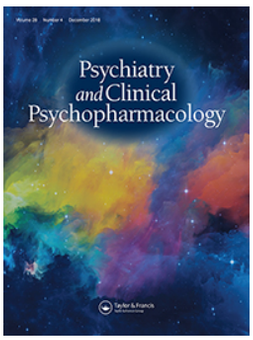

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CASE REPORT

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Hyperprolactinaemia and menstrual irregularity emerging in association with risperidone use and treated with aripiprazole in an adolescent diagnosed with schizophrenia: a case report

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ABSTRACT

Risperidone is one of the most commonly used antipsychotic agents in the treatment of psychosis in children and adults. However, it can lead to hyperprolactinaemia by blocking dopamine D2 receptors in the anterior pituitary. This can result in galactorrhea, menstrual irregularity, amenorrhoea and gynaecomastia and can impact adversely on medication compliance and quality of life. Very few data are available in the literature concerning the management of hyperprolactinaemia developing in association with antipsychotics in children and adolescents. This report describes improvement with the addition to treatment of low-dose aripiprazole in hyperprolactinaemia and menstrual irregularity emerging as side effects of risperidone therapy in an adolescent girl diagnosed with schizophrenia.

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KEYWORDS
Risperidone; aripiprazole; hyperprolactinaemia; menstrual irregularity; schizophrenia

Introduction

Early onset schizophrenia starts before the age of 18, is characterized by an adverse clinical course and poor psychosocial functioning, involves more negative symptoms than schizophrenia starting in adulthood, and causes problems in the social-cognitive sphere. Although therapeutic options such as typical and atypical antipsychotics are available, difficulties are frequently experienced during treatment. Risperidone is one of the most commonly used antipsychotic agents in the treatment of psychosis in children and adults. However, it can lead to hyperprolactinaemia by blocking dopamine D2 receptors (DRD2) in the anterior pituitary [1]. This can result in galactorrhea, menstrual irregularity, amenorrhoea, and gynaecomastia and can impact adversely on medication compliance and quality of life [2]. Long-term hyperprolactinaemia has also been shown to cause a decrease in bone mineral density [3]. Prediction and good management of psychological and physical effects that may occur in the short and long term when such side effects (hyperprolactinaemia, for instance) are seen in patients requiring long-term antipsychotic medication (such as risperidone) are therefore important in terms of the patient's and family's compliance with treatment. Although the first preference in patients developing symptomatic hyperprolactinaemia is to switch to a drug not causing prolactin elevation [4], the addition of aripiprazole to existing treatment is also recommended as an alternative option [5].

We report a case of hyperprolactinaemia developing in an adolescent girl in association with risperidone use due to schizophrenia, with prolactin levels subsequently returning to normal following the addition to treatment of aripiprazole therapy.

Case

F.Y., a 15-year-old girl, presented to our clinic accompanied by her mother due to "decreased personal care, aggressive behaviors, incoherent speech and sleep irregularity." Symptoms of unprovoked laughter, wishing to remain alone in her room, and introversion had first begun approximately two years previously. Persecutory delusions involving being harmed by those around her then developed. In the subsequent period, assistance with housework and self-care declined. Her mother bathed and dressed her and cut her nails. On the basis of clinical evaluation and the history elicited from the family, the disease manifestation in which delusions of persecution and introversion predominated had persisted for two years. In her premorbid history, the patient had never attended school, and spent the majority of her time assisting her mother in domestic tasks and watching television. No addition physical or mental pathology was present in the patient's history other than an aversion to social settings. No psychopathology was present in the family history. Psychological examination revealed blunted affect in this female patient exhibiting appropriate-for-age development with decreased personal care and limited cooperation. Orientation to place, time, and person were normal. No perceptual disorder was

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determined, although impoverished thought content and delusions of persecution were present. Her thinking began and continued in an object-oriented manner, but frequently subsequently deviated away from the subject and objective. Associations of ideas were incoherent. Attention and concentration were poor. Knowledge levels were insufficient. At the interview, the patient stated that she had no disease, but no introspection was present. Psychomotor activation was decreased. On the basis of clinical evaluation and the history elicited from the family, the disease manifestation in which delusions of persecution and introversion predominated had persisted for two years. No addition physical or mental pathology was present in the patient's history other than an aversion to social settings. No psychopathology was present in the family history. The patient's biochemical, hormonal, and complete blood count tests were normal. No pathology was determined at neurological examination, magnetic resonance imaging of the brain or EEG. Early onset schizophrenia was diagnosed [6], and the patient was started on risperidone 2 mg/day. Her initial Clinical Global Impression-Severity of Illness (CGI-SI) score was 6. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). The patient's PANSS scores: positive scale 35, negative scale 40, and general psychopathology scale 62. The patient was invited to attend periodic check-ups, and her symptoms decreased progressively. Risperidone therapy at 1.5 mg/day was maintained for one year. Her CGI-GI score decreased to 2, and she achieved a PANSS total score of 29. At the end of one year, the risperidone dosage was gradually increased to 3 mg/kg due to inappropriate affect and to unprovoked laughter. Her CGI-SI score increased to 6, while her PANSS scores were positive scale 32, negative scale 37, and general psychopathology scale 58. Following this increase in the risperidone dosage, a significant improvement was observed in such symptoms as unprovoked laughter, incoherent speech, and auditory hallucinations. At subsequent follow-up, she scored 2 on the CGI-GI and achieved a PANSS scale total score of 28. However, the patient represented five months later due to menstrual irregularity. She stated that this had persisted for the previous three to four months. A serum prolactin level of 67.66 ng/mL was determined (normal range 2.8–29.2). No additional pathology was determined at endocrinological or gynaecological evaluations or other biochemical and hormonal tests. We suspected that the hyperprolactinaemia and menstrual irregularity might be risperidone-associated. A CGI-GI score of 3 (significantly interfering with the patient's functioning) was determined. However, due to the benefit derived from this treatment, rather than decreasing or modifying the medication dosage, low-dose aripiprazole (5 mg/day) was added instead. The patient's menstrual cycle returned to normal two months after starting on aripiprazole, and a serum prolactin level of 17.28 ng/mL was determined.

Discussion

This report describes improvement with the addition to treatment of low-dose aripiprazole in hyperprolactinaemia and menstrual irregularity emerging as side effects following risperidone therapy in an adolescent patient diagnosed with schizophrenia.

Prolactin is secreted by lactotropic cells in the pituitary gland, and is inhibited by DRD2. D2 receptor blockage on the dopaminergic tubuloinfundibular pathway has been implicated in hyperprolactinaemia developing in association with antipsychotics [7]. This effect may vary depending on antipsychotics' D2 antagonism potential. In contrast to other antipsychotics, aripiprazole, a partial dopamine D2 agonist, has a low hyperprolactinaemia potential, and studies have shown that it reduces prolactin secretion in adult patients [8]. Aripiprazole exerts its effect through partial D2 receptor and serotonin 1A (5-HT1A) receptor agonism and 5-HT2A receptor antagonism [9]. Aripiprazole blocks D2 receptors under hyperdopaminergic conditions, and exhibits an agonist effect under hypodopaminergic conditions [9,10]. Aripiprazole is able to correct hyperprolactinaemia developing in association with a hypodopaminergic state caused in the anterior pituitary as a result of risperidone D2 receptor antagonism. It does this by creating a hyperdopaminergic environment through its partial agonistic effect on these receptors. One study of adult patients showed that prolactin levels decreased approximately 10-fold compared to placebo with the addition of adjuvant aripiprazole for hyperprolactinaemia developing during risperidone therapy [11]. The addition of adjunctive aripiprazole to paliperidone [12] or risperidone therapy have been reported to relieve hyperprolactinaemia [12–17], but have no effect on testosterone or oestradiol levels [13]. Adjunctive aripiprazole may be useful in the treatment of sexual dysfunction including hyperprolactinaemia in schizophrenia [18]. Some previous studies have also reported that prolactin-sparing antipsychotics may be a useful alternative [19] or that aripiprazole may be considered as adjunctive therapy in selected cases of psychotropic-induced hyperprolactinaemia [19,20]. Hyperprolactinaemia was reported to resolve with the addition of aripiprazole in a 30-year-old female patient receiving paliperidone for paranoid schizophrenia [21], and in a 48-year-old man receiving risperidone therapy for impulse control disorder and obsessive-compulsive disorder [22]. Amenorrhoea and hyperprolactinaemia developing in association with paliperidone palmitate use also resolved with the addition of aripiprazole in the case

of a 25-year-old woman [23]. Aripiprazole was added and paliperidone was gradually reduced over one month in the management of hyperprolactinaemia (hpl: 185.2 ng/mL) developing during 6 mg/day paliperidone therapy in a 17-year-old male patient with bipolar disorder with psychotic features. His prolactin level measured three weeks subsequently was 124 ng/mL. However, since flare-up of mood and psychotic symptoms were observed, valproic acid had to be added to treatment. Although prolactin levels then decreased to 5.2 ng/mL, no improvement was observed in other psychotic symptoms, and paliperidone was again added to 2.5 mg/day aripiprazole therapy. Improvement of psychotic symptoms was achieved after two weeks [24]. The correction of drug-associated hyperprolactinaemia in this adolescent male patient with the addition of aripiprazole is compatible with our female adolescent patient. Interestingly, aripiprazole monotherapy was effective in suppressing prolactin in a woman with microprolactinoma who developed cabergoline-induced cyclical mood swings [25]. However, although aripiprazole generally tends to reduce prolactin levels, it has also been reported to cause symptomatic hyperprolactinaemia at high doses such as 15 mg/day [26] and at relatively low doses such as 10 mg/day by exhibiting a dopamine antagonistic characteristic [27].

It is important to manage side effects such as hyperprolactinaemia without reducing the dosage of antipsychotics that maintain an existing stable state in the treatment of psychosis, particularly in children and adolescents, through the addition of an adjuvant agent. In our case, recurring psychotic attacks following a reduction of risperidone resolved with an increase in the antipsychotic dosage, but we then encountered hyperprolactinaemia. Rather than reduce the dosage of the antipsychotic agent, both the hyperprolactinaemia and the psychotic symptoms were brought under control with the addition of the partial D2 agonist aripiprazole. In conclusion, drugs used in the treatment of schizophrenia can often cause hyperprolactinaemia, and may also produce additional physical symptoms. Compliance with drug therapy is important in patients with schizophrenia, and such side effects must also be well managed. Very few data are available in the literature concerning the management of hyperprolactinaemia developing in association with antipsychotics in children and adolescents. We wish to increase awareness on the part of physicians by reporting this case of successful correction of risperidone-associated hyperprolactinaemia and menstrual irregularity with the addition of aripiprazole. Further studies are now needed on this subject.

Disclosure statement

No potential conflict of interest was reported by the authors.

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