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Bridging the Gap: Acute Neurology and a Metabolic Acidosis.
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Guest: Dr. Dylan Mac Lochlainn is currently an academic clinical fellow in immunology at the Oxford University Hospitals NHS Foundation Trust.

Randye Kaye: Hello and welcome to this edition of JALM Talk, from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Metabolic acidosis, a condition characterized by high levels of acid in the body and blood is common in hospitalized patients. While there are numerous potential causes of metabolic acidosis, many cases can be diagnosed by clinical history examination and routine lab chemistries. Calculation of the anion gap which reflects the difference between the positively charged cations and the negatively charged anions in the blood is often a part of this diagnostic work up.

An elevated anion gap acidosis is often observed with the ingestion of toxic alcohols or drugs, such as aspirin. However, sometimes more rare or unsuspected compounds may be involved. A Case Report published in the May 2020 issue of *The Journal of Applied Laboratory Medicine* describes a case of high anion gap metabolic acidosis caused by pyroglutamic acid, an organic acid associated with long-term acetaminophen ingestion.

The first author of this report is Dr. Dylan James Mac Lochlainn. Dr. Mac Lochlainn is currently an academic clinical fellow in immunology at the Oxford University Hospitals NHS Foundation Trust. At the time of writing the Case Report, he was a foundation program doctor in the Acute Stroke Unit of Royal Victoria Hospital in Belfast, Northern Ireland. Dr. Mac Lochlainn is our guest for this podcast. Welcome Dr. Mac Lochlainn. In laboratory medicine, we hear a lot about metabolic acidosis but what is pyroglutamic acidosis?

Dylan Mac Lochlainn: Well, pyroglutamic acidosis is a type of metabolic acidosis that causes a raised anion gap. It's a process where there is accumulation of pyroglutamic acids which is an endogenous organic acid that's an intermediate in what's known as the gamma glutamyl cycle. This is a cycle that's involved with amino acid transported to cell as well as glutathione metabolism, and it's appreciated when the normal functioning of this cycle is disrupted, pyroglutamic acidosis can occur.

Historically, we knew that there were rare inherited deficiencies in certain key enzymes that could result in pyroglutamic acidosis, but in recent decades, reports have emerged of this being an acquired condition in people who had otherwise normal enzymes.

Randy Kaye: All right, thank you. Now, when should this condition be suspected and what tests are necessary to confirm the diagnosis?

Dylan Mac Lochlainn: I think you should consider the possibility of pyroglutamic acidosis when you're presented with a patient who has a raised anion gap metabolic acidosis that is not accounted for by other more common causes such as lactic acidosis or ketosis.

Through case reports, we appreciate there are a number of risk factors for pyroglutamic acidosis and these can be sought out as clues in the presentation or in the clinical history. These include things like being female, being pregnant and having co-existing renal failure, having malnutrition, having sepsis and being on certain medication such as flucloxacillin or the anticonvulsant dabigatran or perhaps most importantly being on acetaminophen or paracetamol. It's appreciated that therapeutic doses of this can result in pyroglutamic acidosis especially with long-term use.

With regard to confirming the diagnosis, in our case, we did this through gas chromatography-mass spectrometry. We ordered a urine re-organic acid profile and this showed raised levels of pyroglutamic acids. Although, I appreciate from reading other case reports that plasma assays are available also.

Randy Kaye: All right, thank you. This is very interesting because pyroglutamic acidosis is not described much in the literature. How come it isn't actually, and can it be overlooked or misdiagnosed?

Dylan Mac Lochlainn: That's correct. The literature is mostly confined to isolated case reports and a few larger case series. I don't think we know the true prevalence of the condition, but there's reasonable consensus that it's under-diagnosed, particularly given how common some of its risk factors are. I read one study last year in *Scientific Reports* that suggested around 6% of their small cohort of patients with a raised anion gap metabolic acidosis had pyroglutamic acidosis.

But it probably varies between different hospital settings. It certainly can't be overlooked and it's appreciated that many centers won't have access to testing for pyroglutamic acidosis. There's also a general lack of awareness of it as a cause of a higher gap metabolic acidosis, and this is probably

exacerbated by the fact that traditional mnemonics to recall the causes of metabolic acidosis do not mention pyroglutamic acids.

Many people have called for us to use different mnemonics that include pyroglutamic acidosis and some of the other lesser appreciated differential diagnoses. I know this speaks to our experience with this case because I remember vividly being on a ward round with my consultant at the time Dr. Wigeman(ph). We referenced one of these traditional mnemonics and we didn't come up with a satisfactory explanation for our patient's case.

It wasn't until we consulted Dr. Paul Hamilton who's a co-author on this paper and his colleagues in the biochemistry department that we were able to establish the true diagnosis. I think the lesson is that even with some of the newer mnemonics, these are not generally exhaustive lists of diagnoses and where there is diagnostic uncertainty, it's always prudent to seek the input of specialists.

Randy Kaye: Okay. Well, that makes a great deal of sense. Now in your case report, the patient presented with neurological abnormalities such as speech disturbance and facial droop. Are acute neurological features commonly associated with pyroglutamic acidosis?

Dylan Mac Lochlainn: I think the short answer to that is no. A vast majority of case reports that I've read make no mention of focal neurology such as a deficit that we described in our case. Altered consciousness is somewhat commonly mentioned but not these types of focal neurological deficits. It's striking that our case resembled somewhat the case, the first ever reported case, of pyroglutamic acidosis, but we don't think, as they did not think then, that the pyroglutamic acidosis itself is causative for the neurological deficits. So, we don't think that.

You might ask me, how do we explain the acute neurological features in our case? Well, it's appreciated that the phenomenon of stroke mimic is quite common. This is where non-cerebrovascular pathology presents like acute stroke and in our patients, there was infection and perhaps medication causes that might account for this.

There's another consideration which is post-stroke recrudescence. This is the re-emergence of previous stroke related deficits in the setting of an acute illness, and while our patient didn't give a clinical history of a previous stroke, we did find an old area of infarction on brain imaging. So, there may have been some decompensation in the setting of acute illness as well to explain it. I supposed the take home message is that pyroglutamic acidosis can present in a

number of different ways to a number of hospital specialties. So, we have to be vigilant if we're going to pick it up.

Randy Kaye: All right, thank you. So just finally, are there any specific therapies for patients with pyroglutamic acidosis?

Dylan Mac Lochlainn: The mainstay of treating pyroglutamic acidosis is to address any underlying causes. So, this might involve stopping any medications that would be implicated in causing pyroglutamic acidosis, treating any sepsis or infection that the patient might have. It would also involve addressing any renal failure and also optimizing nutrition as it's appreciated that many patients with this condition are in a malnourished state.

Some cases have -- case reports have made mention of using of sodium bicarbonate also an acetylcysteine on empirical grounds because an acetylcysteine will replenish glutathione stores and glutathione deficiency is felt to be part of the underlying pathophysiology in many of these cases. However, it's important to note that the evidence for the effectiveness of these therapies is limited to case reports. So, it hasn't been robustly established.

Randy Kaye: All right, that was very interesting. Thank you so much for joining us today doctor.

Dylan Mac Lochlainn: Thank you.

Randy Kaye: That was Dr. Dylan James Mac Lochlainn, from the Oxford University Hospitals NHS Foundation Trust, describing his JALM Case Report "Bridging the Gap: Acute Neurology and a Metabolic Acidosis." Thanks for tuning in to this episode of JALM Talk. See you next time and don't forget to submit something for us to talk about.