If case reports be the food of knowledge, write on: our *Cases of the Quarter*

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Abstract

The value of publishing case reports has long been debated and the arguments are summarised. Last year, to encourage trainees, the Royal College of Physicians of Edinburgh's Senior Fellows Club inaugurated an annual prize for the best case report or case series published in the *Journal of the Royal College of Physicians of Edinburgh* by a doctor in training. Some of the highlights of last year's entries are reviewed, commented on and developed. They include cases of myelofibrosis and cherubism due to secondary hyperparathyroidism from renal failure; reversible blindness in diabetic ketoacidosis; the long QT syndrome; ictal asystole; giant cell arteritis; tumour necrosis factor-α inhibition in Lyme borreliosis; and cannabis hyperemesis syndrome.

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Throughout medical history the case report has been indispensable in advancing knowledge. However, progress in experimental methods, developments in clinical trials and resolute focus on evidence-based medicine has relegated case reports, as one observer has put it, 'to the lowest form of intellectual life'.[1] The arguments have been well rehearsed. Case reports certainly have limitations. Their findings are not generalisable, yet there is a tendency for their authors and readers to over-interpret them. They are subjective and open to information bias.[2] There is an emphasis on the rare and the 'me too', like 'we report only the fourth such case in the literature', without adding any new insight or hypothesis.[3] They may be poorly written and referenced, left to the most junior member of the team. Many journals avoid them because of the negative influence on their impact factor or, as amusingly described, 'banish them like some primitive peoples, to the tribal reservations of the correspondence columns and the electronic pages'.[4]

Yet their value out-weighs their limitations. They can flag-up new conditions or potential new aetiologies or treatments, add to knowledge and experience of rarities, generate hypotheses, opening the gate to more refined and complete research, aid learning and change practice.[1,2,5] They are an important vehicle for adverse anecdote,[6,7] despite 'anecdotal' being a pejorative in scientific medicine. The reporting of errors or near misses should be encouraged. They are often a stimulating and entertaining read, and their detail immediately educative for the busy doctor.

The past year has seen a particularly good run of case reports in the *Journal of the Royal College of Physicians of Edinburgh* (*JRCPE*). Gratifyingly, this has coincided with the introduction by the Royal College of Physicians of Edinburgh's (RCPE) Senior Fellows Club of an annual Case of the Quarter Prize (CQP) for the best case report or case series whose first-named author is a trainee. The Club has sponsored the College Journal Prize (CJP) since 2011 for the best clinical paper. Now there will be two trainee prizes: the CJP, for the best clinical investigation or audit, and the CQP.

Eleven case reports from the quarterly *JRCPE* issues, December 2018 to September 2019, were eligible for consideration by a panel of six: two *JRCPE* editors, two senior fellows, and the chairman and recent past chairman, now consultant, of the RCPE's Trainees and Members Committee. Each marks according to a scheme and the top score agreed at a meeting.

The following highlights, comments on and develops some of the year's learning points.

Renal failure, parathyroid hormone, myelofibrosis and cherubs

Yeo et al.'s fascinating paper, *Renal failure and progressive pancytopenia*,[8] reports the fact, unknown to the panel (including two endocrinologists), that hyperparathyroidism (HPT), primary and secondary, can cause myelofibrosis. It also introduced the panel to cherubism.

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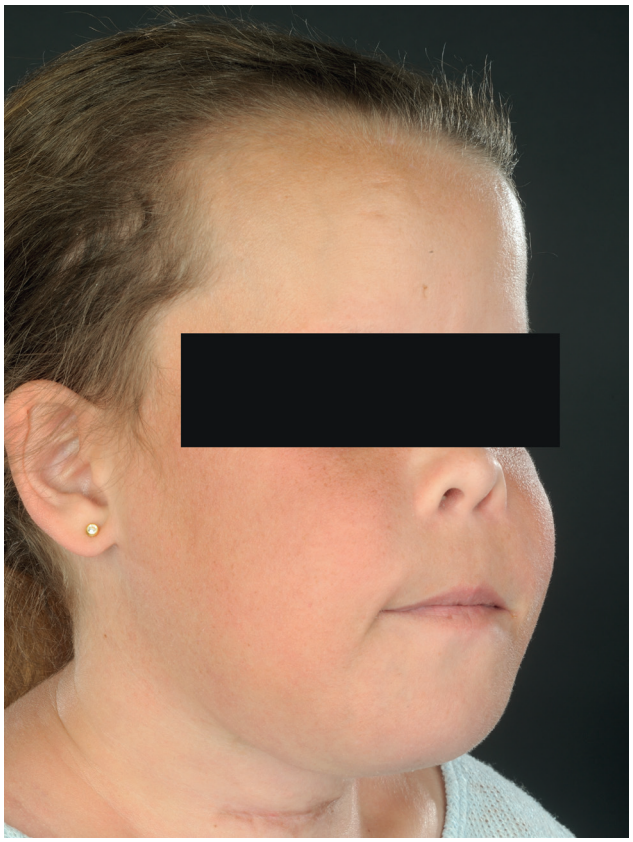
Figure 1 Cherubism appearance from bony swellings in the maxilla and mandible in a case of myelofibrosis due to secondary hyperparathyroidism from renal failure



The patient was a 24-year-old female with chronic renal failure due to reflux nephropathy, on haemodialysis for 4 years following a failed live kidney donor transplant. Despite erythropoietin she remained anaemic, haemoglobin 78 g/l, white blood cells 0.4 × 10^9/l and platelets 131 × 10^9/l. Her blood film was leucoerythroblastic. Bone marrow aspirate was dry and trephine showed reticulin grade 4/4 fibrosis. While hypocalcaemia was corrected, her parathyroid hormone (PTH) rose to 550 pmol/l. Her facial appearance became cherubic (Figure 1) and CT confirmed fibrocystic lesions – presumed 'brown tumours' – in her maxilla and mandible. After total parathyroidectomy, her blood count and film normalised within 3–6 months. She awaits a second transplant.

Brown tumours are a form of osteitis fibrosa cystica, composed of masses of fibrous tissue and bone and appear brown to the naked eye. They can affect any bone but typically occur in the maxilla and mandible, the resultant facial swelling resembling the artistic depiction of cherubs. Cherubism can also occur in very rare familial disorders in which there are self-limiting fibrous multilocular cysts in the maxilla and mandible.[9] There is the equally rare familial (primary) hyperparathyroidism-jaw tumour syndrome, with which various renal abnormalities can be associated, but the ossifying fibromas in the jaw and maxilla seem not to cause the symmetrical swellings of cherubism and their histology is distinct from brown tumours.[9]

Yeo et al. discuss possible mechanisms whereby PTH may cause myelofibrosis: by releasing cytokines, including platelet-derived growth factor-α, that stimulate fibroblasts; and by activating the cAMP pathway that stimulates bone marrow stromal cell proliferation. PTH also has a direct toxic effect on erythropoietin synthesis and erythroid precursors. The concept that molecular mechanisms regulating bone homeostasis can have a fundamental influence on the haemopoietic marrow is established.[10] It would seem unsurprising that the processes responsible for the 'fibrosa' of osteitis fibrosa cystica might also more generally impact on the marrow.

Yeo et al. conclude that since the pancytopaenia, and by implication the myelofibrosis, recovered after parathyroidectomy, they must have been due to the secondary HPT. The message is: suspect secondary myelofibrosis in renal failure with pancytopaenia or erythropoietin-refractory anaemia.

It would be interesting to know if there was other radiological evidence of HPT, as expected here; to repeat the bone marrow; and to hear if the cherubism is regressing.

Possible pH-dependent reversible blindness

Reversible blindness secondary to severe diabetic ketoacidosis,[11] is another most educative paper. The case was a 45-year-old, type 1 diabetic with sudden bilateral blindness after 2 weeks gastrointestinal upset. She had severe diabetic ketoacidosis (DKA): plasma glucose 34.9 mmol/l, pH 6.8, serum bicarbonate 3 mmol/l, capillary ketones 4.9 mmol/l, blood pressure 112/76 mmHg. There were roving eye movements but no retinal or other eye sign, though her pupils had been pharmacologically dilated. With standard treatment, her acidosis and eyesight normalised in 3 days.

Oun et al. list other causes of acute reversible blindness in DKA: bilateral posterior circulation stroke, posterior reversible encephalopathy syndrome, nonarteritic anterior ischaemic optic neuropathy and posterior ischaemic optic neuropathy. All of these were excluded. They found only four recorded cases like their own and three (though there are five) with similar acute reversible blindness in alcoholic ketoacidosis or lactic acidosis. The common factor in all was a severe metabolic acidosis, pH 6.71–6.96, with one outlier at 7.12.

Oun et al. reference a study in rabbits, showing that at pH 7.0 or less there is electrical uncoupling of retinal horizontal cells.[12] These cells modulate signals from the photosensitive rods and cones and it has been postulated that similar uncoupling might explain the blindness in these patients. But, if so, why this blindness should be so rare is unclear to me. Retinal horizontal cell ablation in mice only mildly affected vision, though the cell loss was gradual, giving time for compensatory remodeling.[13]

One aspect not broached is whether such patients should receive sodium bicarbonate ($NaHCO_3$). This is prohibited in

the Scottish DKA Care Pathway by which Oun et al.'s patient was managed. Given the known potential disadvantages of $NaHCO_3$, in particular that it may worsen intracellular acidosis and seems not to hasten pH recovery, perhaps it is best avoided even in this alarming presentation. However, it was given without obvious detriment in at least seven of the nine other severely acidotic cases identified in the literature. Whether it helped is impossible to say.

Blackouts: cardiac or neurologic?

Two extremely well-written papers describe errors in attributing transient loss of consciousness (TLOC) to the wrong aetiology: one by Wereski et al., *Syncope in a new mother: a case of long-QT syndrome presenting after childbirth*,[14] in which the cardiac diagnosis was missed and mistaken for epilepsy; the other by Mbizvo et al., *Ictal asystole: a diagnostic and management conundrum*,[15] in which asystole was considered the cause of seizures when the converse proved true.

Misdiagnosing the long QT syndrome (LQTS) for epilepsy is not uncommon, mistaking myoclonic jerks from cerebral anoxia for primary seizure activity and somehow missing clinical signs of syncope. In this case, polymorphic ventricular tachycardia (torsade de pointes) on an electrocardiogram (ECG) was also mistaken for artefact from rhythmic limb jerking during an attack. A concurrent abnormal electroencephalogram was thought to confirm epilepsy. It is helpful – and brave – of Wereski et al. to report this, for the confident interpretation of the ECG waveform may well be difficult in this situation. Their patient proved to have the KCNH2 gene mutation of type 2 congenital LQTS.

It is also easy to miss the diagnosis on ECG. A study 15 years ago documented that <50% of cardiologists and <40% of noncardiologists could properly calculate a corrected QT interval (QTc).[16] The most common error was underestimating it in patients with LQTS and overestimating in healthy subjects. Hopefully, we are better now because we can not yet rely on automated reports. Wereski et al. emphasise that the QTc is rarely static and can be normal at times in LQTS, as happened in their patient. They suggest that a QTc of 500 ms or more should raise the possibility of LQTS. I would worry at any value above normal (males 440 ms, females 460 ms) in repeated unexplained TLOC, especially on vigorous physical activity or in acute emotion, while swimming, at night or on awakening, with sudden loud noises, when febrile or, as emphasised by Wereski et al., during the 9-month postpartum period or where there is a family history of sudden death. These are all features suspicious of LQTS.[17–19]

Untreated, fatal dysrhythmias can occur, whereas early identification and treatment much reduces mortality. The International LQTS Prospective Registry, inaugurated in 1979, soon documented a dramatic reduction in mortality from 53% untreated with antiadrenergic interventions, to 9% treated, at 15 years from the first syncopy.[17] Moreover, as Wereski et al. state, because of the autosomal dominant inheritance of many cases early diagnosis can benefit a whole family. Yet, in 39% of patients with LQTS diagnosis can be delayed for years, especially in those treated for epilepsy.

Mbizvo et al. describe two patients with TLOC in whom careful history revealed a prodrome of déjà vu. However, found to have asystole during attacks, permanent pacemakers (PPM) were inserted and antiepileptic drugs (AED) withdrawn on the assumption the blackouts were primarily cardiac. While TLOC were abolished, the seizures worsened, ictal asystole was diagnosed and AED resumed.

Ictal asystole, perhaps not as rare as thought,[20] is defined as an R–R interval of >3–4 s during a seizure, the mean duration of ventricular standstill being 20 s. In a minority, asystole continued into the postictal phase and half of these were fatal. 90% of seizures are temporal lobe, asystole possibly due to stimulation of the central autonomic network.

Mbizvo et al. discuss the justification for PPM. They argue that the initial response to AED and the maintenance of seizure control, which alone might prevent asystole, are unpredictable; the risk of harm from syncope is high; and a causal role for ictal asystole in sudden unexplained death in epilepsy, though debatable, remains possible. So, too, is a causal role for LQTS misdiagnosed as epilepsy. One recent latter case is an excellent exemplar of this, the patient, treated as epileptic for 15 years, was found in ventricular fibrillation during a nocturnal seizure and was very lucky to survive.[19]

The lesson: take a good probing history in anyone with TLOC.

Delay in diagnosing and treating giant cell arteritis

Why does this still happen? Healy et al.[21] report a man, aged 72 years, in whom corticosteroid treatment for giant cell arteritis (GCA) did not prevent further cerebellar infarction from bilateral vertebral artery occlusion and infarcts, both already evident on MRI and CT angiography at presentation and before treatment. He gave a 10-month history of jaw claudication, scalp tenderness and general malaise. His temporal arteries were not tender but his erythrocyte sedimentation rate was 120 mm/hour. Whether or not he had headache or his temporal arteries were pulsatile is not mentioned, nor why he had the initial MRI made clear.

He was treated with aspirin and clopidogrel. GCA was then clinically diagnosed and corticosteroids begun, starting with 3 days intravenous methylprednisolone. On the fourth day he developed ataxia, nystagmus and dysarthria and was transferred to a regional neurosciences centre. Repeat MRI showed infarct progression and temporal artery biopsy confirmed GCA. Because of worsening cerebellar symptoms, cyclophosphamide was added. Surprisingly, the patient did well, bilateral vertebral artery occlusion in GCA having a 75–80% mortality rate.

Progression in neurological pathology despite corticosteroid treatment is the main implied message. However, the

deterioration seems hardly surprising, considering the very long delay in diagnosis and treatment and the already well-established vasculitis. The important learning point should be to think of GCA, particularly in the elderly. His 10-month history was classical. Healy et al. diplomatically acknowledge that even on admission the diagnosis only became apparent 'on thorough review of the history'. The patient was lucky to retain his sight and recover so well.

We are reminded that temporal artery biopsy has a sensitivity of 70–90+%, a negative test not excluding the diagnosis, and that prior steroid treatment for 1–2 weeks has little effect on the diagnostic histology. Treatment in suspected cases need not, therefore, be delayed for a biopsy. The British Society for Rheumatology states that the histology can remain positive for 2–6 weeks.[22] I would not delay biopsying that long.

Drugs for steroid-refractory cases are helpfully discussed and also the important question of whether adjuvant antiplatelet drugs or even anticoagulants should be used. A recent clinical update advises aspirin 75 mg daily be considered in all cases.[23]

Tumour necrosis factor-α inhibition and Lyme disease

Bulteel et al.'s[24] interesting paper seeks to provide reassurance that in patients on tumour necrosis factor-α (TNF-α) inhibiting drugs who contract Lyme borreliosis it is safe to reintroduce these drugs once the Lyme disease has been treated. This is important because there are an increasing number on immunosuppressant therapy and the incidence of Lyme disease is rising. The concern is that TNF-α may be protective in the immune response to the Lyme spirochaete and help prevent its dissemination. Bulteel et al.'s patient was taking certolizumab for a seronegative inflammatory arthritis and presented with a systemic febrile illness with a widespread targetoid rash. Investigations confirmed an early disseminated *Borrelia burgdorferi* infection and her immunosuppressive medication stopped. One week after completing a 2-week course of doxycycline it was restarted without trouble.

The paper discusses the immune response to *Borrelia* and the possible role of TNF-α. It makes educative reading for the nonspecialist. My only criticism is that, given this appears to be the first case of disseminated borreliosis in which, following antibiotic treatment, TNF-α inhibition has been reintroduced, I would have been more cautious in declaring this safe. Bulteel et al. support their positive tone by quoting a paper in which infliximab was used without detriment in antibiotic-refractory Lyme arthritis.[25] However, this paper included only four patients on the drug and its authors expressed a reluctance to generally recommend it for Lyme arthritis because of their limited experience and the risk of aggravating any ongoing joint infection. Indeed, the certolizumab in Bulteel et al.'s patient may well have been responsible for the early dissemination of infection, as Bulteel et al. themselves point out.

Cannabis hyperemesis syndrome: still under-recognised

Cannabis (or cannabinoid) hyperemesis syndrome (CHS) – cyclical vomiting in chronic cannabis users relieved by frequent hot water bathing and cured by stopping cannabis – was first reported in 2004.[26] Yet, as Lua et al.'s paper[27] describes, it remains under-recognised and failure to think of it in cyclical vomiting leads to unnecessary investigations.

Their patient was a 23-year-old female with a 2-year history of profuse vomiting, around 10 times a day, requiring hospitalisation on at least 13 occasions. It was only when it was discovered she was a regular cannabis user – a question that had never been posed – that she was advised to stop it, her symptoms resolving almost immediately.

This paper is distinguished by the inclusion of the patient's story in her own words and she is included in the authorship, a nice touch. It is an engaging vignette and there should be more such narratives. Lua et al. discuss the differential diagnosis of cyclical vomiting; the possible pathophysiology of CHS, cannabis paradoxically having antiemetic properties; and its symptom relief by hot water. The prevalence of CHS in heavy cannabis users in one study was estimated to be as high as 32.9% and it may be fatal.[28] One, at least, of my prize-adjudicating colleagues is now enquiring about cannabis use in cyclical vomiters.

Allen et al.'s seminal paper[26] gives useful further clinical information: that chronic marijuana abuse precedes the development of CHS by several years; that there may be a prodrome of early morning sickness; and that hot water showers or baths – often by day and night – relieve the nausea, vomiting and abdominal pain within minutes, the hotter the water the better, to the extent that some have scalded themselves or run out of hot water. They considered that this continual bathing was not part of a psychosis or obsessive-compulsive disorder, but a learned behaviour which, if observed in the ward, should prompt the diagnosis.

Conclusion

Allen et al.'s paper, a case series published in 2004, demonstrates that in the twenty-first century simple clinical observations can still be vital and journals need to give them space. However, case reports must be written and referenced with the same care and clarity as any other form of research. They must have something new to say or which contributes significantly to medical experience or education. Consultants must help trainees in drafting what, for many, will be their first tentative and exciting venture in publishing. Our cases of the quarter were written and referenced well, some exceptionally so. They were educative and thought provoking.

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