Adams-Oliver syndrome (AOS; MIM 100300), is a rare genetic condition, for which terminal transverse limb defects (TTLD) and aplasia cutis congenital (ACC) are the major diagnostic criteria (1). The syndrome was first described by Forrest Adams and C. Peter Oliver in 1945 in a three-generation family with autosomal dominant inheritance with variable expressivity (2). However, several studies have suggested a recessive pattern of inheritance (3–9). The wide spectrum of clinical expressions of AOS includes cardiovascular malformations, lesions in the central nervous system (CNS), with various impact on the psychomotor development, as well as impaired growth (1, 10–12). However, there is a lack of data on possible underlying endocrine mechanism in the latter disturbance.

To our knowledge this is the first report on growth pattern accompanied by hormonal assessment in patients with AOS, as well as the first description of a short-statured child with AOS features treated with recombinant growth hormone (GH).

**Patients and methods**

Three children with clinical features of AOS were followed in terms of growth and development for the mean period of 3.2 years. In each case, the hypothalamic-pituitary axis was evaluated on the grounds of basal or stimulated hormonal assays,
Kalina et al.

depending on clinical indications. At the first endocrine evaluation, children were at the age of 1.9 years (Patient 1), 3.6 years (Patient 2) and 8.2 years (Patient 3), and did not show any pubertal signs.

Auxologic birth data were taken retrospectively, whereas during the observational period following parameters were derived from anthropometric measurements: number of standard deviations (SD) for the height (hSDS), occipital-frontal circumference (OFC SD), and the weight appropriate for the height. Besides, change of hSDS in a year on the basis of 6-month follow-up (delta hSDS), as well as the difference between the child and mid-parental hSDS (hSDS-mpSDS) were evaluated. All calculations were carried out in relation to the national auxologic charts (13). Sexual development was assessed according to the Tanner staging.

Concentrations of pituitary hormones [thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin (PRL)], and peripheral hormones (free thyroxine fT4, cortisol), as well as the insulin-like growth factor type 1 (IGF-1) were assayed in each case. Additionally, in Patient 1, the human chorionic gonadotropin (HCG) test with determination of testosterone levels was carried out according to a 5-day protocol. In Patient 3, GH was assessed in the night profile and in two provocative tests with clonidine and insulin respectively, according to the national protocol qualifying children for the GH therapy. All the aforementioned parameters were assayed using chemiluminescent immuno-metric method (Immulite, Euro/DPC, Llanberis, UK). Besides, glucose profile (fasting, postprandial, and night glycemia) was performed in all cases. Oral glucose tolerance test was carried out in Patient 3.

Neuroimaging before and after intravenous contrast injection was performed by means of the magnetic resonance imaging (MRI) in Patients 1 and 3, and by the computed tomography (CT) in Patient 2. Neurologic examination also comprised electroencephalograms and evaluation of the psychomotor development by a neurologist and a psychologist. Cardiological assessment included electrocardiograms and echocardiography.

Karyotypes were normal in all cases.

Patients’ parents gave informed consent to participate in the diagnostic procedures and the follow-up.

Clinical report

Patient 1

The boy was the first and the only child of young, healthy, non-consanguineous parents. In the 7th month of gestation oligohydramnios was visualized and the child was delivered at 37 weeks of gestation by caesarean section, with Apgar score 4/5/6, birth weight of 1570 g (−3.36 SD), length 47 cm (−0.94 SD), OFC 28 cm (−3.71 SD), and signs of intrauterine growth retardation (IUGR). Newborn period was complicated by bacterial sepsis and hyperbilirubinemia. Complex congenital defects were found at birth, including hydrocephalus, hypertrophy of the right heart ventricle due to premature closure of the ductus arteriosus, and Peters’ anomaly in the form of hydropsalos of the left eye, corneal staphyloma of the right eye and cataract. Bone defects comprised absence of distal phalanges 1–5 of the right hand, digits 1–5 of the left foot, and right metatarsal bones. Remaining nails were hypoplastic. Skull sutures were wide, with area of aplasia cutis measuring 10 cm × 10 cm over the vertex of the scalp with an underlying bony defect. There was facial dysmorphism due to eye defects, prominent frontal suture and midfacial hypoplasia. Other abnormalities included simian crease, cobbler’s chest and scoliosis.

At the age of 6 months, myoclonus followed by atypical absences and tonic seizures were observed. Electroencephalogram revealed paroxysmal changes more pronounced in temporal regions, and combined pharmacotherapy was introduced. At the age of 7 months, due to increasing ventriculomegaly, endoscopic ventriculocysternostomy and implantation of a ventriculoperitoneal shunt were performed.

Neurological examination showed horizontal nystagmus, decreased axial muscle tone, increased in extremities, preserved tendon reflexes and dystonic movements. Psychomotor development was significantly delayed, evaluated at the age of 19 months at the level of 1 month (Brunet-Lezine scale). MRI revealed signs of disturbed neuronal migration and segmental polymicrogyria, as well as abnormalities of midline CNS structures, including hypoplasia of the corpus callosum, mild ectopy of cerebellar tonsils, and a cyst of the septum pellucidum.

Owing to poor growth rate and hypoplastic CNS structures, the boy was submitted to further auxologic and endocrine assessment. At the age of 1.9 years his body length, weight and OFC were all below 3rd centile (76 cm; 5.79 kg; 40 cm; respectively), indicating significant length
deficit (hSDS = −5.0), 4 kg of underweight for the height, and microcephaly (OFC SDS = −7.3). The deviation from the parental height hSDS-mpSDS was significant, and was as low as −4.3 SDS. During the follow-up, further slowing of the growth rate (delta hSDS/year = −1.0; Fig. 1) and poor weight gain were observed. Besides, cryptorchidism and inguinal hernia were found on the left side, whereas the right testis was migrant, but easily drawn to the scrotum.

All the hormonal assays were normal and appropriate for the prepubertal period, apart from repeated low IGF-1 levels. Maximal basal IGF-1 concentration was 20 ng/ml (≤2 SD, according to local laboratory norms). In the HCG test appropriate testosterone response was noted, with over fivefold increment after HCG administration. No hypoglycemic incidents were detected.

Owing to numerous surgical and neurological interventions, further diagnostics for GH deficiency have not been undertaken yet. There was some weight improvement after gastrostomy; however, the patient needs careful follow-up of further growth and development.

Patient 2

The girl was the second child of young, healthy non-consanguineous parents. Her older sister was healthy. A further pregnancy resulted in a spontaneous abortion in the 10th week of gestation. The pregnancy of which the proband was born was complicated by vaginal bleeding in the second month of gestation and since then the pregnancy had been pharmaco logically sustained. There was suspicion of IUGR; however, the girl was born by vaginal delivery at term, with the weight of 3220 g (0.42 SD), length 53 cm (1.41 SD), and OFC of 32 cm (−2 SD). At the age of 2 months she underwent cardiosurgical operation of the double outlet right ventricle. Due to the postoperative second/third degree atrioventricular block, a pacemaker and an epicardial electrode were implanted at the age of 6 months. Bone defects included absent right toes 3–5 and the right metatarsal bones, as well as bilateral lack of distal phalanges 5. Remaining nails were hypoplastic. Later, one scalp defect 3 cm × 3 cm at the vertex, without underlying bone defect was noted. Dysmorphic features included microcephaly, malocclusion, hypothelorism, flat, wide nose base, short neck and scoliosis. Neurological examination was normal. At the age of 3 years a paroxysmal episode was observed, with abnormal electroencephalographic pattern without paroxysmal activity. No pharmacotherapy was introduced. Brain CT showed wide fourth ventricle and wide peristern cisterns without increased intracranial pressure. Global psychomotor and intellectual development were normal (IQ = 98; Terman-Merrill scale).

At the age of 3.6 years, her height (98.5 cm; hSDS = −0.46) was within 25–50th centile range, weight appropriate for the height, but OFC remained deficient (47 cm; OFC SD = −2.44). In the first and the second year of the follow-up her growth was satisfactory (delta hSDS1 = 0.36 and delta hSDS2 = 0.14, respectively); however, showing a slowing down trend in the recent year (delta hSDS = −0.58) (Fig. 2).

The concentration of TSH was assayed during neurological examinations, revealing elevated values. Owing to the fact that two other patients with AOS under our supervision were then suspected for endocrinopathies, basic hormonal parameters influencing growth and development, as well as carbohydrate metabolism, were also assessed in Patient 2. The only abnormality found was subclinical hypothyroidism, manifesting with increased TSH levels, along with normal FT4, low anti-thyroid antibodies, and normal thyroid ultrasound image. Levothyroxine treatment was introduced. At the moment the girl is euthyroid.

Patient 3

The girl was delivered at term by spontaneous vaginal labor, as the first child of young, healthy, unrelated parents. The Apgar score was 10, birth weight was 2550 g (−1.92 SD), length 50 cm (−0.24 SD), OFC 32 cm (−2 SD) and there were signs of IUGR. The pregnancy was complicated in the first trimester by respiratory viral infection in the mother. The second child of the parents was healthy.

The proband was born with absent toes 2–5 of the right foot and a hypoplastic nail of the right hallux. There were two areas of atrophic skin (2 cm × 3 cm and 1 cm × 2 cm, respectively) at the vertex. The skin had a texture of cutis marmorata. Dysmorphic features included microcephaly, midfacial hypoplasia, secondary prognatism with wide dental spacing, downslanted palpebral fissures, low-set ears, depressed nasal bridge, and broad nares. Besides, thoraco-lumbar scoliosis was observed. No cardiac defects were found.

Psychomotor development has been moderately delayed. The girl attends school for children with special needs, occasionally presenting behavioral disturbances in the form of tantrums. No epileptic episodes have been reported.

At the age of 8.2 years, she was referred to an endocrinologist due to poor growth rate and
Fig. 1. Growth curve of Patient 1 plotted against the growth chart of healthy Polish boys. Bold, broken line indicates growth based on retrospective data; bold continuous line indicates growth during the follow-up.
Fig. 2. Growth curve of Patient 2 plotted against the growth chart of healthy Polish girls. Bold, broken line indicates growth based on retrospective data; bold continuous line indicates growth during the follow-up.
short stature. The girl presented with significant height deficit, measuring 104.2 cm (hSDS = −5.56), significantly deviating from her parents’ height, with hSDS-mpSDS as low as −4.17. Her height velocity showed a slowing down pattern (delta hSDS1 = −0.66). She weighed 15.8 kg, which reflected 1.2 kg underweight for the height. Her OFC was below 3rd centile and measured 49 cm (−2.6 SD).

Neuroimaging revealed the small pituitary with borderline height for the bone and calendar age, and segmental polymicrogyria. Maximal GH concentration was 8.1 ng/ml. Levels of IGF-1 were also low and the maximal value was 52 ng/ml (<−2 SD). All other assayed hormones were within normal ranges. The bone age was delayed by 1 year according to Greulich-Pyle standards.

In the connection with the above, the girl started GH therapy at the age of 8.6 years. In the first year of therapy there was significant improvement of height velocity (8.5 cm/year vs. 3 cm/year prior to the treatment), and the change in hSDS reached positive value of as much as 1.36. In the second year of therapy, growth rate stabilized, and it was estimated as much as 5 cm/year, the value of delta hSDS remaining positive (0.05) (Fig. 3). The patient did not show any signs of sexual development, despite gradual but harmonic advancement of the bone age. The dosage of GH was gradually increased from 0.025 to 0.04 mg/kg/24 h. Apart from growth-promoting effect, improvement of muscular strength and gross coordination was also observed during GH therapy. No adverse events have been noted so far. Carbohydrate parameters are checked regularly once a year, and both glyemia and insulinemia have always been within normal ranges.

Discussion

Pathogenesis of AOS has not been elucidated yet; however, it has been suggested that the constellation of clinical findings result from early embryonic vascular disruption (7, 14–19). Several gene candidates involved in limb and skull development were also investigated; however, at present no disease-causing gene has been identified (20). In fact, AOS may manifest with wide spectrum of clinical expressions, of which short stature and undescended testes are in the scope of the endocrinologist interest (1, 19, 21–23). Many subjects with ACC/TTLD and additional features may represent unrecognized microdeletion or duplication syndromes (1). However, the molecular basis of these disorders remains to be investigated, and for today they may be considered as Adams-Oliver like syndromes. The diagnosis is still based on clinical criteria (1), which were also met by patients included in our study.

Growth velocity and sexual development are one of the most important indicators of child’s health, reflecting complex interactions of environment, genetics and the endocrine system. Short stature is caused mostly by extra-hormonal factors, including familial and constitutional conditions, systemic disorders and chromosomal aberrations. Increasing number of cases, previously described as idiopathic short stature, find explanation in molecular abnormalities. On the other hand, endocrinopathies constitute for less frequent causes of short stature; however, arising possibility for appropriate treatment with a chance for normal growth and development (24).

Another group which may exhibit poor catch-up growth are children born small for gestational age (SGA) and/or with signs of IUGR (25). Children with AOS may also experience IUGR, as it was described in several reports (6, 7, 19, 23, 26–29). Similarly, impaired fetal growth was suspected in all our patients, and two of them were born SGA with signs of hypotrophy. Patients 1 and 3 manifested poor height velocity from birth, whereas height of Patient 2 followed the 25–50th centile until the age of 6, when the tendency for growth deceleration was observed. Short stature in AOS has been described by several authors (6, 7, 23, 30); however, normal growth parameters have been recorded as well (1, 5, 8, 15). More frequently microcephaly is reported (1, 12, 26, 27, 29), in some cases with OFC evolution to normal in the course of time (15, 29), or even macrocephaly (5, 31). All our patients were born and remained microcephalic during the follow-up.

Auxologic and hormonal deficits may also be associated with CNS lesions, and in particular with midline defects. The latter have been described as markers for hypothalamic-pituitary deficiencies; hence, the raising role of neuroimaging in differential diagnosis of short stature (32–33). Such abnormalities were found in Patient 1, who also presented significant growth retardation. In such cases, from a clinical point of view, the most essential is to exclude severe hormonal deficiencies resulting in hypoglycemia, namely adrenocorticotropic hormone and GH deficiencies. In our patient glucose levels were normal; however, IGF-1 concentrations were low on several occasions. In such a case GH deficiency cannot be excluded. Clearly, Patient 1 suffered from complex disorders.
Fig. 3. Growth curve of Patient 3 plotted against the growth chart of healthy Polish girls. Bold, broken line indicates growth based on retrospective data; bold continuous line indicates growth during the follow-up; GH indicates initiation of GH therapy.
and several factors influenced his developmental outcome.

Patient 2 did not show any severe CNS lesions in the CT scans, and her growth, despite the complex heart defect, was generally normal. Subclinical hypothyroidism is rather an accidental finding in this case. After levothyroxine had been applied, slight improvement of growth velocity within the same centile range was noted. Recently the girl has been reducing growth velocity, demanding further observation. However it is believed, the girl’s growth should not be generally impaired, providing the euthyroid state is maintained.

The case of Patient 3 is of special interest as the girl was diagnosed thoroughly for GH deficiency. Decelerating height velocity was the main indication for such procedures. Detected GH concentrations may be defined as partial GH deficiency. Although it is believed that growth defects in developmental syndromes result mainly from impaired cellular growth, however, some abnormality in GH/IGF-1 axis may also be hypothesized. Broader availability of recombinant GH expanded indications for GH therapy, and apart from correction of height, it may have positive influence on body composition, energy expenditure, cognitive functioning and muscle tone, as it was described among others in patients with Prader-Willi syndrome, Noonan syndrome or Silver-Russel syndrome (34). After significant growth improvement in the first year, subsequent years of GH therapy in Patient 3 might not seem as satisfactory; however, there were other benefits derived from GH treatment, namely strengthening muscle tone and improving motor coordination. We have not observed any GH-related complications, however, issues like long-term safety and cost-effectiveness of GH therapy in such a rare disease must be taken into consideration. The girl’s puberty has not progressed yet, requiring further follow-up and possible dynamic evaluation for gonadotropin secretion. The MRI findings in this patient are not characteristic for hormonal deficiencies, as even the smaller size of the pituitary may evolve in the course of time (35). However, considering polymicrogyria, another CNS finding in this patient, to be associated with developmental delay, we support postulates of some other authors that neuroimaging and appropriate neurological examination are necessary for the identification of AOS patients at risk (12).

Confrontation of these three patients was intentional. Patients 1 and 3 clearly showed short stature and poor growth velocity, which also found laboratory expression of low concentrations of IGF-1 in both cases and additionally low levels of GH in Patient 3. Although Patient 1 was investigated only partially with respect to GH deficiency, clinical symptoms like significantly decreased growth velocity, hypogonadism, neonatal hyperbilirubinaemia and midline defects were indicative of a pituitary endocrinopathy. In such a case invasive investigations, including GH stimulation testing, due to the young age of the patient and coexisting abnormalities, were unnecessary. On the other hand, Patient 2 may be considered as a control subject, because the girl showed normal auxology, followed by normal laboratory markers. Presenting her, in contrast to two other patients, provides evidence that children with AOS and associated clinical features of endocrine disturbances, and particularly those slowing down growth, are probably to require appropriate specialist follow-up. Hence, we support the standpoint that careful clinical evaluation is of priority, selecting patients for further complex diagnostics.

Our intention was to underline the need of differential diagnosis in case of growth disturbances in congenital syndromes. Short stature has been described in several reports concerning AOS; however, there is no clear information on growth velocity and possible overlapping causes or correlation with certain CNS lesions. We believe our report adds new information on the phenotype of children with AOS, as well as on possibilities of their management. There should be an interdisciplinary approach to the follow-up of AOS children, with careful monitoring of their psychomotor development, growth and puberty.

Acknowledgements

We are grateful to Krystyna Chrzanowska, MD, PhD, the Head of the Genetic Out-patient Counseling Unit in the Children’s Memorial Health Institute, Warsaw, for broadening our access to literature references. We would also like to thank the patients and their parents for the kind and permissive cooperation.

Conflict of interest

Nothing to declare.

References

Clinical phenotype of Adams-Oliver syndrome


