is difficult to see that this represented water intoxication or salt depletion; see:

> 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 distinction between causality and epiphenomenology is crucial.

Posterior vertebral encephalopathy syndrome

You refer to "posterior vertebral encephalopathy syndrome". I have searched for this on the internet, and I am unable to find. Please advise.

As for posterior reversible encephalopathy syndrome this is usually a secondary condition. Gaia did not have the associated primary conditions. Gaia's condition was fatal, not reversible.

"Clever diagnosis", "being just too clever", and "dogmatic"

I do not understand your comments about "clever" diagnosis or "being just too clever". My approach is to assess all the evidence, applying diagnostic analysis and clinical reasoning. I then check that my conclusions conform with published evidence. I then invite medical opinion to test my opinion.

By applying this methodology, I have adopted OTC deficiency hyperammonaemic encephalopathy that was proposed by Dr Killingley. By applying this methodology, I am unable to find any other viable diagnosis.

As for "dogmatic" – I do not understand this comment. I believe that the methodology I have used leads to the diagnosis of OTC deficiency; it is not a matter of dogmatism but of evolving differential diagnosis: it is a reasoned and evidence-based approach.

Comment

Your letter gives rise to concerns:

1. The evidence for OTC is limited, simple, and robust; it does not appear "complex" as you suggest. You have not provided a copy of the "extensive review".

2. You have not confirmed or refuted the proposal of fatal OTC deficiency hyperammonaemic encephalopathy. You have not proposed any viable alternative. You have not constructed a plausible differential diagnosis.

3. You appear to be unfamiliar with non-hepatic hyperammonaemic conditions (though you refer to valproate-induced hyperammonaemia); you erroneously suggest that because Gaia's liver function was "normal" it makes the OTC deficiency "diagnosis far more difficult from a scientific perspective".

4. You correctly recognise that the post-mortem report denoted a secondary event; but you do not consider the primary event.

5. You do not appear to recognise the diagnostic value of lack of post-mortem finding apart from secondary changes in the brain; this evidence of absence is immensely informative by stating what Gaia could *not* have died of.

6. You erroneously suggest that the case report in the Hershman paper was a "true one off situation". It was not. It was an example of a recognised pattern of fatal fulminant encephalopathy. Gaia had such a presentation.

7. You do not distinguish between causality and epiphenomenology in respect of hyponatraemia.

8. You refer to the non-existent "posterior vertebral encephalopathy syndrome". As to posterior reversible encephalopathy syndrome Gaia's did not have the associated conditions. Her condition was not "reversible".

Accordingly, some of your comments and opinions appear to be based on incorrect information. They are to be interpreted accordingly.

<u>Conclusion</u>

I repeat that the analysis of the evidence leads to the conclusion that Gaia died from OTC hyperammonaemic encephalopathy.

I am grateful to you for your opinion and analysis. It has provided an opportunity to test the proposal of OTC deficiency hyperammonaemia.

You have provided little reason to refute the proposal. You have not provided any viable alternative formulation.

I invite you again please either to confirm the proposal or refute it by reasoned argument based on evidence.

Similarly, your professional colleagues at the Trust have not refuted the proposal or suggested any viable alternative formulation.

Many thanks for your consideration and I look forward to receiving your substantive response.

Yours sincerely

Dorit

Lady Young of Dartington

CC
Professor David Probert
Dr Charles House
Ms Cathy Mooney
Professor Tom Warner
Dr Robin Lachmann
Dr Elaine Murphy
Dr Ben Killingley
Professor Matthew Walker
Dr Jim Down
Dr Kathryn Jenkins
Dr Helen Simpson
Dr Dominic Heaney
Dr Christian Hasford
Professor Rolf Jager
Dr Ayman Mahfouz
Dr Christine Gregson