

## Plasmapheresis-Induced Hypercalcaemia

\*Anas-Alwogud Abdelmogheth, Islam El-Baroudy, Saif Al-Yaaruby

### فرط كلس الدم الناتج عن فصل البلازما

أنس الوجود عبد المغيث، إسلام البارودي، سيف اليعربي

**الملخص:** متلازمة جيلان باريه هي مرض يصيب الأعصاب والجذور العصبية بالتهاب حاد مما قد يؤدي إلى شلل حركي كلي في بعض الحالات الشديدة. ونادرا ما تم تسجيل ارتفاع مستوى الكالسيوم بالدم في هذه المتلازمة. تحتاج هذه إلى متلازمة إلى العلاج عن طريق فصل البلازما وهو إجراء يتبع لتنقية الدم من الشوائب ذات الوزن الجزيئي الكبير. من الناحية النظرية فإن ارتفاع الكالسيوم بالدم لم يوصف كمشكلة متعلقة بفصل البلازما إلا إذا كان هناك مسبب آخر إلا أن ذلك لا يمنع أنها سجلت بالفعل في بعض الحالات النادرة. نحن نتعرض بالدراسة لحالة نادرة من متلازمة جيلان باريه وهي طفل يبلغ من العمر 8 سنوات، إذ إنه إلى جانب الأعراض المعتادة للمرض والتي تتلخص في الصداع، وازدواج الرؤية، والحوال متبوعة بفقدان الوعي والشلل الكلي بعد مرور أسبوع إلا أنه وبعد استجابة الطفل للعلاج الذي يتمثل في إعطاء الأجسام المضادة عن طريق الوريد وفصل البلازما تم ملاحظة ارتفاع حاد بمستوى الكالسيوم بالدم عن طريق الفحص المعمل. كما وجد أن هذا الارتفاع مرتبط بشكل وثيق بجلسات فصل البلازما دون العثور على أى مسبب آخر. مما دعانا إلى استعراض مثل تلك الحالات النادرة في المراجع الطبية في محاولة لإيجاد تفسير معقول لها.

**مفتاح الكلمات:** فصل البلازما، فرط كالسيوم الدم، متلازمة جيلان باري، تقرير حالة، عمان.

**ABSTRACT:** Guillain-Barré syndrome (GBS) is an acute inflammatory polyradiculoneuropathy that can cause total motor paralysis in severe cases. Reports of hypercalcaemia in patients with GBS are rare. Plasmapheresis, an extracorporeal blood purification procedure for the removal of large molecular weight substances, is a well-established therapy for ventilated GBS patients. Although it has been observed in a few reported cases, theoretically, hypercalcaemia is not described as a plasmapheresis-related problem unless there is an underlying cause. We present a rare case of an 8-year-old child presenting with headache, diplopia, and squint, followed by disturbed conscious levels and paralysis. He was treated with both intravenous immunoglobulin and plasmapheresis, with a favourable outcome. We made a laboratory observation of hypercalcaemia which was associated with the plasmapheresis therapy without any related underlying cause. This raises the need for similar observations and the gathering of other possible acceptable explanations.

**Keywords:** Plasmapheresis; Hypercalcemia; Guillain-Barré syndrome; Case report; Oman.

**G**UILLAIN-BARRÉ SYNDROME (GBS) is characterised by acute areflexic paralysis with albuminocytologic dissociation (i.e. high levels of protein in the cerebrospinal fluid and normal cell counts). Since poliomyelitis has nearly been eliminated, GBS is currently the most frequent cause of acute flaccid paralysis worldwide and constitutes one of the serious emergencies in neurology. A common misconception is that the GBS has a good prognosis, but up to 20% of patients remain severely disabled and approximately 5% die, despite immunotherapy.<sup>1</sup>

Plasmapheresis is a procedure for the removal, treatment, and return of blood plasma or its components to blood circulation. It is also known as therapeutic plasma exchange and is increasingly

used in critically ill patients.<sup>2</sup> It has been used effectively and safely in the treatment of GBS in children weighing more than 10 kg. The treatment protocol is to perform plasmapheresis 4–6 times on an alternate-day schedule.<sup>3</sup> The basic procedure consists of removing blood, separating blood cells from plasma, and then returning those blood cells, which are diluted with fresh plasma substitute, to the body's circulation. Fresh plasma is not routinely used because of concerns over viral contamination or allergic reactions. The most common substitute is a saline solution with sterilised human albumin protein. Plasmapheresis requires the insertion of a venous catheter, either in a limb or central vein. The discontinuous flow centrifugation method needs only one venous catheter line. Using this,

approximately 300 ml of blood is removed at a time and centrifuged to separate plasma from blood cells. When blood is outside the body, a citrate-based anticoagulant is given to prevent it from clotting—most commonly trisodium citrate or acid citrate dextrose (ACD) formula A, the latter being the one that is used in our institute. It has become popular as a regional anticoagulant for these procedures as it minimises the risk of haemorrhage or thrombocytopenia, which is associated with the use of heparin.<sup>4</sup> Non-critical hypocalcaemia and metabolic alkalosis have been associated with such treatment. To prevent this complication, calcium is infused intravenously while the patient is undergoing the plasmapheresis.<sup>5</sup> Hypercalcaemia, although reported anecdotally, is not a common complication of plasmapheresis.<sup>6</sup>

## Case Report

A previously healthy 8-year-old boy was referred to our paediatric ward from the ophthalmology department (OPD) of Sultan Qaboos University Hospital, Muscat, Oman, for evaluation of persistent severe headaches. His history was unremarkable until a few days before presentation when he suddenly had an episode of severe headache followed by diplopia and a convergent squint. The clinical examination revealed normal temperature (36.8° C), a pulse rate of 55–65 beats/minute, a respiratory rate of 30 breaths/minute, and an O<sub>2</sub> saturation of 96–98% on room air with good peripheral perfusion. There were no signs of dehydration. The initial neurological examination and the rest of the clinical examinations were unremarkable. An urgent computerised tomography (CT) scan of the brain followed by a magnetic resonance imaging (MRI) scan were both completely normal. He was labelled as *pseudotumor cerebri* and was started on intravenous (IV) methylprednisolone and mannitol.

Initial laboratory tests showed the following results: haemoglobin 11 g/dl; platelets 338 x 10<sup>9</sup>/L; white blood cells 11.9 x 10<sup>9</sup>; absolute neutrophilic count 9.5 x 10<sup>9</sup> and lymphocytes 1.8 x 10<sup>9</sup>; haematocrit 0.34 L/L; C-reactive protein (CRP) 1 mg/L; erythrocytes sedimentation rate 10 mm/h; sodium (Na) 132; potassium (K) 4; creatinine 35; urea 6.8 mmol/L; total calcium (Ca) 2.1 mmol/L; ionised Ca 1.1; PO<sub>4</sub> 1.1 mmol/L; alkaline phosphatase

247 u/L; albumin 35 g/L, and total protein 69 g/L. Arterial blood gas was normal (PH 7.38, PCO<sub>2</sub> 37.8, PO<sub>2</sub> 88.3, HCO<sub>3</sub> 23, BE -1.6), and urinalysis, urine culture, and blood cultures were normal until discharge. A coagulation profile was normal with a prothrombin time (PT) of 11.9 seconds, an activated partial thromboplastin time (APTT) of 38 seconds, and an international normalised ratio (INR) of 1.13.

On day 6 of admission, the child had a rapid clinical deterioration of consciousness level with severe hypertension and bradycardia, and was moved to the Paediatric Intensive Care Unit (PICU) where he was ventilated. A repeat CT brain scan and a spinal tap revealed no evidence of increased intracranial tension; it was decided to discontinue the steroids and mannitol. A subsequent set of investigations revealed a positive serum polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) and a delayed nerve conduction study (NCS). A fluoroscopy-guided lumbar puncture revealed clear cerebral spinal fluid (CSF), no white blood cells (WBCs), red blood cells (RBCs) at 450, protein levels at 1.3 g/L, and glucose levels at 3.4 mmol/L.

The child then was diagnosed with an atypical presentation of GBS and treated with a two-day course of IV immunoglobulin (2 gm/kg). His blood pressure (B/P) and heart rate were fluctuating, reflecting a severe autonomic lability that was subsequently controlled by a labetalol infusion. A course of plasmapheresis was tried every other day, for a total of 5 sessions, and the child achieved a dramatic improvement.

In accordance with our guidelines, plasmapheresis was initiated with ACD formula A, an anticoagulant, in combination with a calcium-free, alkali-free dialysate. However, a CaCl<sub>2</sub> infusion was held to assess the response following the session. Surprisingly, both the total serum Ca and the albumin-adjusted Ca were high (3.33 and 3.38 mmol/L, respectively). Moreover, the ionised Ca level was high (1.5 mmol/L). A quick revision for the infused fluid and hydration status, and urine output before and after the procedure was unremarkable as reflected by the following laboratory results: albumin 38 g/L, PO<sub>4</sub> 1.4 mmol/L, Na 139, K 3.4, Cl 102, bicarbonate 26, creatinine 19, urea 6.5, haematocrit 0.32 L/L, anion gap 11, pH 7.37, and alkaline phosphatase was slightly high (483 u/L).

Other specific investigations related to hypercalcaemia included normal 25-hydroxy

**Table 1:** Significant laboratory investigation results before, during, and after the plasmapheresis sessions

Parameter	Timing	Before the sessions	1st Session		2nd Session		3rd Session		4th Session		5th Session		After the sessions	After 1 month
			Before	After										
Ca (albumin adjusted) (2.1-2.55 mmol/L)		2.23	2.3	3.38	2.3	2.94	2.52	3.29	2.59	2.87	2.59	2.64	2.55	2.19
Free ca (0.9-1.1 mmol/L)		1.07	1	1.5	1.1	1.38	1.02	1.4	1.1	1.37	1.06	1.34	1.03	1.08
PH (7.35-7.45)		7.37	7.33	7.43	7.38	7.41	7.36	7.41	7.39	7.41	7.33	7.36	7.37	7.39
Creatinine (30-47 umol/L)		22	20	19	21	17	18	29	21	21	18	19	18	20
Alkaline phosphatase (145-420 u/L)		247	205	483	395	441	405	469	392	436	381	427	308	226

vitamin D 1,25-dihydroxy vitamin D and a normally suppressed parathyroid hormone level of 0.8 pmol/L, free thyroxin 18 pmol/L (10–28 pmol/L), thyroid stimulating hormone (TSH) 3.9 mIU/L (0.7–6.4 mIU/L) and a cortisol level of 354 nmol/L at 8:00 hrs.

Frusemide (2 mg/kg/dose) was given after the first session of plasmapheresis and both total Ca and albumin-adjusted Ca levels normalised before the next session.

Hypercalcaemia followed by normal calcium levels occurred in all the subsequent sessions of plasmapheresis [Figure 1] and the whole set of initial investigations was done following each session [Table 1].

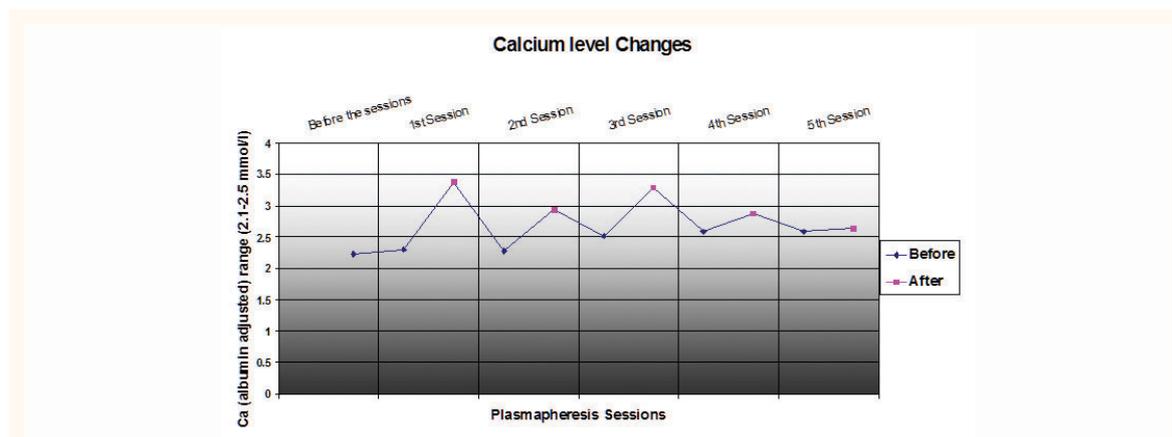
Interestingly, there were no clinical signs of hypercalcaemia such as headache, irritability, ileus, epigastric pain, bone pains, conjunctivitis, respiratory distress syndrome (RDS), or arrhythmia. The episodes were not treated by frusemide and the hypercalcaemia disappeared spontaneously. An electrocardiogram (ECG) was normal after each session. Serum Ca levels returned to normal after the cessation of the sessions and continued to be normal during one month of follow-up after discharge. Intensive physiotherapy was continued over a period of 6 months until the patient experienced a complete recovery.

## Discussion

We report a very rare presentation of hypercalcaemia induced by plasmapheresis in a child with GBS. Hypocalcaemia is a common side-effect in children exposed to plasmapheresis as the anticoagulant used commonly combines with serum calcium. Of interest, the hypercalcaemia was not persistent and occurred only immediately after the plasmapheresis sessions, even though it was normal before, during, and after the sessions.

The aetiology of hypercalcaemia falls into two major categories: parathyroid and non-parathyroid. In children and adolescents, hypercalcaemia is most often related to primary hyperparathyroidism. Primary hyperparathyroidism is characterised by an excessive secretion of parathyroid hormone (PTH) from the parathyroid glands.<sup>7</sup> The diagnosis is best confirmed by demonstrating persistent hypercalcaemia in the presence of PTH concentrations above the reference interval.<sup>8</sup> This diagnosis was ruled out in our case as the hypercalcaemia was transient, with a normal PTH value.

Non-parathyroid causes of hypercalcaemia, including vitamin D toxicity, malignancy, fungal infection, thyrotoxicosis, and Addison's disease were ruled out as their clinical manifestations and the laboratory findings (normal levels of thyroid-stimulating hormone [TSH], total and



**Figure 1:** Changes in calcium levels before starting and in between the plasmapheresis sessions.

free thyroxine, and cortisol, and normal negative cultures and complete blood count [CBC]) did not fit in our case.<sup>9</sup>

Iatrogenic causes such as total parenteral nutrition (TPN) and medications were also reviewed. TPN initially started with 0.5 mmol/kg/day maintenance calcium on the first day and was discontinued immediately after the first high calcium level. Subsequent TPNs were calcium-free. Vitamin A, thiazide, and theophylline were not used at any time. The hydration status of the patient was observed daily for clinical signs and on a laboratory basis. The patient was found to be euvoletic throughout his illness; we targeted a zero balance daily, especially during the plasmapheresis sessions. Moreover, the child did not show any evidence of metabolic acidosis which is commonly associated with hypercalcaemia.<sup>9</sup> Pseudohypercalcaemia was also excluded in our case as both the total and ionised calcium levels were high.<sup>9</sup>

More recently, a lot of interest has been directed toward the calcium-sensing receptor (CaSR) as a regulator of Ca metabolism. It is primarily expressed by the kidneys and parathyroid gland controlling PTH secretion, and Ca reabsorption is performed in the renal tubules based on the extracellular calcium level. Inactivation of this receptor can cause hypercalcaemia.<sup>10</sup>

Calcium-citrate complex may affect the bone resorption mechanism leading to calcium efflux from the bone to the blood stream, elevating both total and ionised Ca.<sup>11</sup> The mildly elevated alkaline phosphatase in our case after each session was indirect evidence that bone resorption had occurred [Table 1].

Plasmapheresis in some unusual settings, such as in the case of atypical GBS, may affect the extracellular Ca balance, therefore inactivating the CaSRs resulting in hypercalcaemia with an increase in both total and ionised Ca. This inactivation is related to the plasmapheresis period; hence, the hypercalcaemia is transient. Moreover, there may be a mild and transient ineffective removal by the kidneys of the Ca-citrate complex which would also lead to hypercalcaemia. Additionally, it is possible that atypical GBS affects the CaSR as part of the neuropathy; however, we failed to find any association in the literature.

## Conclusion

In conclusion, we want to highlight the importance of monitoring changes in plasma Ca concentrations during plasmapheresis in order to avoid the routine administration of unnecessary and even dangerous IV Ca to patients who may be prone to hypercalcaemia in certain situations.

## References

1. Yuki N, Hartung HP. Guillain-Barré syndrome. *N Engl J Med* 2012; 366:2294–304.
2. Kaplan AA. Therapeutic plasma exchange: Core curriculum 2008. *American J Kidney Dis* 2008; 52:1180–1219.
3. Ryan MM. Guillain-Barré syndrome in childhood. *J Paediatr Child Health* 2005; 41:237–41.
4. Haupt WF, Rosenow F, van der Ven C, Birkmann C. Sequential treatment of Guillain-Barré syndrome with extracorporeal elimination and intravenous immunoglobulin. *J Neurol Sci* 1996; 137:145–9.

5. Roberts WH, Domen RE, Walters MI. Changes in calcium distribution during therapeutic plasmapheresis. *Arch Pathol Lab Med* 1984;108:881–3.
6. Meythaler JM, Korko AB, Nanda T, Kumar NA, Fallon M. Immobilization hypercalcemia associated with Landry-Guillian-Barré syndrome: Successful therapy with combined calcitonin and etidronate. *Arch Intern Med* 1986; 146:1567–71.
7. Kollars J, Zarroug AE, van Heerden J, Lteif A, Stavlo P, Suarez L, et al. Primary hyperparathyroidism in pediatric patients. *Pediatrics* 2005; 115:974–80.
8. Davies M, Fraser WD, Hosking DJ. The management of primary hyperparathyroidism. *Clin Endocrinol (Oxf)* 2002; 57:145–55.
9. Jacobs TP and Bilezikian JP. Rare causes of hypercalcemia. *J Clin Endocrinol Metab (JCEM)*. 2005; 90:6316–22.
10. Claudius IA, Nakamoto J, Fattal O. Pediatric hypercalcemia. From: [www.eMedicine.Medscape.com](http://www.eMedicine.Medscape.com) Accessed: Apr 2012.