# Atypical Depression Associated with High-dose Steroid Treatment in an Adolescent Patient Receiving Liver Transplantation

Steroid medications are widely used in treating acute and chronic graft rejection. But the psychiatric adverse effects in youth are not well addressed. We, therefore, report an adolescent patient who had developed depressive episodes under high-dose corticosteroid treatment after the liver transplantation.

## Case Report

An 18-year-old girl patient with a history of liver transplantation had received high-dose steroid treatment for graft rejection at admission. She received liver transplantation three years ago for congenital biliary atresia and liver cirrhosis. She received a low-dose prednisolone (10 mg/day) for five months after the operation. Her mood was euthymic, and she did not have any previous relevant psychiatric disorder or family history.

Two years after transplantation, she had graft rejection and was admitted to the hospital. She had received a methylprednisolone pulse therapy for two days, with an equivalent prednisolone dosage of 1250 mg/day. She developed low mood, general malaise, and loss of energy soon thereafter but was relieved after discharge. At the outpatient clinic, she received a low-dose prednisolone (20 mg/day), immunosuppressant (mycophenolate mofetil, 1000 mg/day), and tacrolimus (4 mg/day). She could attend school and maintained a part-time job.

After three months, the patient was admitted for the second pulse therapy due to immunosuppressant-induced focal segmental glomerulosclerosis. The dose of her immunosuppressant was tapered off. She had received methylprednisolone, with an equivalent prednisolone of 300 mg/day, for two weeks. That medication was then tapered off and shifted to prednisolone to 40 mg/day. One month later, she had received another pulse therapy with equivalent prednisolone of 100 mg/day for one week. She was discharged with a high-dose prednisolone (80 mg/day). But she was readmitted five days later due to her general malaise, bilateral leg edema, and proteinuria.

During the following two-month period, the patient developed Cushingoid appearance with a weight gain of five kilograms. She had depressed facial appearance, loss of energy, and hypersomnia. She felt her limbs being heavy and did not want to move, as well as she became bedridden and was unwilling to talk. Her mood was slightly lifted after some positive events but mostly depressed. Besides, she had suicide idea and wanted to give up treatment. She used to cooperate with treatment during previous admission and had positive attitude toward her illness. Her family members were worried about her newly developed attitude; they stayed with her the whole day and tried to encourage her. The result of her blood test showed leukocytosis, but the findings of blood C-reactive protein, endogenous cortisone, and immune profile were within normal limits.

After being tapered off prednisolone gradually from 80 mg/day to 20 mg/day, the patient's energy became better and she would like to walk and talk with her family. Two months later, prednisolone was further tapered off to 10 mg/day. Her mood and energy were recovered. She could start to prepare for college entrance examination, hanged out with friends, and exercised regularly.

## Comment

In the literature during 2003–2009, there are more reported steroid-induced depressive cases (40.5%) than mania cases (27.8%) compared to the early studies in the 1980s [1-3]. Bolanos et al. also noticed that compared to high-dose and short-term therapy, patients with long-term steroid therapy are more associated with anxiety and depressive symptoms than with manic symptoms. This finding has indicated the impact of length-and-cumulative steroid exposure effect on mood symptoms [4].

In the Boston Collaborative Drug Surveillance Program, the investigators found that 1.3% of patients receiving 40 mg/day of prednisone develop psychiatric symptoms, 4.6% of those 41–80 mg/day, and 18.4% of those 80 mg/day [5]. These findings suggest that most steroid-induced psychiatric reactions are dose dependent. Those investigators also stated that the higher the initial doses of prednisone, the higher the risk in inducing psychiatric symptoms [5].

In our patient, the depressive symptoms happened soon after starting pulse therapy with an equivalent prednisolone dosage of 1250 mg/day for two days, and the symptoms were relieved shortly after having been tapered it off to a much lower dosage (20 mg/day). She had been free from any mood symptom for three months between the two steroid pulse therapies, and her function was also recovered during the free interval. But with higher dosage of prednisolone (> 80 mg/day) and longer treatment period at the second pulse therapy, her depressive symptoms recurred with more severity and longer duration than those at her first episode. This observation is compatible to that in the previous study that the symptom is dose- and duration-dependent [4,5]. Although autoimmune

disease may also cause depressive symptoms, we did not witness any evidence of activated autoimmune profile in the laboratory tests concurrently with the depressive episode.

Three mechanisms between cortisol and depression have been proposed:

- Glucocorticoid exposure may induce acute functional change and neurodegeneration in the hippocampus [1]. Hippocampal neuron loss has been found when laboratory animals are under the stressed or receive corticosteroid treatment [6]. Bremner et al. found that 16 patients with major depressive disorder have decreased hippocampus volume [7].
- Damaged hippocampus loses its regulation on hypothalamic–pituitary–adrenal (HPA) axis [6], which results in developing dysregulated cortisol and glucocorticoid resistance and causing increased glucocorticoid level.
- Elevated cortisol level may inhibit brain-derived neurotrophic factor (BDNF) gene expression, which influences the survival and differentiation of serotonin neurons, and depressed symptoms develop. Studies showed that animals under longtime corticosteroid exposure (> two hours) have reduced BDNF mRNA levels [8, 9].

For treatment, Warrington and Bostwick have suggested to reduce dosage of steroid and to shorten its therapeutic course if feasible [3]. For example, to reduce risk of HPA axis dysfunction in patients receiving treatment of steroid longer than one month, we need to use the lowest possible dosage, tapering off, and then discontinuing steroid as soon as possible. They [3] have also suggested clinicians to reduce the dosage to 40 mg prednisone equivalents per day, followed by tapering it off to a physiologic dosage of 7.5 mg prednisone equivalents per day as quick as possible. For patients who cannot tolerate dosage reduction or cessation, we can use antidepressant, such as a selective serotonin reuptake inhibitor or tricyclic antidepressants, for supportive treatment. The education to patients and families about the psychiatric adverse effect of steroid, especially suicide ideation, is important, and hospitalization might be necessary for those being at risk of suicide [3, 10].

In summary, the steroid-induced depressive symptoms are dose- and duration-dependent. Monitoring the risk and benefit of steroid therapy is important to prevent psychiatric adverse effect. (The institutional review board of Mackay Memorial Hospital approved this case report for publication).

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## Conflicts of Interest

There are no conflicts of interest.

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