Рекомбинантный паратгормон (1—34) для лечения гипопаратиреоза у пациентки с аутоиммунным полигландулярным синдромом 1-го типа: первый опыт в России

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Гипопаратиреоз является одним из основных проявлений аутоиммунного полигландулярного синдрома 1-го типа. Представляя собой причину для назначения гипопаратиреоза любой этиологии, на сегодняшний день существует убедительные данные, что гипопаратиреоз может приводить к трудностям в достижении компенсации. Часто развивается аутоиммунная энтеропатия, которая приводит к тяжёлым нарушениям всасывания витамина D и лекарственных средств в кишечнике и неэффективности заместительной терапии, что требует особого подхода и дополнительных рекомендаций по лечению этих пациентов. При аутоиммунном полигландулярном синдроме 1-го типа ввиду многообразия его клинических проявлений заместительная терапия нередко приводит к трудностям в достижении компенсации. Часто развивается аутоиммунная энтеропатия, которая приводит к тяжёлым нарушениям всасывания витамина D и лекарственных средств в кишечнике и неэффективности заместительной терапии, что требует особого подхода и дополнительных рекомендаций по лечению этих пациентов. При аутоиммунном полигландулярном синдроме 1-го типа ввиду многообразия его клинических проявлений заместительная терапия нередко приводит к трудностям в достижении компенсации. Часто развивается аутоиммунная энтеропатия, которая приводит к тяжёлым нарушениям всасывания витамина D и лекарственных средств в кишечнике и неэффективности заместительной терапии, что требует особого подхода и дополнительных рекомендаций по лечению этих пациентов.

Ключевые слова: аутоиммунный полигландулярный синдром 1-го типа, гипопаратиреоз, мальабсорбция, паратгормон, PТГ1—34.

Treatment of hypoparathyroidism with the recombinant parathyroid hormone (1—34) in a female patient with type 1 autoimmune polyglandular syndrome: the first experience in the Russian Federation

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Hypoparathyroidism is one of the major symptoms of type 1 autoimmune polyglandular syndrome. Currently, vitamin D preparations are the treatment of choice for hypoparathyroidism of any etiology. The treatment with these medications is quite effective to normalize and maintain calcium level. The world experience in application of the recombinant parathyroid hormone for the treatment of hypoparathyroidism is very limited and indications for its use are not determined. However, there are increasingly more publications reflecting the experience in treatment of patients with hypoparathyroidism with the parathyroid hormone.

Type 1 autoimmune polyglandular syndrome is characterized by multiformal clinical manifestations and for this reason it is often difficult to achieve compensation using replacement therapy. Autoimmune enteropathy often develops, which leads to severe malabsorption of nutrients and drugs in the intestine and inefficient replacement therapy, which necessitates a special approach and additional recommendations for the treatment of these patients with combined pathology of several organs and systems. This article describes the first Russian experience in the use of teriparatide pump therapy in a female patients with hypoparathyroidism as a part of severe autoimmune polyglandular syndrome.

Keywords: type 1 autoimmune polyglandular syndrome, hypoparathyroidism, malabsorption, parathyroid hormone, PTH1—34.
Table 1. Manifestation of APS-1 components in a female patient

<table>
<thead>
<tr>
<th>Components of the disease</th>
<th>Age of manifestation</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic mucocutaneous candidiasis</td>
<td>4</td>
<td>Antifungals (systemic and topical therapy)</td>
</tr>
<tr>
<td>Primary chronic adrenal insufficiency</td>
<td>10</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>10</td>
<td>Alfacalcidol, calcitriol, teriparatide, calcium gluconate</td>
</tr>
<tr>
<td>Malabsorption syndrome</td>
<td>20</td>
<td>Pancreatic enzymes</td>
</tr>
<tr>
<td>Patchy alopecia</td>
<td>20</td>
<td>Ethinylestradiol + desogestrel, estradiol + dihydrogestosterone</td>
</tr>
<tr>
<td>Primary hypogonadism</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>Enamel hypoplasia</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>26</td>
<td>-</td>
</tr>
</tbody>
</table>

The patient was examined regularly once in 6—12 months at the ERC. The patient had frequent relapses of candidiasis infection of the buccal mucous membranes and nails and also recurrent candidal infections of the skin, which is a rare sign in patients with APS-1. Fungal esophagitis was also revealed. The girl received courses of systemic antifungal fluconazole medication at least 3 times a year as well as topical antifungals (various antifungal creams, ointments, nail lacquers). Topical glucocorticoid ointments were used for treating skin conditions producing a good effect.

Elevated levels of hepatic enzymes were first reported at the age of 21 years: ALT to 158 U/l, AST to 185.3 U/l, and GGT to 153 U/l. Anti-soluble liver antigen antibodies were not detected. However, occasional episodes of mild autoimmune hepatitis were suspected based on recurrent elevation of transaminase levels, excluded viral hepatitis and confirmed APS-1. At the same age, primary hypogonadism was diagnosed based on a menstrual disorder, elevated levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), and reduced estradiol levels; sex steroid replacement therapy was started. The patient developed first signs of patchy alopecia since the age of 20 years. At 26 years after surgery for complicated cataract on the left eye, retinitis pigmentosa with a significant vision loss was revealed (the presence of cataract interfered with eye fundus examination and assessing the retinal condition). The patient also had enamel hypoplasia. Sinus tachycardia (120—130 beats/min) with unknown genesis was observed during the latter several years. There were no disorders in the thyroid gland functions. Therapy using beta-blockers was indicated for tachycardia producing a positive effect.
Since 18 years, the patient complained of constipation, abdominal pain; gastroscopy and colonoscopy showed megacolon, biliary dyskinesia, and antral gastritis. Laxatives, pancreatic enzymes, antispasmodics, and probiotics were indicated yielding insignificant effects. There was a tendency to hypocalcemia that required an alfalfacidol dose increase. Alfalfacidol overdose (3.5 μg) resulted in hypercalcemia (ionized calcium 1.39 mmol/l) with associated constipation; however, constipation remained also in normocalcemia. At this age, CT scans revealed subcortical ganglia calcification (Fahr disease). Since 20 years, the patient started to complain of loose stool, abdominal swelling, feeling unwell, fatigue, and facial paresthesia. Loose stool also remained with the normal level of calcium and was not relieved with high doses of pancreatic enzymes. Esophagogastroduodenoscopy with small bowel biopsy revealed atrophy of the small intestinal mucosa, and morphology demonstrated the small intestinal mucosal subatrophy. The level of anti-gliadin antibodies was within a normal range [4.19 IU/ml (1—12)] and celiac disease was excluded.

A low level of calcium in the blood was reported and thus the dose of alfalfacidol and calcium supplement was gradually increased but without a positive effect. An attempt to replace alfalfacidol with calcitriol neither produced a positive effect. Calcium loss in the urine was excluded based on the low excretion of calcium secondary to hypocalcemia. Failure of high-dose vitamin D therapy was accounted for by the presence of malabsorption syndrome and poor gastrointestinal drug absorption. High-dose pancreatic enzyme supplementation did not restore normal absorption.

Owing to non-restored normocalcemia, recurrent convulsions (both limbs and facial spasms) in response to very high dose of alfalfacidol (20 μg/day), and requirement for frequent intravenous calcium infusions, a pilot testing of a recombinant parathyroid hormone (teriparatide) was initiated at the age of 24 years. An administration of teriparatide at a starting dose of 20 mg/day increased calcium levels in the first several days following the onset of therapy. On the 18th day, the patient experienced severe bone pain arrested with nonsteroidal anti-inflammatory drugs, but in 3 days the pain disappeared on its own and did not relapse during the whole follow-up. Normal calcium levels were achieved with a twice-daily injection of teriparatide (the total dose was 40 μg/day). Later three teriparatide injections (60—80 μg/day) were required to maintain blood calcium levels within a normal range. Nevertheless, hypocalcemia was noted in the early morning hours due to the short length of time that teriparatide concentrations are elevated. Teriparatide dose was adjusted empirically based on monitored ionized calcium levels during a 24-hour period. Therefore, continuous subcutaneous teriparatide infusion using an insulin pump was decided on. Steady normocalcemia was achieved over a 24-hour period (Figs. 1, 2). Alfalfacidol was gradually totally cancelled and this did not influence the level of calcium. Episodes of hypocalcemia during the latest two years were associated only with teriparatide dose reduction (because this medication was absent). Under the conditions of normocalcemia, calciuria was within the normal range [4.08—5.8 mmol/day (2.8—8 mmol/day)].

Malabsorption syndrome caused impaired gastrointestinal absorption of medications and electrolytes. Thus, for example, sex steroids during hypogonadism therapy were repeatedly replaced due to their low efficacy (preserved irregular cycle, intermenstrual bleeding). The patient received distinct combinations of sex steroids (ethinylestradiol + desogestrel, estradiol + dihydrogestosterone, ethinylestradiol + drospirenone) in different periods. Using the same doses of glucocorticoids and mineralocorticoids was associated with episodes of both adrenal crisis and drug overdose manifested by essential hypertension, increased body weight, and hypokalemia.

At the age of 27 years, there was an episode of severe hypokalemia. Cessation of mineralocorticoids in conjunction with potassium infusion therapy (subsequently oral potassium administration) restored normal blood potassium levels and then mineralocorticoid therapy was prescribed again. An episode of hypokalemia was accompanied by elevated blood pressure requiring angiotensin-converting enzyme inhibitors (enalapril); hypokalemia due to mineralocorticoid overdose was thus suspected. However, fludrocortisone dose was minimal (0.025 mg/day) and initiation of therapy at the same dose did not cause recurrent hypokalemia. We suppose that hypokalemia was associated with malabsorption syndrome. At the last follow-up, the patient undergoes teriparatide therapy at a dose of 40 μg/day with continuous intravenous infusion using an insulin pump, hydrocortisone, fludrocortisone, sex steroids (ethinylestradiol and drospirenone), and bisoprolol. Therapy with hydrocortisone and fludrocortisone requires a frequent correction. With the appearance of candidiasis signs, the patient receives antifungal therapy. The condition of the patient is satisfactory; she works and is actively engaged in sport.

Discussion

APS-1 is a rare hereditary disease characterized by polyorgan and polysystem autoimmune attack. The disease is known by the coexistence of three major components: chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency [1, 5]. Minor components occur less frequently in patients with APS-1: autoimmune thyroiditis, autoimmune hepatitis, autoimmune enteropathy, hypogonadism, alopecia, and vitiligo. The disease is caused by mutations in the autoimmune regulator (AIRE) gene. The autoimmune regulator protein controls immunological tolerance that prevents the immune system from attacking autoantigens. Defective function of AIRE protein causes diffuse autoimmune process. The course of the disease varies; only

DOI: http://dx.doi.org/10.14341/probl2017636379-384  
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PROBLEMS of ENDOCRINOLOGY 2017;63(6):379-384

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one component or several components can be involved simultaneously [2, 5].

The presence of co-occurring components in a patient impedes therapy. The choice of treatment is demanding in patients with malabsorption syndrome due to impaired gastrointestinal absorption of medications. Malabsorption in APS-1 can be caused by exocrine pancreatic insufficiency and inflammation in the intestinal wall. Patients with malabsorption syndrome require more thorough follow-up for the early dose adjustment of glucocorticoids, mineralocorticoids, hydroxylated vitamin D derivatives, and calcium supplement [5].

Our female patient suffered malabsorption syndrome for 10 years and was tolerant to alfacalcidol and calcitriol therapy over the last 6—8 years. Based on the clinical presentation of malabsorption, macro- and microscopic appearance of the small intestinal mucosal atrophy, fluctuated requirements for glucocorticoids and mineralocorticoids as well as a varying effect from sex steroid therapy, we supposed impaired intestinal absorption of medications, including vitamin D derivatives. Since the maximum alfacalcidol doses were ineffective in achieving compensation of hypoparathyroidism (requiring regular intravenous calcium infusions that worsened quality of life of the patient), it was decided to initiate therapy using a parathyroid hormone analogue obtained via genetic engineering. Because of unstable daily calcium levels in the blood associated with peaks and falls of teriparatide concentration after a twice-daily subcutaneous teriparatide delivery, continuous teriparatide infusion using an insulin pump was required that steadily normalized blood calcium concentration within 24 hours.

Therapy of hypoparathyroidism with calcium and vitamin D derivatives is sometimes challenged by dose adjustment. Errors can lead to hypocalcemia and hyperphosphaturia or hypercalcemia and hypercalciuria with calcium phosphate deposits in soft tissues, nephrocalcinosis and chronic renal insufficiency [6, 7]. This is thus the reason for replacement therapy using a parathyroid hormone.

There are two forms of synthetic parathyroid hormone analogues currently available: PTH 1–34 and PTH 1–84. The shortened molecule PTH 1–34 (teriparatide) is the active fragment of human parathyroid hormone. It is
registered as a therapeutic agent for severe osteoporosis. PTH 1–84 was also approved for therapy for hypoparathyroidism [3].

An experience of using a recombinant parathyroid hormone to treat hypoparathyroidism is now limited; however, the literature contains reports on successful application of a synthetic parathyroid hormone analogues in small groups of patients [4, 8—10].

PTH 1–34 and PTH 1–84 have been associated with the risk of osteosarcoma in toxicology studies in mice. Although the mice were administered drug doses exceeding the therapeutic doses several times, the risk of sarcoma cannot be completely excluded in humans [11]. Therefore, these drugs are not recommended for application in childhood. At the same time, there have been no reports of osteosarcoma over 10 years periods of using PTH 1–34 and 6 years of PTH 1–84 application in humans [12].

A number of studies compared the efficacy when PTH 1–34 was delivered subcutaneously by a twice-daily infusion versus insulin pump [10, 13]. It was shown that pump delivery provided minimum fluctuations in blood calcium levels. In our female patient, continuous subcutaneous infusion of teriparatide using an insulin pump provided normal calcium levels with minor daily fluctuations allowing cancelling totally alfalcacidol therapy and raised substantially quality of life of the patient.

**Conclusion**

APS-1 is a rare hereditary polycomponent disease. Hypoparathyroidism is one of the major components. Hydroxylated vitamin D derivatives are the treatment of choice for hypoparathyroidism. This therapy is often associated with difficulties in achieving physiologic calcium homeostasis without fluctuations in calcium concentration towards hypocalcemia and hypercalcemia. A particular problem appears in the treatment of patients with APS-1 who develop malabsorption deteriorating intestinal drug absorption. Replacement therapy using synthetic parathyroid hormone can be recommended when vitamin D derivatives fail to maintain normal calcium levels in the blood. The evident benefits of insulin pumps include more physiological imitation of parathyroid hormone release and normocalcemia without major daily calcium level fluctuations in blood.

**ACKNOWLEDGMENT**

Consent of the patient. The authors received a signed consent of the patient to publish the medical findings in this paper.

Conflict of interests. The authors declare that they have no apparent or potential conflicts of interests with the publication of this paper.

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Информация

Как цитировать:

To cite this article: