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Case report

ISOTRETINOIN INDUCED PSYCHOTIC SYMPTOMS

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ABSTRACT:

Isotretinoin is an effective treatment for severe and resistant forms of acne. It has proven potential for inducing dose-dependent psychiatric side effects, especially in some vulnerable groups of patients.

Objective: The aim of the present article is to report a case of a 22-year-old woman with a family history of schizophrenia who was diagnosed with acne. After unsuccessful antibiotic treatment of acne, a panic disorder accompanied by depressive symptoms manifested. Isotretinoin 20 mg/day was used as a second step of the dermatological treatment for a period of four months, along with psychotropic treatment for panic disorder – sertraline 50 mg/day and flupentixol 1,5 mg/day. When the dose of Isotretinoin was increased to 40 mg/day, paranoid delusions occurred. The manifestation of psychotic symptoms required discontinuation of all medications and initiation of antipsychotic therapy with quetiapine. The psychotic symptoms completely disappeared when the dose of quetiapine was increased to 300 mg/day.

Conclusion: The presented case emphasizes the need for increased vigilance about the manifestation of psychiatric symptoms, especially in patients with a family history, current or past medical history of mental disorder. In such cases, consultation with a psychiatrist before starting treatment with Isotretinoin is recommended in order to better clarify the benefits and the risks of the treatment. The endogenous origin of the psychosis was discussed in the differential diagnostic plan, which requires long-term monitoring of the mental state.

Keywords: Isotretinoin, acne, psychosis, psychiatric side effects,

INTRODUCTION:

Isotretinoin (13-cis retinoic acid) is the most effective medicine for all forms of acne, providing long-term remission. Its rapid and reliable effectiveness reduces the potentially unfavorable consequences associated with acne–skin scars, depression and anxiety disorders [1]. The success of the isotretinoin treatment is due to its mechanism of action – it causes apoptosis of sebocytes. The process of apoptosis is not selective and can affect the cells of other tissues, causing a number of side effects defined as predictable, like teratogenicity hypertriglyceridemia, liver diseases, mucocutaneous adverse reactions and others [2, 3].

Since the 1990s, there has been a lot of evidence of the possible occurrence of psychiatric side effects of treatment with isotretinoin [1]. Cases of affective and anxiety disorders, psychotic episodes, obsessive-compulsive symptoms, suicidal and aggressive behavior have been described [4]. It falls under the Class A medications whose mental side effects are predictable, dose-dependent and can be identified by taking a detailed anamnesis [5].

Isotretinoin belongs to the group of retinoids to which vitamin A also pertains. Retinoids play an important role in the processes of neurodevelopment and neuroplasticity. Endogenous retinoic acid is concentrated in the axons of dopaminergic neurons of the mesostriate and mesolymbic system. Its projections begin from the ventral tegmentum and reach the corpus striatum and the nucleus accumbens. Retinoid receptors in the brain are spread in the limbic zones: the hippocampus, the hypothalamus, the medial prefrontal cortex, the amygdala and the thalamus. They regulate the gene transcription by binding to retinoid receptors located in the nucleus of the cell on the DNA. Thus, retinoids modulate the systems of the main neurotransmitters (dopaminergic, serotonergic and noradrenergic), which are involved in the pathoge-

nesis of mental disorders [6]. Scientists have proven that the RAI-1 retinoic acid-induced gene is significantly increased in the brains of patients with schizophrenia, bipolar affective disorder or depression [7]. These data support the interrelation between Isotretinoin and the manifestation of psychopathological symptoms.

Several risk factors for the manifestation of mental side effects of the isotretinoin treatment have been discussed: 1) administration of doses above 20 mg/day [8], 2) family history of mental disorders, 3) past history of mental disorder [9]. In this regard, taking a detailed psychiatric medical history prior to treatment with Isotretinoin, as well as the active search for psychiatric symptoms during control examinations, is extremely important. It is crucial that the relatives of these patients are well informed of the possible side effects of the treatment and be vigilant with regard to changes in their behavior [10].

CASE REPORT:

We present a case of a 22-year-old single woman who lived with her parents and didn't work. The patient had no past history of using psychoactive substances but had a family history of psychiatric disorder (her maternal uncle suffers from schizophrenia). She initially consulted a psychiatrist in July 2021 about symptoms of depression and panic attacks. The deterioration of her mental state occurred gradually after the appearance of acne lesions on her skin. She started an oral treatment with antibiotics (metronidazole and nitrofurantoin) prescribed by à dermatologist. Due to the failure of the therapy applied, the patient felt desperate, without mood and self-esteem. She was ashamed of her appearance, did not leave her home and interrupted her studies at university. The patient began to experience sudden episodes of paroxysmal anxiety, including symptoms of palpitations, shortness of breath, shivering of the body, paresthesia of the limbs, sweating, derealization experiences (she felt that the walls were narrowing). The duration of one episode was up to 20 minutes, occurring approximately every few days. She was afraid of the next panic attack. In May 2021, she again consulted a dermatologist and à treatment with isotretinoin 20 mg/day was initiated. The patient was well informed by her dermatologist about the potential side effects of the medication and did not share her mental symptoms. Motivated to restore her appearance, she agreed to undergo treatment with Isotretinoin. By July 2021, the lesions subsided, but her mental state remained unchanged. She then, for the first time, consulted a psychiatrist who prescribed treatment with sertraline 50 mg/day and flupentixol 1,5 mg/day, due to which the panic attacks and the depressive symptoms were reduced. At the end of August, the dose of Isotretinoin was doubled to 40 mg/day, due to the appearance of new acne lesions on her face. In September 2021, the patient started functioning better and was motivated to start working. By the end of the same month, she gradually felt "different". She thought that she was discussed about the way she looked and began to feel observed and persecuted. During a job interview, she realized she was in a trap and that her private data had been stolen from people who would employ her. The manifestation of psychotic symptoms required another consultation with a psychiatrist, who discontinued taking all medications and recommended computer tomography of the brain and laboratory tests (complete blood count, biochemistry and level of thyroid hormones). No psychotic symptoms other than paranoid delusions were identified during the examination. Titration of the antipsychotic quetiapine was initiated, and when a dose of 300 mg/day was reached, the psychotic experiences were vanished. The test's results did not show deviations, except for the ALAT value 62 U/l, which required the addition of hepatoprotective treatment. After treating the psychotic production, the patient again consulted a psychiatrist regarding symptoms of depression (feeling miserable, overvalued thoughts of guilt, inferiority and suicidal thoughts). Sertraline was added to the quetiapine therapy in a dose of up to 75 mg/day. In January 2022, the patient fully recovered her psychosocial functioning. She began exercising, socializing and thinking again about finding a suitable job.

DISCUSSION:

Patients with acne are a specific group in which symptoms related to body image disturbances and low self-esteem are often identified [11]. These are the main provoking factors of anxiety and depressive disorders [12, 13], which are, in essence, psychogenic reactions due to acne [14]. In the case presented, the symptoms of depression and paroxysmal anxiety were a consequence of the acne and the unsatisfactory results of the antibiotic treatment of acne. In this regard, some authors emphasize the need to apply methods for the active search for mental symptoms, as well as to conduct aggressive treatment of acne [12].

Often, medications identified as aggressive are associated with both high efficiency and serious side effects. Seeking a balance between the individual risk factors and the patient benefits is not always easily feasible, especially when the patient conceals essential information re-

lated to their medical history. Our patient did not share her mental experiences, and treatment with Isotretinoin 20 mg/day was initiated, which led to a reduction in the skin lesions of the face, but not of the anxiety and depressive symptoms. In principle, the dose of 20 mg/day is accepted as sufficiently effective and with the lowest potential for adverse reactions [8]. Only after treatment with an antidepressant – sertraline in combination with flupentixol, did the patient restore her psychosocial functioning. On the one hand, the increase in the dose of Isotretinoin to 40 mg/day and the manifestation of paranoid delusions suggests the exogenous origin of the psychosis. The concomitant antidepressant treatment with sertraline contributed to the intensity of the psychotic production. On the other hand, the patient has a family history of schizophrenia, which points towards an endogenous origin of the symptoms. Although the most common mental side effect of the treatment with Isotretinoin is depression [1], several studies have demonstrated its association with psychotic episodes [4]. The administration of quetiapine 300 mg after the discontinuation of the sertraline and the Isotretinoin was effective for the psychotic symptoms but not for the depressive ones. The addition of sertraline 75 mg/day to the antipsychotic treatment improves her mental state.

A number of authors describe cases of patients with psychotic symptoms during isotretinoin treatment. Usually, the onset of the psychosis is from three weeks [15] to three months [16] after the initiation of the treatment with Isotretinoin. The described psychotic episodes occurred at different dose regimens: 20 mg/day [15], 30 mg/day [16] and when switching from 40 mg/day to 80 mg/day [17]. Not all reported cases are without a family history of mental illness. Segmiller et al. (2013) present a patient with paranoid-hallucinatory symptoms and disorganized behaviour after a three-week course of treatment with Isotretinoin 20 mg/day. The administration of quetiapine 400 mg/day stabilize his mental state. The same dosage of antipsychotic was used as a maintenance treatment for 10 months because of a family history of bipolar affective disorder [15]. Kontaxakis et al. (2010) consider that such a combination of factors complicates the proof of the purely exogenous origin of psychosis. They suggest that Isotretinoin is an exogenous stressor, the effects of which are modulated by the different (specific) genetic vulnerability [18]. For this reason, it is necessary to monitor the condition of this vulnerable group of patients for the occurrence of another psychotic episode, i.e. for a recurrent course of the psychosis.

Retinoids have the potential to influence gene expression in various cells and tissues, including those of the nervous system [2]. This warrants that the effects caused by them may also be long-term, even after the discontinuation of Isotretinoin, similar to the teratogenic effects they cause. Goodman A. (1998) suggests the hypothesis of retinoid dysregulation in the etiology of schizophrenia. He stresses that the new treatment methods should be aimed at changing the gene expression of the dopamine receptors by using retinoid analogues [19]. These data support the concept of the unity of endogenous and exogenous psychoses. Similar views were held by Snezhnevsky, Goldberg and Malkin, who shared the need for the same approach in both groups of mental disorders [20].

CONCLUSION:

The physical and psychological consequences of acne can significantly worsen the mental functioning of the patients, which requires the application of methods of treatment with a quick and definitive effect. Isotretinoin possesses these qualities, but it also has the potential to induce psychopathological symptoms. Patients with a family history, as well as past and present history of psychiatric disorders, are particularly vulnerable. Consultations with a psychiatrist prior to the treatment with Isotretinoin would be helpful in achieving a more thorough assessment of its benefits and risks. Long-term monitoring of the mental status of patients with identified vulnerability is also necessary.

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