Pernicious Anaemia, Autoimmune Metaplastic Gastric Atrophy and Achlorhydria

Pernicious Anaemia is the most common non-dietary cause of a deficiency in Vitamin B12. But its root cause is something called Autoimmune Metaplastic Gastric Atrophy (AMGA).

AMGA and Vitamin B12

The vitamin B12 molecule is too large, and too hydrophilic/lipophobic (water loving/fat hating) to pass across biological membranes unaided. To be absorbed from the gut into the bloodstream it needs to be carried across by a special protein – Intrinsic Factor (IF).

When you consume food with B12 it can be bound to protein, or free. Free B12 gets picked up by a protein found in the saliva called haptocorrin. This protects the B12 molecule from attack by stomach acid. When the B12 is passed from the stomach into the duodenum pancreatic enzymes detach the B12 from the protein.

IF is made by particular cells in the stomach, called Gastric Parietal Cells (GPCs). It passes into the duodenum where it encounters the free B12 and binds to it. The IF-B12 complex passes through the rest of the small intestine to the ileum, where special receptors grab hold of the IF-B12 and takes it out of the gut. They are separated and the B12 enters the bloodstream.

In AMGA your immune system attacks and kills these GPCs. That means you have no IF and that you cannot absorb any B12. The only way to get B12 into your system is to have injections.

Limited capacity of the IF absorption process

The amount of B12 that can be carried from the gut to the blood has a limited capacity of around 13 mcg at any one time

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AMGA and lack of stomach acid (Achlorhydria)

As well as making IF, GPCs are also responsible for making hydrochloric acid. AMGA sufferers (and, therefore, PA sufferers) will have low or no stomach acid (hypochlorhydria or achlorhydria, respectively).

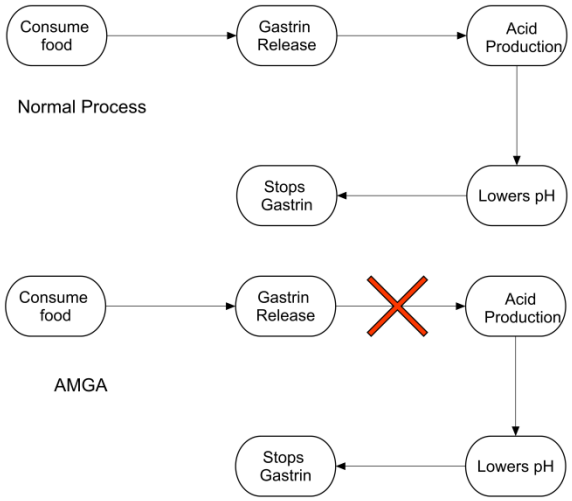
Stomach acid has several roles. It is a part of the digestion process by chemically breaking down nutrients such as proteins, fats and carbohydrates. It also activates the enzyme pepsin – an important part of the digestion of proteins. Without acid present a lot of protein will remain undigested and will make its way to the large intestine. The bacteria that live there will have a big party with that unexpected bonus of protein.

Stomach acid also plays a role in keeping gut bacteria in the large intestine, where they belong. Without stomach acid some bacteria can make their way into the small intestine to cause Small Intestinal Bacterial Overgrowth (SIBO).

Both can cause symptoms of abdominal pain, gas, bloating, diarrhoea and constipation.

Achlorhydria and gastrin

The secretion of hydrochloric acid by GPCs is controlled by the hormone gastrin. When you eat food this stimulates the production of gastrin and gastrin stimulates the production of stomach acid by the GPCs. This lowers the pH of the stomach contents, which switches off the gastrin production. It is a classic negative feedback loop.



But with AMGA there are no GPCs, so there is no acid released, the pH isn't reduced and gastrin production is not switched off. The result is high levels of gastrin in the blood – hypergastrinaemia.

This is the best test for achlorhydria as a high level of gastrin in the blood is most often caused by a lack of stomach acid. I'll look at another possible cause in the next section.

Achlorhydria and Neuroendocrine Tumours

The previous section simplified the process somewhat. Gastrin doesn't act directly on GPCs but on cells called enterochromaffin-like (ECL) cells. The ECL cells then tell the GPCs to make the stomach acid. Gastrin switches on the ECL cells, but it also stimulates the growth of ECL cells. So if there is insufficient acid being produced there will be high levels of gastrin, which will stimulate the growth of ECL cells, to tell the GPCs to make more acid.

Hypergastrinaemia will overstimulate the growth of the ECL cells. This overstimulation can result in the development of Neuroendocrine Tumours (aka NETs or gastric carcinoids).

NETs come in three types. Type 1 NETs are associated with hypergastrinaemia, achlorhydria and AMGA. Type 2 NETs are caused by hypergastrinaemia caused by a gastrinoma (Zollinger-Ellison Syndrome, normally caused by a mutation in the MEN-1 gene). If hypergastrinaemia is present then Type 2 NETs should be looked for. Type 3 NETs are not associated with hypergastrinaemia.

The best way to detect gastric NETs is to look for them in a gastroscopy. For this reason I would recommend anybody with a diagnosis of Pernicious Anaemia, or anybody with a B12 deficiency that is not due to obvious causes, should have a gastroscopy and a blood test for gastrin.

Gastric NETs (of Type 1, caused by AMGA) are described as indolent. They tend to sit around for years doing nothing at all, but there is a small chance of them progressing on the gastric cancer. That is why the treatment is commonly to monitor them with regular (annual or biennial) gastroscopies.

Review article: the investigation and management of gastric neuroendocrine tumours