Unusual presentation of more common disease/injury

'An unusual response of dental sepsis to antibiotics: parallels with the Jarisch–Herxheimer reaction'

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Spreading odontogenic infections are a common source of hospital admissions to Oral and Maxillofacial Surgery (OMFS) units. This report describes an unusual reaction to routine treatment for a spreading odontogenic infection in a healthy male with no known allergies, requiring the patient to be managed supportively in the resuscitation room. The patient deteriorated rapidly after the administration of paracetamol, intravenous fluids, steroids and antibiotics, demonstrating delusional behaviour, fever, rigors, tachycardia and hypoxia. Fever associated with sepsis can lead to confusional states, but similar symptoms have been described in the literature as a reaction to antibiotic therapy known as Jarisch–Herxheimer (J-H) reaction. This is potentially the first time a J-H like reaction has been described in the context of dental sepsis. The authors feel that the OMFS team should be aware of possible sequelae of medical therapy in patients with acute dental sepsis and be confident in their management of these complications.

BACKGROUND

Systemic response to inflammation and infection includes fever, tachycardia, tachypnoea and hypocapnia. A febrile state can lead to an altered mental state and delirium.^{1 2} The fact that this unusual presentation of febrile delirium in an otherwise healthy adult manifested a short period of time after administration of penicillin presents the possibility of this being a 'Jarisch–Herxheimer' (J-H) type reaction. J-H^{3 4} describes a reaction that occurs where large quantities of toxins are released from bacteria as their cell walls lyse due to penicillin treatment. The death of the bacteria and subsequent release of endotoxins is too rapid to allow the body to excrete them, leading to a systemic upset. Symptoms of the reaction have been described as early as the 15th century in response to mercury treatment of syphilis.⁵

The clinical presentation in this case fits with a J-H reaction and we are not aware of any similar odontogenic infection case documented.

CASE PRESENTATION

A 21-year-old man presented to accident and emergency (A&E) and was referred to Oral and Maxillofacial Surgery unit with a 1 day history of pain and swelling to the left hand side of the face. The upper left eight tooth had been extracted 2 days previously due to recurrent cheek biting and pericoronitis relating to his left lower third molar. The patient's main complaints were of significantly limited mouth opening, difficulty eating and drinking and swelling of the left side of the face. His medical history was unremarkable; he was on no regular medications, had no known allergies and no previous history of drug abuse, febrile convulsions or confusional states.

On initial examination, the patient appeared acutely unwell and was having difficulty in speaking. There was a

marked left-sided swelling in the buccal and submandibular regions. His mouth opening was restricted to 6 mm and there was no apparent swelling in the floor of the mouth.

Initial observations

Temperature 40 degrees, pulse rate (PR) 125 bpm. His blood results showed a slightly raised white cell count of 11.7 and significantly increased levels of C reactive protein 249.

Approximately 35 min after intravenous medications: amoxicillin 1 g, metronidazole 500 mg, dexamethasone 8 mg, Hartmann's solution (1 1/8 h) were administered, the patient developed rigors and became very distressed, agitated and unable to communicate normally, displaying excitable and delusional behaviour. The patient was sweating profusely and developed tonic contraction of the muscles of the hands ('la main d' accoucheur'), which was likely to be due to respiratory alkalosis from hyperventilation.

Observations at this stage

PR 166bpm, blood pressure 171/111 and oxygen saturation of 94% on 15 l/min oxygen via a facemask. Arterial blood gases revealed pO₂ decreasing from 21.5 to 9.91 kPa; pCO₂ increasing from 2.36 to 4.33 and an ECG showed sinus tachycardia. Attempts were made throughout to keep the oxygen mask on the patient but he repeatedly removed it and attempted to make himself vomit.

This episode lasted for several minutes and then the patient was more settled. He subsequently explained that during the rigors he had auditory and visual hallucinations and experienced an 'impending feeling of doom'. He was monitored closely in the resuscitation room and given morphine for analgesia. He had one further similar episode, again lasting several minutes when he was very distressed and confused, and refused to keep the oxygen mask in place.

Two hours after these episodes, the patient became much more alert and orientated and was able to communicate coherently. Observations showed his temperature and pulse to be within normal limits. He was monitored in A&E for several hours and assessed by an anaesthetist before being transferred to the ward for further management of his infection.

INVESTIGATIONS

A full mouth orthopantomogram radiograph was taken as part of the initial assessment, which showed the socket of the recently extracted upper left wisdom tooth and impacted lower left wisdom tooth.

An ultrasound of the parotid and submandibular regions showed no convincing collection at time of examination on first admission.

DIFFERENTIAL DIAGNOSIS

The patient was believed to be suffering from a rapidly spreading left submandibular and buccal fascial space infection, the primary source likely being the impacted lower left wisdom tooth. The upper left wisdom tooth had been extracted 2 days previously in an attempt to resolve the pericoronitis from the lower left wisdom tooth, which also provided a possible source of infection.

There are a number of possibilities to explain the very unusual behaviour and haemodynamic deterioration in a fit and healthy young male, which developed following administration of routine pharmacological treatment.

Sepsis

Symptoms: fever >38 degrees, PR >90 bpm, RR >20, blood gas paCO_2 <4.3 kPa, tachypnoea – all of which were present with this patient.

Sepsis, particularly when associated with high fever, can present with confusion and delirium.¹ However, febrile confusional states described in the literature refer more commonly to the geriatric population or patients with other underlying co-morbidities.²

J-H reaction

'J-H' describes a reaction that occurs when large quantities of toxins are released from bacteria as their cell walls lyse due to penicillin treatment.

The lysis of the bacteria and the associated release of bacterial endotoxins flood the body faster than they can be excreted. This can manifest as fever, chills and rigors, headache, myalgia, acute rise in temperature, tachycardia, tachypnoea and hypoxia.⁶⁻⁹

These symptoms resolve with supportive therapy. Clinically the picture in our patient is very similar to presentations described in the literature of patients diagnosed with a J-H reaction and also in those with massive endotoxin release leading to a significant systemic upset.¹⁰

Drug allergy to the dexamethasone, metronidazole, amoxicillin or paracetamol can be considered. The clinical manifestations of antibiotic allergy may be cutaneous, organ-specific, systemic or combinations of these,¹¹ however the patient had no previous history of hypersensitivity reactions. The complex auditory and visual hallucinations described by the patient are not a reported symptom of drug allergy in significant adverse IgE mediated or serum

sickness-like reactions. The patient also proceeded to continue intravenous and oral courses of these drugs with no further side effects.

Steroid induced psychosis should also be included in the differential diagnosis as this is a rare but well-recognised complication of corticosteroid administration, including in relation to elective oral and orthognathic surgery.¹² The manifestations of steroid psychosis include delusional behaviour and therefore overlap with those presented in this case. It is of note that all corticosteroids, including the long-acting one administered in this case (dexamethasone), act at a nuclear level to reduce the production of early pro-inflammatory mediators. Consequently, there is a significant delay between drug administration and any therapeutic or adverse effect. The literature is vague on the speed of onset of steroid-induced psychosis but varies between 6 and 12 h for intravenous and 3–4 days for oral preparations.¹³ Female sex, systemic lupus erythematosus and high doses of prednisolone have also been documented as being risk factors for the development of a steroid-induced psychiatric syndrome.¹⁴ If steroid induced psychosis is diagnosed, reduction or discontinuation of the corticosteroid treatment may remedy these adverse side-effects, however psychotropic medications are often required because of the medical necessity of the corticosteroid or the severity of the psychiatric symptom.¹⁵

Due to the very short period between administration of intravenous steroid and the vital signs and symptoms of delirium; the relative low dose of steroid administered and lack of other risk factors, we feel that steroid administration was an unlikely aetiology of psychosis in this patient.

Drug interactions were ruled out by the patient and his friend, who confirmed no previous medication (other than paracetamol and ibuprofen) or recreational drugs had been consumed before admission.

OUTCOME AND FOLLOW-UP

Clinical improvement following intravenous antibiotic therapy was noted and the patient was discharged continuing on oral antibiotics, analgesia and jaw opening exercises.

He represented 4 days later with left-sided facial swelling, this time spreading into the left temporal region. A CT neck with contrast was carried out showing fascial space collections, which required general anaesthetic (GA) incision and drainage of multiple fascial spaces. The pus microbiology results from surgery revealed Gram positive cocci and rods on microscopy and *Streptococcus constellatus* sensitive to amoxicillin and erythromycin on culture.

Blood cultures grown from the initial admission were negative.

DISCUSSION

Microbiology following surgical intervention on re-admission revealed gram positive cocci and gram positive rods on microscopy with *S constellatus* being cultured from the operative pus sample. *S constellatus* is usually β -haemolytic, mainly Lancefield group F, and is part of the *Streptococcus milleri* group. It can be identified by the 'caramel' smell typically produced from the culture plates. Although this group of organisms are identified as an oropharyngeal commensal, their ability to produce thick pus and form abscesses are well documented.¹⁶⁻¹⁸ *S milleri* abscess formations are

known to occur at multiple body sites, with one report demonstrating that *S milleri* was the most common organism from the *Streptococcus viridans* group associated with abscess formation accounting for 71% of brain abscesses, 40% of abdominal abscesses and 34% of extra-abdominal abscesses.^{17–19} Disruption of the mucosal barrier, such as post tooth extraction, allows for invasion into underlying tissues and local spread as well as the potential for the organisms to spread haematogenously causing metastatic abscesses.^{17–19} Abscesses caused by *S constellatus* are more likely to be polymicrobial, with the co-isolates reflecting the site from which the specimen was obtained.^{20–21}

Previously noted episodes of J-H have been described in relation to spirochaetal infections, most commonly syphilis, including J-H as a sequelae for previously undiagnosed syphilis.²² Syphilis was not tested for in this case, but no obvious risk factors were demonstrated in the patient's medical and social history. Spirochaetes (particularly *Borrelia vincentii*) and other fusiform bacteria are also oral commensals but are recognised to play a role in severe oral infections such as Vincent's angina (acute necrotising ulcerative gingivitis). Spirochaetes cannot be cultured in the laboratory and the definitive vincent's stain was not specifically requested from operative oral samples, therefore this group could not be demonstrated in the microbiology results. However, it can still be suggested that spirochaetes could have contributed to the polymicrobial flora in the patient's initial infection.¹⁶ The clinical pattern of behaviour that occurred after antibiotic treatment, which included a penicillin, are comparable to J-H cases described in the literature and therefore we conclude J-H reaction is one of the top differential diagnoses.

Comparisons can also be made with symptoms of septic shock, where transient elevations of tumour necrosis factor, pro-inflammatory cytokines IL-6 and IL-8 have been hypothesised to be factors in both systemic conditions.^{10–22–24}

Learning points

- ▶ Patients with spreading orofacial infections can deteriorate rapidly and require emergency management.
- ▶ Oral commensals have the potential to cause sepsis with high morbidity.
- ▶ Sepsis and associated fever can produce confusional states and unusual behaviour which is challenging to manage and distressing for the patient and clinician if unaware of this complication.
- ▶ J-H type reactions are managed supportively and antibiotic therapy continued for the primary condition.
- ▶ With increasing numbers of cases of syphilis, clinicians may wish to be aware that a J-H reaction could indicate inadvertent treatment of undiagnosed syphilis.

Competing interests None.

Patient consent Obtained.

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