Psychotic disturbances in adult female patient with congenital hypopituitarism due to mutation in *PROP1* gene

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Abstract

INTRODUCTION: Untreated congenital hypopituitarism in adult patient is – nowadays – a very rare observation.

CASE: A 52 years old female patient, was referred to the Department of Psychiatry for psychotic symptoms, manifested as auditory pseudohallucinations with delusional interpretation, significant psychomotor agitation, anosognosia, attempts of symptom dissimulation and negativism. At admission, attention was drawn to her short stature and low body weight. Because of general weakness, she was hardly moving, her skin was pale, dry, cold, little elastic and desquamating. Neither axillary nor pubic hair could be traced. Basic studies revealed anaemia, significant hyponatraemia and hypercholesterolaemia. Hormonal tests confirmed diagnosis of hypopituitarism. Genetics studies revealed mutations (150delA and 296_297delAG) in *PROP1* gene. Combined somatic and neuroleptic treatment considerably improved the physical and psychic status of the patient, as well as strengthened her social functioning.

CONCLUSIONS: An exogenous, psychotic episode identified in the patient was induced by multihormonal hypopituitarism and disappeared after hormonal replacement therapy.

CASE REPORT

Abbreviations:

ACTH	- adrenocorticotropic hormone
BMD	- bone mineral density
CNS	- central nervous system
CO-COPD	- childhood-onset combined pituitary hormone deficiency
CRH	- corticotropin-releasing hormone
Free T3	- free triiodothyronine
Free T4	- free thyroxine
FSH	- follicle stimulating hormone
GH	- growth hormone
GTC	- guanidyne thiocyanate
IGF-I	- insulin-like growth factor I
IGFBP-3	- insulin-like growth factor-binding protein 3
IQ	- intelligence quotient
LH	- luteinizing hormone
PCR	- polymerase chain reaction
Prl	- prolactin
PROP1 gene	- Prophet Pit-1 gene
PTH	- parathormone
TMT	- Trail Making Test
TRH	- thyrotropin-releasing hormone
TSH	- thyroid stimulating hormone
WAIS	- Wechsler Adult Intelligence Scale
WCST	- Wisconsin Card Sorting Test

INTRODUCTION

Childhood-onset combined pituitary hormone deficiency (CO-COPD) belongs to rare endocrinopathies, its prevalence in newborns being assessed at 1:8,000 (Ascoli & Cavagnini 2006). At present, such cases are diagnosed already in early childhood and are effectively treated. Any identification of untreated case of this disease in adult person belongs to casuistry. In this paper, we present a case of a 52 years old female patient with CO-COPD and psychotic disturbances.

Figure 1. A photograph of the patient, juxtaposed with a random person from the medical personnel for comparison of body height and build proportions.

CASE

A 52 years old female patient was referred to the Department of Psychiatry with psychotic symptoms, lasting for a few days and including auditory pseudohallucinations, with delusional interpretation and significant psychomotor drive. At admission, the patient had normal auto- and allopsychic orientation. Her mood was neutral, while the psychomotor drive was slightly depressed, inclined towards irritating tension. She was in good logical-verbal contact. She confirmed that, prior to hospitalisation, she had experienced auditory hallucinations, while negating them at the time of admission. She was not fully critical towards those experiences. She did not verbalise any delusions and negated suicidal thoughts and tendencies. Physical examination revealed an anemic, very short patient (height 116 cm, weight 19 kg; Figure 1). Her blood pressure was 100/60 mm Hg, pulse 80/min. No secondary nor tertiary sex characters were traceable. The patient was cachectic, weakened, demonstrated decreased appetite, had pale, dry, cold, little elastic and desquamating skin, thinned hair on her head and no axillary or pubic hair.

Medical history

The patient was born as the first child in the family, finished a special school and did not attempt any professional activity. She used to live with her mother who passed away a few years before. Since that time, she had been taken care of by her younger sister who had been her legal guardian. In the patient's childhood, there were short attempts of growth hormone therapy which was, however, discontinued because of objections raised by the patient's mother. The patient had not received any hormonal medication for the last several years. In 2001, the patient was neurologically treated for headaches and vertigo. During the same year, she suffered from epicondylar fracture of the femur. In 2005, she was hospitalised at the Department of Internal Diseases because of bilateral pneumonia and significant dyselectrolitaemia. It was then confirmed that the patient had not received any hormonal treatment for several years.

Laboratory results

At admission anaemia, hyponatremia and hypercholesterolemia (Table 1) and significantly decreased concentrations of FT_3 and FT_4, despite of normal level of TSH were revealed. Then, the patient has been transferred to the Department of Endocrinology and Metabolic Diseases, where features of combined pituitary hormone deficiency and secondary hyperparathyroidism were demonstrated (Table 2). Results of TRH test are shown on Figure 2. The patient's bone age – 13 years and 6 months – was determined by wrist X-ray (Figure 3). Since the patient lost her milk teeth in 2006, her dentition was radiologically examined, revealing five (5) permanent teeth in the jaw, including one erupted tooth,

and five (5) permanent teeth in the lower jaw, including one erupted tooth.

Lumbar spine densitometry (DXA, Prodigy, GE, USA) was performed, finding BMD L_2–L_4 0.624 g/cm^2, T-Score –4.8, Z-score –3.0.

MRI imaging was performed in FSE and SE sequences, in PD, T1- and T2-dependent images and in axial, sagittal and coronal planes, before and after contrast administration. MRI revealed anterior pituitary of reduced size, with better preserved posterior lobe, total diameters were 2 × 4 × 4 mm. Pituitary stalk and optic chiasm were normal.

Psychological examination

Some serious lesions in CNS (central nervous system) of patient were stated. In the Benton Visual Retention Test (Sivan 1996), significant memory deterioration was observed and in the Verbal Fluency Test – the weakness of verbal fluency were also observed (Vlaar & Wade 2003). In the Visual-Movement Gestalt Test by Bender (1998), and in the Trail Making Test by Reitan (TMT) (1958), deep impairments were observed, regarding to the psychomotor speed and efficiency, as well as deep deficits of the visual-spatial operative memory and executive functions. In the Wisconsin Card Sorting Test (WCST) (Jaworska 2002), the executive functions and the working memory seemed obviously mostly affected. The patient's intelligence quotient (IQ), measured by Wechsler's test [Wechsler Adult Intelligence Scale, WAIS-R (PL)] (Brzeziński & Hornowska 1993), was at the borderline of its normal values and mental retardation.

Genetic studies

Genomic DNA was extracted from the whole blood with the use of guanidyne thiocyanate (GTC). Then purification of DNA with the use of phenol and chloroform was performed. Genomic DNA was precipitated with 95% ethanol, then dried, resuspended in sterile water and stored at –20 °C until direct sequencing. The first step consisted of PCR reaction, in which fragment of exon 2 of *PROP1* gene was amplified. PCR product was 366 bp long, and was amplified with the use of Cy5 labeled primers: Forward 5'-TGGTCCAGCACC-GAGGAG-3' and Reverse 5'-TGCCCAACATTCTAT-GATAGC-3'. The reaction mixture consisted of 2 µl of DNA (50 ng/µl) in a final volume of 25 µl, containing 19 µl of nuclease free water, 2.5 µl PCR buffer, 0.25 µl of the forward oligonucleotide primer, 0.25 µl of the reverse oligonucleotide primer, 0.8 µl dNTPs and 0.2 µl Taq polymerase (Sigma). After an initial denaturation at 94 °C for 4 minutes, the PCR protocol included 32 cycles of denaturation (at 94 °C for 30"), annealing (at 62 °C for 30") and extension steps (at 94 °C for 90"), followed by a final extension step for 5 minutes at 72 °C. The PCR product was purified with the use of Wizard® PCR Preps minicolumns (Promega), according to the manufacturer protocol. During the direct sequencing step 2 µl of appropriate ddNTPs were added to the tubes. Then the reaction mixtures of total volume 17 µl, containing 6 µl of nuclease free water, 2.5 µl reaction buffer, 2.5 µl of the forward or reverse oligonucleotide

Tab. 1. Results of biochemical tests in the patient on admission and 6 months later.

	Units	On admission	6 months later	Reference range
RBC	× 10^6/µl	2.99	4.66	4.2–5.4
Hb	dl	9.1	14.2	12–15
Htc	%	26.1	41.1	36–45
Fe $^{++}$	µg/dl	41	90	49–151
Cholesterol	mg/dl	291	275	120–200
Sodium	mmol/l	126	140	135–145
Potassium	mmol/l	3.7	4.3	3.5–5.0
Creatinine	mg/dl	0.47	0.6	0.6–1.4

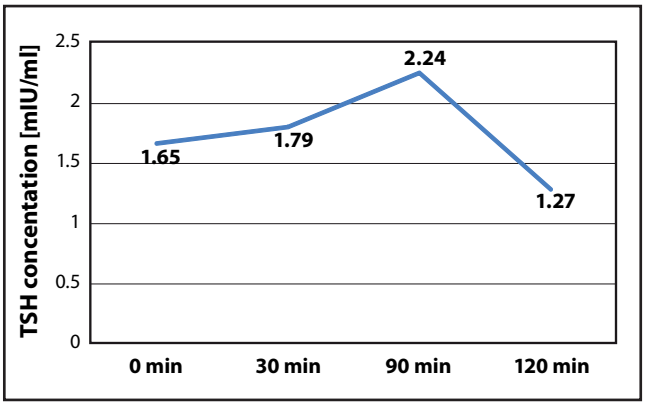

Figure 2. Results of TRH test. TSH concentrations obtained after administration of 200 µg of TSH. Normal response: >6 mIU/ml or increase 3–4 × in 30 min.

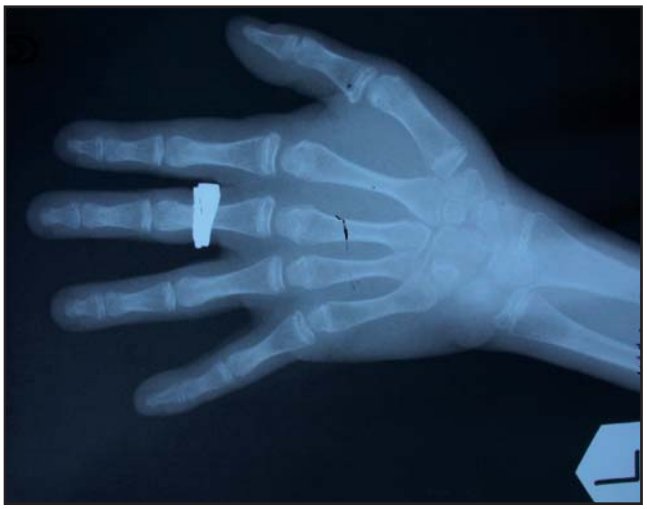

Figure 3 . The X-ray of the left wrist demonstrated skeleton standards typical for 13 years and 6 months

Tab. 2. Results of hormonal tests in the patient on admission and 6 months later.

		On admission	6 months later	Reference range
TSH	mU/l	1.26	<0.05	0.27–4.2
Free T_4	ng/dl	0.170	1.04	0.93–1.7
Free T_3	pg/ml	0.302	4.52	1.8–4.6
LH	IU/l	< 0.100	<0.1	1.7–8.6
FSH	IU/l	0.200 IU/l	0.24	1.5–12.4
Testosterone	ng/ml	< 0.02	<0.02	0.06–0.82
Estradiol	pg/ml	<5	<5	Prepubertal: <10.0 Early follicular: 24.5–195.0 Luteal: 40.0–261.0 Postmenopausal: <10.0–39.5
IGF-1	ng/ml	<25.0	<25.0	94–252
IGFBP-3	µg/ml	2.1	2.1	3.3–6.7
Cortisol Basal 8 am Max. stimulation after CRH Max. stimulation after ACTH	µg/dl	 7.92 10.56 11.34	 12.16 – –	 6.2–19.4
ACTH	pg/ml	<10.0	<10.0	
After stimulation of CRF	pg/ml	<10.0	<10.0	
Prl	ng/ml	0.959	0.62	3.4–24.1
PTH	pg/ml	126.2	39.88	15–65
Total calcium	mmol/l	2.17	2.37	2.2–2.5

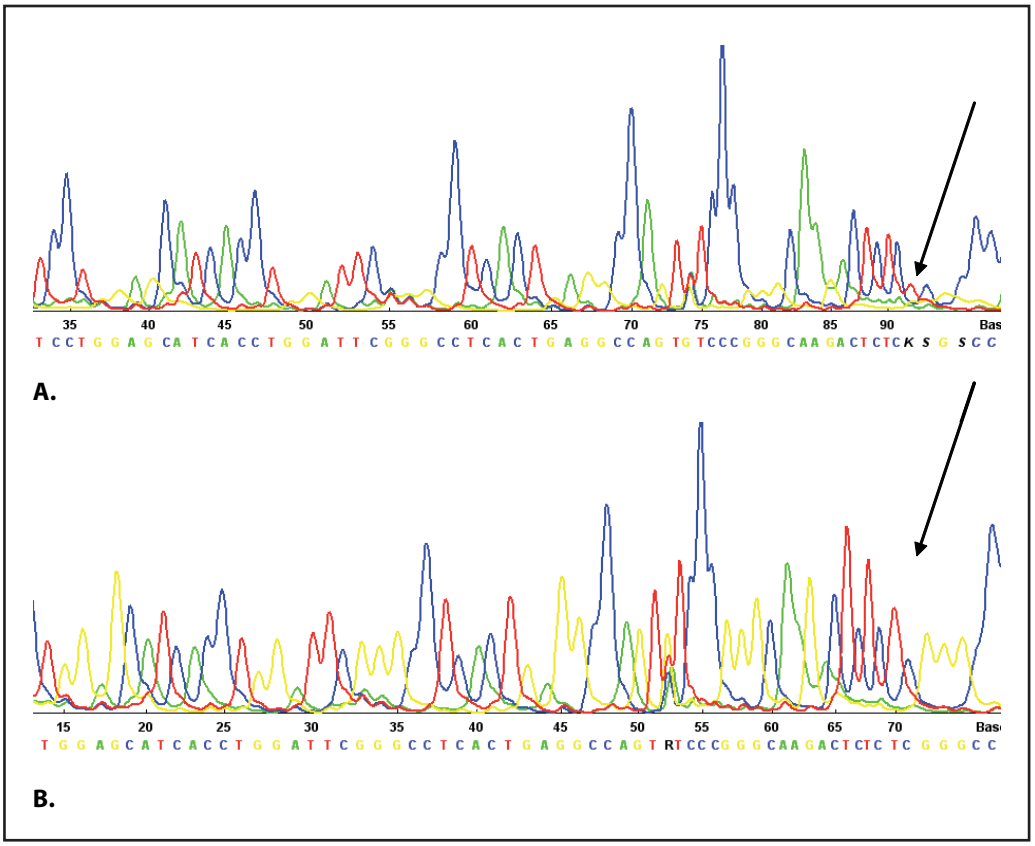

Figure 4. Heterozygous 296_297delGA mutation. A) Sequencing from Reverse primer. The 296_297delGA mutation indicated by an arrow. B) Sequencing from Reverse primer. The wild-type sequence.

primer 1 µl of polymerase and 5 µl of purified PCR product were prepared. The protocol included 50 cycles of reaction. After an initial denaturation at 94 °C for 3 minutes, the sequencing protocol included 50 cycles of denaturation (at 94 °C for 30"), annealing (at 62 °C for 30") and extension steps (at 94 °C for 90"), followed by a final extension step for 1 minute at 72 °C. Reaction was terminated by the addition of STOP buffer and thermal denaturation at 94 °C for 3 minutes. Samples were transferred from the tubes to the appropriate lanes of a polyacrylamide gel. Electrophoresis and detection was carried out on an AlfExpress system at 55 °C for 10 hours. As the result, two (2) mutations of *PROP1* gene were found – 150delA and 296_297delAG (Figures 4 and 5).

Medical therapy

Initial treatment involved gradual correction of electrolyte and hormonal deficits in order to obtain sodium concentrations in the initial stage not higher than 125 mmol/l. L-thyroxine administration was started (initial dose of 6.25 µg), while controlling hormone concentrations, together with hydrocortisone in dose of 10 mg/d. Calcium and vitamin D_3 supplementation was instigated. At present, the patient receives 25 µg of L-thyroxine, 10 mg of hydrocortisone, calcium carbonate (500 mg in conversion to elementary calcium) and alphacalcidol (Alfadiol) in dose of 0.25 µg/d. Iron and vitamin preparations were prescribed because of anaemia and decreased iron concentrations. The administration of iron was withdrawn after normalisation of blood count.

In the initial period of therapy, no antipsychotic agent was recommended, while benzodiazepines were extemporaneously administered. The patient's somatic condition demonstrated gradual improvement. Taking into account the patient's psychic condition, she became more talkative and her complex activity was, in general, more intensive. Her mood remained still indifferent, however, it had begun to change. The patient was still expressing persecutory delusions, as well as reference and Capgrass delusions. She negated hallucinations, being totally uncritical towards those sensations. Having obtained a relative electrolyte and hormonal stability, olanzapin administration was introduced in dose of 2.5 mg/d. The patient's psychic condition continued to improve over the course of three (3) subsequent weeks. Remission of creative symptoms was followed by patient's insights into real events. Sleep quality improved together with increased appetite, contributing to body weight gain by approximately 4 kg. It was decided to maintain olanzapin therapy at 2.5 mg/d. On discharge, the patient was properly allo- and autopsychically oriented and demonstrated balanced mood

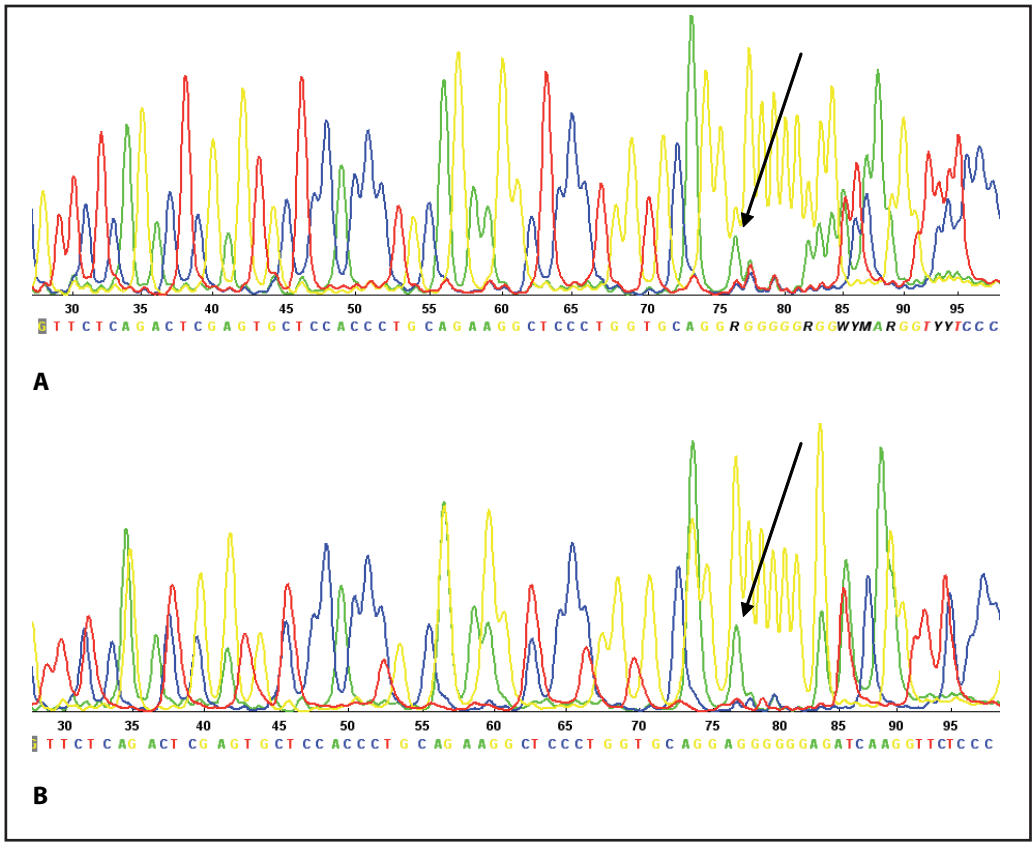

Figure 5. Heterozygous 150delA mutation. A) Sequencing from Forward primer. The 150delA mutation indicated by an arrow. B) Sequencing from Forward primer. The wild-type sequence.

and psychomotor drive. She did not reveal any creative symptoms, while declaring criticism towards her health condition. She was discharged with recommendation of further psychiatric and endocrine therapy and administration of hormonal supplementation (L-thyroxine, hydrocortisone) and an antipsychotic agent. The treatment was continued for two subsequent months and, then, gradually withdrawn. At present, the patient is in good psychic condition without any antipsychotic intervention. She has gained some body weight and her skin and hair demonstrate considerable improvement.

DISCUSSION

The reported case concerns the occurrence of psychotic symptoms in the course of untreated CO-COPD, caused by mutation in *PROP1* gene.

The most characteristic symptoms of congenital hypopituitarism include dwarfism, hypogonadism, lack of sexual maturation features, hair loss and progressive weakness (Ascoli and Cavagnini 2006), while psychotic disturbances are very rarely described as a symptom of hypopituitarism (Leo *et al.* 1998).

However, an exact reason for psychiatric disturbances in presented patient is hard to unequivocally ascertain. It might result from endocrine disorders or occurred quite independently. We incline to accept the hypothesis that the occurrence of creative (psychotic) symptoms is caused by hormonal deficits. This view is supported by the observed remission of psychotic symptoms, following hormonal status improvement; the symptoms did not recur despite the psychotropic agent withdrawal.

Factors responsible for development of psychiatric symptoms include hypothyroidism, GH deficit, hyponatremia due to secondary hypothyroidism and hypoadrenalism (Kurtulmus & Yarman 2006, Haralampos *et al.* 2002). Finally, the general psychic condition may also be influenced by hypogonadism and the patient's feelings associated with her short stature and appearance.

There are numerous data on the effects of hypothyroidism on mental status (Leigh & Kramer 1984; Reus 1986), including depression, which is the most common disease (Reus 1986, Heinrich & Grahm 2003), as well as cognitive disorders. On the other hand, 5–15% of hypothyroid patients present various forms of psychosis, including Capgras syndrome (Heinrich & Grahm 2003), similarly to the presented case. However, though many reports demonstrating induction of psychiatric disorders by GH deficits were published (Reus 1986, Bülow *et al.* 2002), such hypothesis may – in this particular case – be rejected, as the disorders subsided without GH supplementation.

Clinical symptoms of sodium deficit become visible, when its concentration falls below 120 mmol/l (Kurtulmus & Yarman 2006). At first, the symptoms include headaches, appetite loss, nausea, vomiting, orientation disturbances, irritability, anxiety, excitement and – less frequently – psychotic symptoms (Soupart & Decaux 1996). The hypothesis, explaining the occurrence of psychotic symptoms only by hyponatraemia, is contradicted by the fact that the patient had already experienced sodium levels of approximately 108 mmol/l, with none of the above-mentioned clinical symptoms, what may indicate very a good adaptation of the patient to low sodium levels. In our opinion, the worsening in patient state was caused by the developing ACTH deficiency. In *PROP1* gene mutated patients, hormonal deficiencies, including GH, TSH, prolactin (Prl), LH, and FSH are present from childhood but ACTH deficiency reveals later, in 4th or 5th decade of life (Agarwal *et al.* 2000, Pernasetti *et al.* 2000).

Mutations of *PROP1* gene (coding transcription factor, taking part in regulation of proper development and differentiation of somatotropes, lactotropes, thyrotropes and gonadotropes) are the most common genetic cause of CO-COPD. Prevalence of these mutations among population of patients with CO-CPHD reached about 55% of cases (Cogan *et al.* 1998). That encouraged us to start genetic analysis in described patient from *PROP1* gene. Mutations, as revealed (150delA and 296_297delAG) by us, are the most frequent molecular defects, leading to multiple pituitary hormone deficiency (Wu *et al.* 1998, Voutetakis *et al.* 2004). Deletion of adenine in position 150 of *PROP1* gene (150delA) causes a frameshift in the coding sequence. Therefore, transcription stops at codon 164 (V164X) and protein lacks transactivation domain. Similar situation appears in 296_297delAG defect that also leads to truncation of protein which – in consequence – does not possess DNA-binding and C-terminal transactivation domains. These two defects cause lack of transcriptional activity of *PROP1* factor and pituitary hormone deficiency, usually with pituitary hypoplasia, similarly to our patients.

Management of such a patient requires extraordinary approach and collaboration of many specialists. When neuroleptic agents are administered, they should be dosed with care, avoiding agents with strong adrenolytic effects in order not to expose the patient to arterial pressure drops, as in cases of the adrenal cortex and thyroid hormone deficits, a tendency towards low arterial pressure is observed. It seems that it should be recommended the administration of such drugs which – in their receptor profile – demonstrate stronger effects on the histaminergic system. Stimulation of appetite seems in such cases favourable, acting synergistically with hormonal therapy (Bleuler 1951).

The analysis of the above case confirms good clinical effects of gaining control over deep endocrine abnormalities, resulting in improved clinical condition, thanks to collaboration of specialists from different medical branches. It also raises a reflection about irreversible consequences of too late therapy implementation and about the necessity of persuading the patient and her family to adhere to prescribed therapy in long-term perspective.

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