CASE REPORT

Aripiprazole reversed gastroparesis in a child with 1q21.1–q21.2 microdeletion

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SUMMARY

An 11-year-old Caucasian boy, with a microdeletion in the 1q21.1–q21.2 region, had multiple medical conditions including gastroparesis documented initially at the age of 5. The patient had a history of poor feeding since infancy and had been treated for gastro-oesophageal reflux disease (GERD), constipation and multiple food allergies. As a consequence of the GERD and his concurrent immunoglobulin (IgG) subclass deficiency, the patient had multiple otolaryngologic (ENT) infections and required two sinus surgeries. The patient had poor weight gain (below the third percentile for weight-for-age) and required a short course of parenteral nutrition and eventually a gastrostomy tube. He was started on metoclopramide as treatment for gastroparesis with an increase in his appetite, oral intake and weight gain. However, severe headaches and worsening in his behaviour caused the agent to be discontinued. He had little weight gain and after a course of parenteral nutrition he was converted to a transpyloric feeding tube. Because of ongoing behavioural problems that interfered with his school performance, a psychiatrist started him on aripiprazole. After aripiprazole was prescribed at age 11, his appetite and oral intake dramatically increased and a repeat gastric emptying study was normal. The increased oral intake and weight gain continued, allowing removal of the feeding tube. More than 2 years later, on aripiprazole, he continues to gain weight without any supplemental feedings.

BACKGROUND

Gastroparesis is a condition marked by delayed gastric emptying without a mechanical obstruction, which affects up to five million persons in the US alone. The prevalence and cost associated with this condition in adults¹ and children² has dramatically increased in the last decade. In children it frequently follows a viral illness and is transient, while it is more often secondary to a variety of established conditions and remains chronic in adults. However, in children it still can persist long enough to adversely impact caloric intake and growth and lead to hospitalisation and surgical interventions. Metoclopramide (brand name: Reglan), the only Food and Drug Administration-approved medication for gastroparesis, is a dopamine D2 receptor antagonist and is also a mixed 5-HT3 (serotonin) receptor antagonist/5-HT4 receptor agonist. As a prokinetic agent, it helps to empty the stomach and increase peristalsis. However, it also penetrates the blood–brain barrier, where its antiemetic action

occurs. Long-term complications prompted a black box warning because of potentially irreversible side effects, most notably tardive dyskinesia.³

Microdeletions (MDs), the loss of small amounts of DNA from specific regions of the human genome, are now being increasingly recognised as the cause of recurring patterns of variable multiorgan dysfunction and disease. One MD which has been studied is on chromosome 1 in the region of q21.1 which has been reported to have a variable phenotype that includes failure to thrive, feeding issues, gastro-oesophageal reflux, frequent infections, and neuropsychiatric and behavioural issues.^{4,5}

Aripiprazole (brand name: Abilify) is used in adults and children to treat the symptoms of schizophrenia, mania, depression, autism and irritable behaviours, such as aggression, temper tantrums and frequent mood changes. Aripiprazole is a unique psychopharmacological agent that acts as a partial agonist on the dopamine D2 receptors. It binds with similar affinity as the *in vivo* ligand, dopamine, but yields a muted physiologic response and has been characterised as a dopamine modulator. In seemingly paradoxical fashion, aripiprazole is both an antagonist at the 5-HT2A serotonin receptor which is associated with gastric and small intestine contractions and a partial agonist on the 5-HT1 receptor which has been associated with hyperphagia.⁶ Furthermore, aripiprazole is now recognised to also induce transcription factors and cell structure proteins that influence multiple neurotransmitter circuits, unlike any other D2 receptor antagonist.⁷

CASE PRESENTATION

The oldest of three brothers, who all have an MD in the 1q21.1–q21.2 region, presented with failure to thrive related to anorexia, emesis and irregular bowel movements at the age of 16 months. He was barely able to grow at the third percentile for weight-for-age. Chromosomal analysis using fluorescence *in situ* hybridisation identified the 0.8 Mb deletion in the patient. He had received extensive therapy with a multidisciplinary team which included gastroenterologist, otorhinolaryngologist, pulmonologists, immunologists, psychologists, surgeons, a variety of therapists and geneticists. Treatments included frequent antibiotics for reflux-related otolaryngologic infections, dietary restrictions, a substantial proportion of his daily calories as an elemental formula, monthly parenteral gamma globulin replacement, acid suppression, a variety of stool

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Figure 1 Growth curve of patient highlighting clinical events. (1) Patient given short course of total parenteral nutrition. Gastric emptying study documented gastroparesis and metoclopramide started. Oral intake improved and patient gained weight. (2) Because of severe headaches, metoclopramide discontinued and intake decreased. (3) Erythromycin was started with little change in appetite and no weight gain. (4) Because of ongoing bilious emesis and diagnosis of antroduodenal dysmotility, gastrojejunal (GJ) tube placed. (5) Aripiprazole started for behavioural issues with a dramatic increase in appetite. (6) Decrease in GJ tube calories began and continued until tube feeds discontinued. After 6 months of weight gain without tube feeds, it was removed.

softeners and cathartics, nebulisers for respiratory symptoms and infections, psychopharmacological agents and ongoing counselling for behavioural issues.

INVESTIGATIONS

- ▶ A gastric emptying study was performed that documented markedly delayed gastric emptying, with a 60% of residual activity still remaining in the stomach after 4 hours. A repeat scan, years later at a paediatric gastrointestinal (GI) motility centre, yielded the same result.

DIFFERENTIAL DIAGNOSIS

- ▶ GERD.
- ▶ *Helicobacter pylori*.
- ▶ Duodenal ulcer.
- ▶ Malrotation.
- ▶ Duodenal web.
- ▶ Coeliac disease.
- ▶ Allergic gastritis.
- ▶ Allergic gastroenterology.
- ▶ Eosinophilic GI disease.

TREATMENT

Figure 1 highlights the chronology of treatments employed and their longitudinal impact on his growth. After a short course of parenteral nutrition with a rapid weight gain, he was started on metoclopramide at the age of 6 years and continued to increase his weight. At that time his weight-for-age Z-score dramatically increased from -2.2 to $+0.5$. The medication led to worsening behaviour and it was stopped after several months with a worsening of his Z-score over the next several years, reaching a nadir at -0.95 . He was referred to a regional motility centre where gastroparesis was again confirmed and a more widespread disorder, including antroduodenal dysmotility, was diagnosed at the age of 9 years. Subsequently at the age of 10, a gastrojejunal (GJ) feeding tube was placed to allow him to increase enteric feeds to gain weight without experiencing gastro-oesophageal reflux complications. Tube feeding allowed him to gain

weight rapidly and his weight-for-age Z-score again improved to -0.2 . Because of worsening school behaviour that had led to a transfer to his third school, aripiprazole was started by a psychiatric consultant at age 11. Soon afterwards, the persistent mild nausea disappeared. He began to eat more frequently and larger amounts, leading to more rapid weight gain. The tube feedings were slowed down and ultimately were discontinued with sustained weight gain at age 12.

OUTCOME AND FOLLOW-UP

A repeat gastric emptying study on aripiprazole demonstrated less than 8% of radiolabeled material remaining in the stomach after 4 hours, which was interpreted as normal. After 6 months without any administration of enteral feedings through the tube (23 months after starting aripiprazole), it was removed with ongoing weight gain and no nausea. The increased appetite, increased intake and weight gain has continued for more than a year. His Z-score is slowly approaching average, with the most recent value of -0.6 . At one point, the psychologist attempted to lower the dose of aripiprazole; in less than a week, nausea returned with anorexia. When the dose was restored, the patient's appetite returned. This observation is consistent with the clinical profile of this agent which can include increased appetite and weight gain.

DISCUSSION

Gastroparesis is a challenging problem to treat pharmacologically in children and adults whose prevalence and cost are rising dramatically. The only approved therapies involve dopamine receptor antagonists but they are associated with significant central nervous system side effects.

As of now, there have been no reported cases of aripiprazole being used to treat gastroparesis.

Aripiprazole is a unique dopamine agonist that has been characterised as a dopamine regulator or stabiliser. In our case study, it yielded a significant subjective and objective improvement in gastric emptying and nutritional intake. As the onset of action is rapid, a trial of aripiprazole in patients with gastroparesis is a

simple, non-invasive, cost-effective option that can be employed in patients who are suffering from this condition. If aripiprazole is proven to reverse gastroparesis in placebo-controlled trials, investigating its pharmacology may lead to a better understanding of the complex signalling pathways which regulate gastric emptying.

Olanzapine is another psychopharmacological agent believed to work by antagonising dopamine D2 receptors and 5-HT_{2A} receptors. Presently, a clinical trial is recruiting participants to measure the effectiveness of olanzapine in treating gastroparesis in an adult population. This study may yield further insights into the role of these transmitters as anti-nausea and promotility agents in the stomach.

Learning points

- ▶ Microdeletions pose multiple problems to care providers and require a multidisciplinary team to deliver optimal care.
- ▶ Gastroparesis when chronic is extremely challenging to treat effectively and safely.
- ▶ Because of its unique pharmacology, aripiprazole can be considered as a potential safer, less costly and non-invasive alternative to permanent transpyloric feeding tube placement. Understanding all aspects of its mode of action may also provide clues into the complex set of signals which regulate gastric emptying.

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