PSI LOGOS

Caso Clínico / *Case Report*

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Acute Confusional State after Inhaled Corticotherapy

Estado Confusional Agudo após Corticoterapia Inalada

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ABSTRACT

Background: The connection between corticotherapy and neuropsychiatric symptoms is widely known, being one of the first questions we need to assess when presenting with first episode psychiatric symptoms or confusional state.

Aims: To date, data on cases related to inhaled corticotherapy and neuropsychiatric effects is scarce. In this paper we describe a rare case in a young woman.

Methods: The clinical case presented led us to try to understand the data published on the subject in order to discuss it in greater length.

Results and Conclusions: We present and discuss a 27-year-old patient's case, with no previous psychiatric disease, who was admitted to our Psychiatric ward after the onset of severe acute behavioural disturbance characterized by aggressiveness, visual and auditory hallucinatory activity, misidentification and altered conscience status. It was later found that seven days earlier she had been prescribed inhaled corticotherapy for a minor respiratory infection. A few days after corticotherapy withdrawal, the clinical symptoms improved significantly.

Key-Words: Delirium; Steroids; Inhaled Therapeutics; Iatrogenic; Side Effects.

RESUMO

Introdução: *A relação entre corticoterapia e sintomas neuropsiquiátricos é sobejamente conhecida, sendo uma das primeiras questões a colocar face a uma apresentação inaugural com sintomas psiquiátricos ou estado confusional.*

Objetivos: *A apresentação de um quadro de Delirium secundário à administração de terapêutica corticoide inalada é aqui descrita pela primeira vez num paciente jovem.*

Métodos: *O caso clínico aqui apresentado levou-nos a tentar entender os dados publicados sobre o assunto no sentido de melhor o compreender e discutir.*

Resultados e Conclusões: *Apresentamos e discutimos o caso de uma doente de 27 anos, sem história de doença psiquiátrica, internada após episódio agudo de alteração grave de comportamento com heteroagressividade, atividade alucinatória auditiva e visual, falsos reconhecimentos e alteração do estado de consciência. Retrospetivamente*

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pode-se apurar inicio de terapêutica corticoide na forma inalada há 7 dias por um quadro infecioso respiratório. Após retirada dos corticoides ocorreu melhoria significativa do quadro ao fim de poucos dias.

Palavras-Chave: *Delirium; Corticoides; Nebulizadores e Vaporizadores; Iatrogenia; Efeitos Colaterais e Reações Adversas Relacionadas com Fármacos.*

CASE PRESENTATION

The patient is a 27-year-old single female, living with her foster parents. She has completed 12 years of school and is currently employed at a woodwork shop. She was presented at the Emergency Room (ER) of her local hospital after a preceding two-day behavioural disturbance. The patient had become agitated at home, destroying her belongings in her own room where she had locked herself in, afraid of her own parents, presumably because of hallucinatory activity and misidentifications.

From her background we could only point out a history of syphilis in her infancy (without any current laboratory or clinical features), no regular prescription drugs and this was her first contact with mental health services.

She had been prescribed inhaled corticotherapy - salmeterol and fluticasone propionate 250/50 mcg/dose every twelve hours - for flu-like symptoms (cough and malaise). For about seven days she overused it, taking it about once per hour.

A state of fluctuating consciousness, disorganized speech sometimes incomprehensible, irritability and restlessness, developed progressively over the eight days since she had begun the steroids. At that time she presented with psychomotor agitation with heteroaggressiveness, visual and auditory hallucinations and misidentification - she believed she saw her grandparents in her parent's bodies. The next day she was evaluated at the ER for these behavioural symptoms. She was given 1g acetaminophen intravenous (IV), fluids and a new dosage of 1mg inhaled budesonide for her persisting cough before she was evaluated by Neurology and Psychiatry.

The laboratory and imaging study was performed with complete blood count, basic biochemistry, chest x-ray and head computed tomography scan (CT) – with no clinical signs

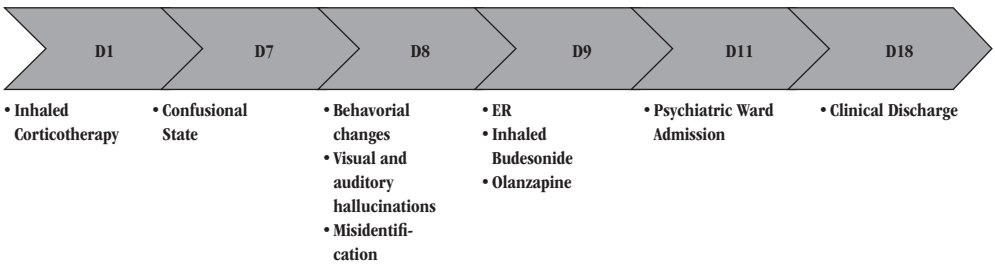

Figure 1. Timeline.

of a cause for the presenting complaints. The patient also performed a urine test for abusive drug consumption which turned out negative for all the substances searched. Therefore, the attending physicians felt that an adequate exclusion of organic disease had been performed and requested a psychiatric evaluation.

Attending to the presenting behavioural changes with aggressiveness, attention and consciousness disorders, hallucinatory activity and misidentification, she was voluntary admitted to a psychiatric ward for further clinical investigation and treatment. The patient stopped using inhaled corticotherapy and was started on an atypical antipsychotic (olanzapine 10 mg per day). From this point on, the hallucinatory activity and misidentifications ceased.

As an inpatient she completed the laboratory tests with virological and syphilis markers, thyroid function tests, B12 vitamin and folic acid dosing. All of these were also innocent except for a minor folic acid deficit. After discharge the patient underwent a psychological assessment which determined a minor intellectual impairment.

During her stay at our inpatient unit she maintained a generally calm and orderly behaviour, a healthy interaction with health care professionals and other patients, notwithstanding a puerile posture. Initially she was a little restless but she was able to focus and maintain attention, always awake and was fully oriented to self, as well as time and space, without any behaviour that would suggest she was experiencing delusional or hallucinatory activity. The *insight* into the hallucinatory phenomena previous to her admission was addressed but, probably due to her cultural background and her intellectual disability, full *insight* was not achieved.

The patient was discharged home, seven days after admission, with a clinical diagnosis of acute hyperactive *delirium* induced by propionate of fluticasone (according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[2]). She was maintained on olanzapine 10 mg/day until her first outpatient appointment a month later. By that time, she presented complaints of somnolence and weight gain, without any psychiatric symptoms so it was decided to discontinue olanzapine. The patient was also advised to abstain from the use of any type of corticotherapy as it is known that after an episode of neuropsychiatric illness induced by corticotherapy, the risk of recurrence is present with new usage[3].

DISCUSSION AND CONCLUSIONS

The case here reported refers to a 27-year-old woman, with no previous psychiatric history, presenting an acute episode (around two days evolution) of aggressiveness, agitation, fluctuating consciousness, visual and auditory hallucinatory activity and misidentification.

After an organic screening with blood tests and head CT scan, a psychiatric aetiology was assumed despite several clues to a possible organic origin (first episode, acute presentation, altered mental status, visual hallucinations, misidentification and recent infection).

After a careful revision of the case, it came to our attention that the patient had recently started inhaled therapeutics for a minor respiratory infection - salmeterol and fluticaso-

ne propionate 250/50 mcg/dose every twelve hours – and also that she had been using it in a much higher dose than prescribed.

Currently, it is widely known that steroid therapy is associated with *delirium*, depression, mania, psychosis and cognitive impairment[4]. A study of 261272 patients on steroid therapy, matched by gender and age with patients with the same types of medical disease, but no corticotherapy, were accessed for different neuropsychiatric presentations during a three-month period revealing a 5.14 Odds Ratio (IC 95% - 4.54 a 5,82) for *delirium*, confusion or maze[3]. Only recently did we start to understand the mechanisms underlying these neuropsychiatric symptoms. Cortisol is the end product of the hypothalamic-pituitary-adrenal (HPA) axis and it has two different receptors widely distributed in the brain especially in the hypothalamus, pituitary gland and hippocampus– mineralocorticoid and glucocorticoid – the first being implicated in appraisal processes and the onset of *stress* reactions and the second in terminating the *stress* response[3,4]. There seems to be a connection between steroid responses in the brain and other neurotransmitter systems[1], namely the dopamine, acetylcholine and also the serotoninergic system which is strongly implicated in mood, cognition and behaviour[4]. Synthetic steroids preferentially activate glucocorticoid receptors while also depleting (by means of negative feedback) the adrenal cortisol secretion. Therefore, an extreme imbalance between glucocorticoid receptors and mineralocorticoid receptors caused by the exogenous steroid can cause cognitive impairment, disturbed emotions and other neuropsychiatric manifestations[3]. There is evidence that, in prolonged high dosages, various forms of neural damage can also explain these symptoms[3]. There is still much to be known about these mechanisms as they appear to be complex and unpredictable.

Inhalatory use is generally associated with a small systemic dosage, but in this case, it seems that higher doses reached the lung tissue (and the gastro-intestinal tract by unintentional swallowing) and the bloodstream as consequence of an excessive intake. This is very important as the risk for neuropsychiatric disturbances is associated with the dosage of corticotherapy[3].

The clinical improvement about three days after corticoid withdrawal supports the hypothesis of an iatrogenic cause. Likewise, the clinical deterioration after a dosage of budesonide at the ER makes this hypothesis very likely. However, this was also the moment when an atypical antipsychotic drug was started. Using the Naranjo Scale – a scale used to access the likelihood of an adverse reaction being associated with a specific drug – a probable association was stablished (6 out of 13)[6]. The previous infection history may also have been a risk factor for a confusional state. The other drug used – salmeterol - is a long acting beta-2 agonist used as a bronchodilator; we found no evidence to associate its use to psychiatric disturbances or confusional syndromes.

Confusional states usually present with psychiatric-like symptoms, but the presentation of altered mental status, even a hyperactive one, together with the patient's recent clini-

cal history should have raised the possibility of a non-psychiatric cause for her symptoms. The screening for organic causes of behavioural changes should be made whilst completing the patient's medical history, together with a physical examination and directed auxiliary study. There are several factors associated with confusional states[7]: patients characteristics such as age, gender, isolation, alcohol and tobacco use; chronic disease as cardiac or respiratory disease or cognitive impairment; environment issues such as admission through the ER, physical restraint, absence of time markers; acute disease with fever, sedation, and changes in food intake. This case highlights the clinical significance of obtaining a careful medical history, especially in a person with no apparent previous psychiatric history presenting with sudden and acute behavioural disturbance.

When presented with a case of *delirium*, the main strategy should be to identify the causing or underlying factors in order to remove them. In this case, the interruption of the inhaled corticotherapy seems to have been crucial for the clinical outcome. Treating behavioural changes, secondary to a confusional state should be made with low dosage haloperidol or an atypical antipsycotic[7]. These two options seem to have similar outcomes, except in the need for higher doses where haloperidol shows increased extrapyramidal symptoms. These drugs aim to reduce any risks for the patient and others, mechanical restraint should be used as a last resort and only for the shortest time possible. The connection between oral corticotherapy and neuropsychiatric symptoms has already been established[3], however, in this case the use of inhaled corticotherapy seems to have caused a confusional state. Therefore, especially in patients with risk factors for confusional states, it seems important that this connection should be considered.

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