CASE REPORT

Hyperactive delirium following administration of intra-articular corticosteroid

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Accepted 3 February 2017

SUMMARY

Intra-articular administration of corticosteroids is a commonly used treatment for osteoarthritis as well as other inflammatory disorders of the joints. It is well known that delirium and psychosis can arise following the administration of oral corticosteroids but there are few documented cases of the development of acute hyperactive delirium with psychosis following intra-articular administration. We describe a case of an 82-year-old female patient with moderate dementia who developed a delirium with psychosis which responded well to a first-generation antipsychotic.

BACKGROUND

This was a challenging case to manage in a community setting. The presentation was acute and followed a corticosteroid injection to the patient's knee. The patient's general practitioner (GP) carried out a thorough medical work up but no identifiable cause for the patient's symptoms was found. A referral was consequently made to the local psychiatry of old age service and a diagnosis of delirium was made. There is little documented information in the literature of this mode of corticosteroid administration resulting in a delirium as severe as the one described below. The authors therefore believe that it is a worthwhile and noteworthy case to describe.

CASE PRESENTATION

The patient was an 82-year-old woman who was living at home with family in rural Ireland. She was in receipt of full-time home care as she was suffering from moderate dementia. She was referred to the local psychiatry of old age community team by her GP as she had developed an acute confusional state with psychosis.

Information from her GP revealed that she had received a routine intra-articular corticosteroid injection to her left knee joint (*DepoMedrone* 80 mg/methylprednisolone acetate) and within 48 hours had developed persecutory delusions, appeared to be hearing voices and had become increasingly more confused. On reviewing the patient 3 days after she was administered the corticosteroid injection, her doctor prescribed a course of quetiapine 12.5 mg once per day for 2 days and this dose was then increased to 25 mg twice per day as no improvement to symptoms was noted. A septic screen which included full blood count, urea and electrolytes, inflammatory markers, midstream urine for culture and sensitivity as well as a CT brain scan and ECG was carried out. All results were unremarkable.

On review of the patient in her home by the community psychiatry team, she presented as being extremely suspicious and paranoid. She had now received 5 days of quetiapine 25 mg twice per day (quetiapine had been taken for 7 days in total, ie, 2 days of 12.5 mg per day and 5 days of 25 mg twice per day). She would not believe that her visiting doctor and nurse were who they claimed to be. She acted in a hostile manner and would not engage fully with the assessment. She was observed to be muttering to herself and appeared to be responding to auditory stimuli. She was distracted with impaired attention.

Collateral information was provided by the patient's family and included the following: her sleep was disturbed and she was particularly agitated and aggressive at night time, for example, striking carers. She was intermittently refusing food claiming that it was poisoned. She was more confused than before and seemed to not recognise her surroundings at times. Her agitation and confusion appeared to fluctuate throughout the day with night time being particularly difficult. Family described a 'complete personality change' from a previously 'quiet, gentle lady'. Despite being administered regular quetiapine, no improvement to symptoms was observed by family.

Psychiatry history—dementia (Alzheimer's type, moderate).

Family history—no known family history of mental illness or dementia.

Medical history—hypertension, hypercholesterolaemia, osteoarthritis, recurrent urinary tract infections, mesenteric infarct—2013, stroke—2009, neck of femur fracture—2008, left Colles' fracture—2009. No previous documented history of behavioural or psychological symptoms of dementia or history of hyperactive delirium as per the patient's GP and following review of the hospital file.

Medications—aspirin 75 mg once per day (for more than 10 years), lisinopril 2.5 mg once per day (5 years), amlodipine 5 mg once per day (5 years), alendronic acid 70 mg once per month (3 years), omeprazole 40 mg once per day (>10 years), folic acid 5 mg once per day (unknown duration but most likely for >3 years) and nitrofurantoin 50 mg at night (prescribed for prophylactic treatment of urinary tract infections. The patient was taking this medicine for the past 3 years).

Personal/social history—the patient was a retired housewife. She was from rural Ireland. She was a non-smoker and non-drinker. She was living with

To cite: Lally L, McCarthy G, Meehan K. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2016-217483

family and a full-time carer. She mobilised with the aid of a walking frame.

Mental state examination—she presented as a neatly attired lady who was overweight. She was suspicious, guarded and hostile in her manner. There was evidence of increased motor activity—she was restless and pacing her kitchen. She refused to sit down. Eye contact was appropriate. She appeared distracted with impaired attention. Questions were repeated several times but the patient was unable to concentrate on answering. Her speech was loud and content was threatening at times. Her mood subjectively was 'fine' and objectively was irritable and labile. There was evidence of persecutory delusions—she believed that we were not who we claimed to be and appeared fearful of us. She did not believe that her family doctor had arranged an appointment with the psychiatry team. The patient was noted to be muttering to herself, which was suggestive of possible auditory hallucinations. Insight was impaired.

INVESTIGATIONS

A septic screen which included full blood count, urea and electrolytes, inflammatory markers, midstream urine for culture and sensitivity as well as a CT brain and ECG was carried out. All results were unremarkable.

Cognitive testing—A Mini-Mental State Examination (MMSE) was attempted at the time of the initial psychiatric review but the patient was not orientated to day, date, month or year. She refused to engage further becoming increasingly distracted and suspicious. Her GP reported that a MMSE test carried out 6 months previously when she was well was 20/30. According to her GP, a formal diagnosis of moderate dementia was made by her geriatrician ~5 years previously.

DIFFERENTIAL DIAGNOSIS

1. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)[1] hyperactive delirium with psychosis.
   - *Disturbance in attention and awareness*—she was unable to focus and maintain attention on the interview.
   - *Change in cognition (eg, memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a pre-existing, established or evolving dementia*—the patient's cognition had markedly declined over a short period of time with reports that she no longer recognised family members. She was not orientated to day, date, year or month.
   - *The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day*—her symptoms began ~48 hours following administration of the cortico steroid injection.
   - *There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by a direct physiological consequence of a general medical condition, an intoxicating substance, medication use or more than one cause*—a full medical examination and investigations were carried out by the patient's GP. The results were all unremarkable. The administration of the corticosteroid injection appeared to have precipitated symptoms.

Other evidence suggestive of delirium included Delirium Rating Scale Revised 1998 (DRS-R-98), which is a widely used delirium rating instrument that measures delirium symptoms. This was administered and the patient's scores suggested a diagnosis of delirium. The DRS-R-98 is a 16-item scale with 13 severity items and 3 diagnostic items and it has high inter-rater reliability, sensitivity and specificity for detecting delirium in mixed neuropsychiatric and other hospital populations.[2]

2. DSM-V[1] major neurocognitive disorder due to Alzheimer's dementia with behavioural disturbance.

Behavioural and psychological symptoms occurring in dementia have been described by Finkel *et al*.[3]

- Behavioural symptoms:

Physical aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviours, sexual disinhibition, hoarding, cursing and shadowing.

Our patient exhibited physical aggression, restlessness and agitation.

- Psychological symptoms:

Anxiety, depressive mood, hallucinations and delusions.

Our patient exhibited *auditory hallucinations and persecutory delusions*.

This diagnosis is important to consider given her pre-existing cognitive impairment, but it is less likely in view of the acute and severe nature of her symptoms, her markedly impaired attention and the relatively fast resolution of symptoms with treatment.

TREATMENT

Given the patient's lack of response to a second-generation antipsychotic (quetiapine 25 mg twice daily), a decision was made to switch to a more potent first-generation agent after weighing up the risks and benefits and discussing the same with family. The patient lacked the capacity to consent to treatment and, as a result, a decision to prescribe medication was made with the patient's best interests in mind and following close collaboration with the next of kin—the patient's daughter. Owing to the distressing nature of her symptoms and the risk she posed to others, a decision was made to prescribe an alternative psychotropic medication.

Haloperidol 0.5 mg twice per day was prescribed. Non-pharmacological interventions were suggested including nursing in own environment (the patient was already residing in her own home), the presence of familiar care staff to encourage reorientation (she was being cared for by two female carers who were known to her for many years), a quiet non-stimulating environment with clocks, calendars, etc, available to help reorientate the patient.

OUTCOME AND FOLLOW-UP

Following 4 days of regular haloperidol, the patient's symptoms began to improve and within 7 days were completely resolved. She was oversedated and haloperidol was reduced to 0.5 mg once per day for a further week and then discontinued altogether. The family reported a return to baseline personality and cognitive function. Her sleep pattern improved with full resolution of psychotic phenomena. She was agreeable to a follow-up visit and MMSE was attempted successfully with the patient scoring 22/30. (She lost marks for recall 1/3, orientation 6/10, repetition 0/1, pentagram drawing 0/1.) She had little recollection of her distressing symptoms. She was pleasant and cooperative with no evidence of psychosis.

DISCUSSION

Corticosteroids are among the most widely used drugs in the world, being particularly effective at reducing inflammation. The mechanism of action is thought to involve the switching off of proinflammatory genes.[4] High doses are often required to effectively treat inflammatory conditions. Corticosteroid-induced psychosis refers to a wide range of symptomatology including mood disorders, cognitive deficits and acute psychoses.[5] It is thought that patients receiving 40 mg of prednisolone equivalent

or more are at a higher risk of developing psychiatric symptoms.[6] Our patient received 80 mg of methylprednisolone acetate.

Product information indicates that the recommended dose of *DepoMedrone* (methylprednisolone acetate) is 20–80 mg for a knee joint. It also states that there are no specific dose recommendations for the elderly.[7] However, it has been shown that blood levels achieved after receiving 80 mg of intra-articular methylprednisolone are equivalent to an oral dose of 20 mg prednisolone when taking into account their 4:5 dose equivalency ratios.[8] Given this finding and the patient's underlying increased risk of delirium, it would, in retrospect, have been worth considering administering a lower dose.

Intra-articular cortico steroid injections are a common treatment for rheumatoid and osteoarthritis. It is accepted that the anti-inflammatory response is confined to the joint area and that a general improvement to systemic markers of inflammation is noted.[9]

In a multicentre prospective study carried out in Boston in the 1970s, psychiatric symptoms were described in 1.3% of participants receiving <40 mg per day of prednisolone. This increased to 4.6% in those receiving 41–80 mg per day, while psychiatric symptoms were observed in 18.4% of those receiving more than 80 mg per day. This is in keeping with the observation that symptoms are most likely to occur following a short course of high-dose corticosteroid.[10]

Peak serum corticosteroid levels are noted to occur from 2 to 12 hours after injection, and the drug was shown to be completely cleared within 3–5 days. Corticosteroid levels remained suppressed by up to 80% at 24 hours postinjection. Levels usually return to normal within 1 week. It is believed that *DepoMedrone* (methylprednisolone acetate) 40 mg is sufficient to induce maximum suppression of cortisol.[11]

A case described in the literature in 2000[8] reported an acute onset of psychosis in an elderly woman with osteoarthritis who received 80 mg corticosteroid to her hip joint. Within 36 hours, she developed paranoid delusions and perceptual abnormalities and required a first-generation antipsychotic to ameliorate symptoms.

In the case of our patient, she developed symptoms 48 hours after administration of the drug and symptoms began to resolve ~11 days from when antipsychotic therapy was first started (7 days of quetiapine followed by 4 days of haloperidol). The time to recovery is longer than described in the existing case report. However, given the extensive search for other potential causes for her symptoms and acknowledging that she had not received any change to her regular medication prior to the onset of symptoms of delirium, it is likely that the intra-articular administration of corticosteroids was the main precipitant.

Other potential causative factors for this patient's delirium were considered, including the following—urinary tract infection (given her documented history of repeated urinary tract infections), dehydration, constipation, a recent change in environment or pain. From the physical examination and investigations carried out by the patient's GP infection, dehydration or other electrolyte imbalance were ruled out. The brief change of environment which occurred when the patient visited her rheumatologist's clinic and the pain associated with her osteoarthritis may also have possibly contributed to the severity of her symptoms.

The pathophysiology of corticosteroid-induced psychosis is poorly understood but is thought to relate to deficits in the hypothalamopituitary axis.[12]

Diagnostically and in terms of management, this case posed challenges to the treating team. The acuity and severity of the patient's symptoms, the physical aggression she displayed towards others, her advanced age, medical comorbidities and the potential for side effects of psychotropic medications were all factors that needed to be considered when formulating a management plan. The patient had an established underlying cognitive impairment which increased her risk of developing delirium.[13 14] She fulfilled diagnostic criteria for delirium as per *DSM-V*.[1]

Delirium is a common and complex neuropsychiatric condition occurring in 29–64% of medical inpatients.[15 16] It is an often underdiagnosed or misdiagnosed condition which can result in adverse patient outcomes including increased hospital stay, poorer functional outcomes and increased mortality.[16] This patient's treating GP, psychiatry team and family were in agreement that she should be managed at home if possible, although her symptoms were resulting in her posing a risk to others in terms of physical aggression. A decision to prescribe psychotropic medication was made in accordance with National Institute for Health and Care Excellence (NICE) guidelines when non-pharmacological interventions were deemed to have failed and when her symptom severity was such that the patient posed a risk to others.[17] Antipsychotics are considered to have a role in the treatment of delirium and are considered superior to benzodiazepines.[18] NICE guidelines suggest a short course of haloperidol or olanzapine in the treatment of delirium. Haloperidol was chosen over olanzapine for a number of reasons including the treating team's prior experience with using low doses of haloperidol in successfully treating delirium symptoms in the elderly. Given the patient's level of obesity, the team also wished to minimise the likelihood of precipitating any adverse metabolic effects.[17] Prescription of antipsychotics in the elderly population carries risks including cardiovascular risks, sedation, increased risk of falls and extrapyramidal side effects.[19] Therefore, these medications should be prescribed cautiously while aiming for a minimal effective dose and a short duration of therapy.

It is thought that improvement of symptoms occurred in our patient as a result of a combination of pharmacological intervention and non-pharmacological measures. The natural course of the syndrome may of course also have played a role in her recovery.

Learning points

- Elderly patients with existing dementia are at high risk of developing delirium.
- Corticosteroids are a common cause of delirium and psychosis. Neuropsychiatric symptoms can arise from intra-articular administration of same.
- Importance of close liaison between medical physicians and psychiatry in diagnosing and managing these cases.
- Pharmacological agents are often required to effectively treat symptoms but should be used with caution.
- Non-pharmacological measures are shown to have an important role in improving symptoms of delirium.

Acknowledgements The authors thank the patient for agreeing to the description of her illness in the medical literature.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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