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Amiodarone-induced thyroid dysfunction in the developmental period: prenatally, in childhood, and adolescence — case reports and a review of the literature

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Abstract

Introduction: Amiodarone is an important antiarrhythmic drug used in paediatric practice, mainly in children with complex congenital cardiac diseases and/or severe arrhythmias. One of the side effects of amiodarone therapy is thyroid dysfunction, which is observed in about 20% of patients. The thyroid dysfunction may present with various forms: from subclinical changes in hormone levels to amiodarone-induced thyrotoxicosis (AIT) and amiodarone-induced hypothyroidism (AIH).

Material and methods: We reported six patients in the age range from two weeks to 14 years, with complex congenital cardiac diseases and severe arrhythmias, who developed amiodarone-induced thyroid dysfunctions: thyrotoxicosis or hypothyroidism or both together. The clinical signs and symptoms of all thyroid dysfunctions were atypical, most patients presented with an aggravation of heart insufficiency. Our patients with thyrotoxicosis were treated with combined therapy including thionamides and corticosteroids due to the presentation of mixed-identified type of AIT.

Results: Currently, five patients (one patient's status is unknown) are in biochemical and clinical euthyreosis; however, in one of them it was impossible to discharge amiodarone treatment. Three of them are still treated with levothyroxine, and two do not need thyroid treatment.

Conclusions: Amiodarone-induced thyroid dysfunction is usually atypical; therefore, monitoring of thyroid status before, during, and after amiodarone is demanded. AIH could significantly influence the development of the child, while AIT could significantly deteriorate the clinical status of children with complex cardiac diseases. Early and proper diagnose of AIT and AIH allows the introduction of immediate and appropriate treatment considering the cardiac condition of the young patient. **(Endokrynol Pol 2019; 70 (5): 392–400)**

Key words: *amiodarone; thyrotoxicosis; hypothyroidism; congenital heart disease*

Introduction

Amiodarone, despite its side effects, including thyroid dysfunction, is often used in paediatric patients with arrhythmias associated with complex congenital heart defects [1, 2].

In 20% of patients, amiodarone may cause subclinical or clinically overt hypothyroidism or hyperthyroidism [3]. Amiodarone can induce thyroid dysfunction via different mechanisms, such as: (1) high iodine content, (2) cytotoxicity to thyroid follicular cells, (3) autoimmunisation, and (4) inhibition of T3 production [4]. The influence on thyroid gland function is related also to the general iodine intake, previous overt or subclinical thyroid diseases, and a genetic susceptibility [4].

Amiodarone-induced thyrotoxicosis (AIT) can occur as AIT type 1, AIT type 2, or AIT type 3 (mixed). The types differ from each other in their pathogenesis, which determines the required treatment.

Amiodarone-induced thyrotoxicosis type 1 develops due to excessive thyroid hormone synthesis induced by iodine overload. This type of AIT often occurs in patients with pre-existing thyroid gland abnormalities (multinodular goitre or Graves' disease) and is associated with the presence of autonomic thyroid tissue and the Jod-Basedow effect, according to which iodine is used in an uncontrolled way to synthesise thyroxine and triiodothyronine. Amiodarone-induced thyrotoxicosis type 2 is a destructive drug-induced thyroiditis leading to leakage of hormones from damaged follicles. AIT type 2 primarily develops in patients with apparently normal thyroid gland. Amiodarone-induced thyrotoxicosis type 3 combines the characteristics of type 1 and 2, and results also from overproduction of

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thyroid hormones induced by the oversupply of iodine, as leakage of hormones due to destructive thyroiditis.

Amiodarone-induced hypothyroidism is induced by the iodine load. Excessive exposition of iodine leads to suppression of synthesis and release of thyroid hormones in the Wolff-Chaikoff mechanism (an inhibition of iodide oxidation). This phenomenon in healthy individuals is transient and lasts up to 48–72 hours. In people with impaired escape phenomenon (which develops between weeks 36 and 40 of pregnancy) excess of iodine may lead to permanent hypothyroidism.

Amiodarone could also influence thyroid function independently of iodine. Amiodarone inhibits 5-deiodinase activity (type 1 and 2), which inhibits generation of triiodothyronine (T3) from thyroxine (T4) in peripheral tissues and pituitary, blocks intracellular transport of T4, and blocks T3 from receptor binding. The above-mentioned mechanisms, in the initial phase of treatment, may result in transient subclinical hypothyroidism [5].

Thyroid dysfunction has a profound impact on the heart. Triiodothyronine has a direct effect on cardiac myocytes and the electrical conduction system of the heart by increasing beta-adrenergic receptor levels in myocardium, thus stimulating the sympathetic nervous system and increasing oxygen consumption [6].

The aim of our study was the presentation of children with congenital heart diseases, who, at different ages, developed different forms of amiodarone-induced thyroid dysfunction.

Material and methods

We reported six patients with cardiac diseases, who developed amiodarone-induced thyroid dysfunctions and were treated in our department in the years 2010–2018. The clinical outcome of the thyroid dysfunction in particular patients is presented in Table I.

Three of our patients developed amiodarone-induced thyrotoxicosis, which presented with no typical signs and symptoms but with severe heart insufficiency. In two of them, the periods of hyperthyroidism and hypothyroidism were intertwined.

Three of our patients developed amiodarone-induced hypothyroidism that required immediate thyroxin supplementation.

Patient 1, a 14-year-old Caucasian girl with heterotaxy syndrome, dextrocardia, and complex congenital heart defect (after modified Fontan operations), was admitted to hospital due to general status deterioration [increasing cyanosis, fatigue, vomiting, diarrhoea, and heart palpitations, as well as goitre (WHO stage II)]. She had been treated with amiodarone since the age of 12 years after aborted cardiac arrest due to heart failure and supraventricular tachyarrhythmia (100 mg daily, five times a week, after a month 50 mg daily, five times a week). Before onset of the treatment, underlying thyroid disease was excluded. Thyrotoxicosis with negative thyroid autoantibodies was diagnosed. Ultrasound revealed heterogeneous parenchymal echogenicity of the thyroid without increased vascularity. Treatment included discontinuation of amiodarone and administration of anti-thyroid drug and glucocorticosteroids. After a six-week period, no significant clinical progression was observed. At that time, lithium or potassium perchlorate therapy was considered, as well as radiotherapy with iodine-131; however, such therapy was impossible due to cardiac contraindications. Therefore, the decision was made to increase the dose of methimazole, which resulted in gradual improvement of the patient's state and normalisation of thyroid function tests. Finally, the treatment was withdrawn after eight months.

In Patient 2, a 12.8-year-old Caucasian boy with hypoplastic left heart syndrome (after modified Fontan operations), amiodarone was administered due to a deterioration of his general condition (with signs of congestive heart failure and atrial flutter). After one week of the therapy, subclinical hypothyroidism was diagnosed, with negative thyroid autoantibodies but with ultrasound picture of hypoechogenic and heterogeneous thyroid gland, which suggested autoimmune thyroiditis. Levothyroxine was introduced. After one month of in-ward treatment the patient was discharged in good condition with the recommendation of taking amiodarone (100 mg daily, five times a week) and levothyroxine (12.5 μg daily).

After two months of the therapy with amiodarone in Patient 3, a 13.9-year-old Caucasian boy with hypertrophic cardiomyopathy with an implanted cardioverter defibrillator (ICD) (after aborted cardiac arrest at the age of 12 years, with previous episodes of cardiac arrhythmia), subclinical hypothyroidism occurred, and levothyroxine was added to amiodarone. Ultrasound revealed heterogeneous thyroid gland. No autoantibodies were detected. Eleven months later, the boy's clinical condition improved and amiodarone was discontinued. Subsequently, levothyroxine was also discontinued four months later. After half a year, hormonal testes revealed thyrotoxicosis without a typical clinical picture of hyperthyroidism. No autoantibodies were detected. Ultrasound revealed heterogeneous thyroid with solid and cystic nodules in both lobes, and the vascularity pattern was normal. Methimazole was introduced combined with prednisone. After a further three months the patient was admitted to hospital due to supraventricular tachyarrhythmia and an inappropriate ICD-shock rate. Because of numerous episodes

Table I. *The clinical outcome of thyroid dysfunction associated with amiodarone therapy in the presented patients. Normal ranges for TSH 0.3–4.0 uIU/mL*

Patient	Sex	Cardiac disease	Age of diagnosis of thyroid dysfunction	Thyroid disease	Time from amiodarone introducement	Treatment	Results of treatment — time of resolution	Observation period since resolution	Current status
1	F	Dextrocardia and complex congenital heart defect (transposition of the great vessels, unbalanced atrioventricular septal defect, hypoplastic left ventricle, anomalous pulmonary venous connection to systemic atrium, pulmonary valve stenosis with systolic pressure of 46–48 mm Hg and right sided aortic arch)	14 yrs	Mixed type of thyrotoxicosis (TSH < 0.02 uIU/mL, ft3 18.9 pmol/L; N: 3.0–8.1 pmol/L; ft4 144.5 pmol/L; N: 10.0–25.0 pmol/L)	16 months	Methimazole (initially 30 mg daily up to 45 mg daily) Prednisone (initially 45 mg daily; 1 mg/kg)	8 months	3 yrs	Constant clinical and biochemical euthyreosis (TSH 1–2 uIU/mL)
			14 yrs 5 months	Transient increase of TSH up to 67.21 uIU/mL and decrease of serum concertation of ft4 to 7.3 pmol/L	5 months after treatment	No add levothyroxine			
2	M	Hypoplastic left heart syndrome	12 yrs 8 months	Subclinical hypothyroidism (elevated level of TSH 11.49 uIU/mL with normal levels of thyroid hormones ft3: 3.7 pmol/L; N: 3.0–8.1 pmol/L; ft4 16.3 pmol/L; N: 10.0–25.0 pmol/L)	7 days	Levothyroxine (initially 25 μg daily, followed by 25 μg and 37.5 μg)	1 month	5 yrs	Constant clinical and biochemical euthyreosis (TSH: 1,06–4.0 uIU/mL) Levothyroxine (12.5 μg daily) Amiodarone (100 mg daily, 5 times/week)

Table I. *The clinical outcome of thyroid dysfunction associated with amiodarone therapy in the presented patients. Normal ranges for TSH 0.3–4.0 uIU/mL*

Patient	Sex	Cardiac disease	Age of diagnosis of thyroid dysfunction	Thyroid disease	Time from amiodarone introducement	Treatment	Results of treatment — time of resolution	Observation period since resolution	Current status
3	M	Hypertrophic cardiomyopathy with implanted cardioverter defibrillator (ICD)	13 yrs 11 months	Subclinical hypothyroidism (TSH 19 uIU/mL)	2 months	Levothyroxine (50 ug daily)	4 months	9 months	Unknown
			15 yrs 6 months	Mixed type of thyrotoxicosis (TSH < 0.005; ft3 10.8 pmol/L; N: 3.0–8.1 pmol/L; ft4 35.5 pmol/L; N: 10.0–25.0 pmol/L)	10 months after treatment	Methimazole (initially 30 mg/d, up to 60 mg daily) Prednisone (0.75 mg/kg/d)			
			15 yrs 9 months	Mixed type of thyrotoxicosis (TSH 0.02–0.03 uIU/mL; ft3 5.1 pmol/L; N: 3.0–8.1 pmol/L; ft4 33.4 pmol/L; N: 10.0-25.0 pmol/L)	13 months after treatment	Continuation of methimazole (25 mg daily, up to 30 mg daily) Prednisone (0.4–0.7 mg/kg/d) (Amiodarone was included)	7 months		
			16 yrs 2 months	Hypothyroidism (TSH < 0.004 uIU/mL; ft3 4.6 pmol/L; N: 3.0-8.1 pmol/L; ft4 28.5 pmol/L; N: 10.0–25.0 pmol/L	5 months	Levothyroxine (88–100 μg daily)	1 months		
4	M	Hypoplastic right heart syndrome, transposition of the great arteries, tricuspid atresia, ventricular septal defect, atrial septal defect, pulmonary stenosis	5 yrs 2 months	Thyrotoxicosis (ft3 35.1 pmol/L; N: 3.0–8.1 pmol/L, normal TSH 3.84 uIU/mL and ft4 19.9 pmol/L; N: 10.0–25.0 pmol/L)	4 months	None	5 months	1 yr 2 months	Constant clinical and biochemical euthyreosis
			9 yrs 8 months	Subclinical hypothyroidism (TSH 7.07 uIU/mL)	4 yrs 6 months	None			Levothyroxine (12.5 μg daily)
			9 yrs 10 months	Thyrotoxicosis (TSH < 0.02 uIU/mL)	4 yrs 8 months	None (amiodarone was withdrawn)	1 month		
			11 yrs 5 months	Subclinical hypothyroidism (TSH 15.03 uIU/mL; ft3 4.1pmol/L; N: 3.0–8.1 pmol/L; ft4 19.1 pmol/L; N: 10.0–25.0 pmol/L)	1 month	None			
			12 yrs 7 months	Subclinical thyrotoxicosis (TSH < 0.1 uIU/mL, ft4 2.27; N: 0.98–1.63 ng/dL, ft3 4.73; N: 2.53–5.01 pg/mL)	1 yr 2 months	Methimazole	1 month		
			12 yrs 10 months	Thyrotoxicosis (TSH < 0.02 uIU/mL; ft3 9.0 pmol/L; N: 3.0–8.1 pmol/L, ft4 48.0 pmol/L; N: 10.0–25.0 pmol/L)	1 yr 5 months	Methimazole (up to 30 mg daily; 0.65 mg/kg) Prednisone (0.45 mg/kg)	4 months		
			13 yrs 2 months	Hypothyroidism	1 yr 9 months	Levothyroxine 12,5 μg daily	1 month		

Table I. *The clinical outcome of thyroid dysfunction associated with amiodarone therapy in the presented patients. Normal ranges for TSH 0.3–4.0 uIU/mL*

Patient	Sex	Cardiac disease	Age of diagnosis of thyroid dysfunction	Thyroid disease	Time from amiodarone introducement	Treatment	Results of treatment — time of resolution	Observation period since resolution	Current status
5	F	Total anomalous pulmonary venous return	10 days	Hypothyroidism — screening test for congenital hypothyroidism (TSH 22.95 uIU/mL; N: < 12 uIU/mL)	6 days	None	1 month	1 yr	Constant clinical and biochemical euthyreosis (levothyroxine 6.25 μg daily and it is planned to its withdrawal)
			22 days	Subclinical hypothyroidism (TSH 13.88 uIU/mL; ft3 4.9 pmol/L; N: 3.0–8.1 pmol/L; ft4 17.1 pmol/L; N: 10.0–25.0 pmol/L)	18 days	None (amiodarone was withdrawn)			
			26 days	Subclinical hypothyroidism (TSH 47.27 uIU/mL; ft3 5.1 pmol/L; N: 3.0–8.1 pmol/L; ft4 13.9 pmol/L; N: 10.0–25.0 pmol/L)	4 days after treatment	Levothyroxine (12.5 μg daily; 4 μg/kg daily; up to 37.5 μg daily)			
6	M	Cardiac arrhythmias diagnosed prenatally	10 days	Hypothyroidism — screening test for congenital hypothyroidism TSH 114 uIU/mL; N: < 12 uIU/mL	10 days (amiodarone from 28 Hbd to delivery)	Levothyroxine (25 ug daily)		8 months	Constant clinical and biochemical euthyreosis (levothyroxine 6.25 μg daily and it is planned to its withdrawal)
			14 days	Hypothyroidism (TSH 272.7 uIU/mL; ft3 5.52 pmol/L; N: 3.0–8.1 pmol/L; ft4 8.48 pmol/L; N: 10.0–25.0 pmol/L)	1 day after treatment	Levothyroxine (up to 37.5 μg daily)	1 month		

of rapid ventricular tachycardia, amiodarone in a dose of 200 mg per day was included in the treatment for life indications, despite persistent thyrotoxicosis, simultaneously the doses of prednisone and methimazole were modulated. Gradual improvement of symptoms was achieved with increasing doses of these drugs. After seven months of therapy, with tapered doses of both antithyroid and glucocorticosteroids, the therapy was discontinued. Finally, hypothyroidism was diagnosed, and levothyroxine was introduced. Amiodarone treatment was continued (200 mg daily), and the patient was offered ablation.

In Patient 4, 4.8-year-old Caucasian boy with congenital complex heart disease (after modified Fontan operations), thyrotoxicosis occurred four months after the introduction of amiodarone due to atrial flutter. The patient did not present with typical signs and symptoms of hyperthyroidism. Within a five-month period, without treatment, thyroid function tests normalised. For more than four years thyroid function has been monitored and has remained normal; therefore, antiarrhythmic therapy has not been modified. However, again at the age of 9.10 years, thyrotoxicosis was diagnosed after an episode of syncope. Therefore, amiodarone was withdrawn resulting in euthyreosis, without additional treatment. One year later, due to refractory arrhythmia, amiodarone was again used, and thyroid function tests revealed subclinical hypothyreosis. After 14 months, and again 17 months later, two episodes of thyrotoxicosis appeared. Combined treatment with amiodarone and methimazole was administered. Ultrasound of the thyroid was normal. Anti-thyroid peroxidase antibody (TPOAb) level was elevated (380 IU/mL; N: < 64 IU/mL), with negative anti-thyroglobulin antibodies (TGAb) and anti-thyroid-stimulating hormone receptor antibodies (TRAb). The methimazole dose was increased and prednisone was added, resulting in the decreasing of free-thyroxine (fT4) (34.6 pmol/L; N: 10.0–25.0 pmol/L) and free-triiodothyronine (fT3) levels (5.3 pmol/L; N: 3.0–8.1 pmol/L), while the thyroid stimulating hormone (TSH) level remained the same (< 0.02 uIU/mL; N: 0.3–4.0 ulU/mL). Methimazole was adjusted to 20 mg daily, and prednisone was continued. During follow-up the patient presented with neither clinical signs nor symptoms of thyrotoxicosis. Finally, four months later, antithyroid agent and glucocorticosteroids were withdrawn, and levothyroxine was administered due to hypothyroidism.

Patient 5, a female newborn (delivered at 38 weeks 5 days of gestation) at the age of 21 days of life, after cardiac surgery correction of a heart defect and Patient 6, a male newborn at the age of nine days of life (delivered at 39 weeks' gestation) with cardiac arrhythmias (diagnosed prenatally in the 28th week of pregnancy) were consulted by a paediatric endocrinologist due to abnormal results of a screening test for congenital hypothyroidism. Tests had been performed on the 10th day of the children's life and revealed elevated TSH at the level between 12 and 28 U/l; therefore, the results of the test demanded re-testing.

At that time, Patient 5 had been continuously infused with amiodarone (7.5 ug/kg/min) and digoxin due to tachycardia since the second day of life. The thyroid function parameters were re-assessed at 22 and 26 days of age (patient 5) and revealed subclinical hypothyroidism. The continuous intravenous infusion of amiodarone was discontinued by a consultant cardiologist on the 23rd day of life due to a good response to treatment with propranolol and digoxin. On the 26th day of life levothyroxine supplementation was introduced.

The mother of Patient 6 had been receiving amiodarone from the 28th week of pregnancy until delivery. Afterwards the newborn was given amiodarone from 1 to 13 days of life because he was resistant to adenosine (supraventricular tachyarrhythmia persisted after administration of adenosine — the first choice drug in these arrhythmias in children). Then the child was transferred to the department of cardiology, where the treatment was modified — amiodarone was discontinued and propranolol was introduced on 14th day of his life). The parameters of thyroid function were re-assessed at 14 days of age (Patient 6) and revealed hypothyroidism. Levothyroxine supplementation was introduced, and it has been administered until now.

Results

Currently all patients remain in constant clinical and biochemical euthyreosis. Patient 1 and 5 do not receive thyroid treatment or amiodarone. Patient 2 receives levothyroxine and amiodarone (at varying daily doses depending on periodically occurring atrial fibrillation episodes). Patient 4 and 6 also receive levothyroxine, but the results of hormonal tests allowed a gradual reduction of its dose. The fate of Patient 3 is unknown (in the last three years he did not report to the Paediatric or Adult Clinic).

Discussion and conclusions

In our study, we present the clinical outcome of different types of amiodarone-induced dysfunctions of thyroid gland in six patients with different cardiological problems. Amiodarone is structurally similar to thyroxine. It contains iodine which makes 37% of its weight (10% is released every day as free iodine). Therefore, daily intake of 100 mg of amiodarone results in 3.5 mg iodine supplementation, which greatly

exceeds the recommended daily intake of 150–200 ug. Amiodarone is metabolised in the liver to desethyloamiodarone (DEA), which has a similar effect on thyroid. The excess of iodine may be a cause of both hypothyroidism and/or hyperthyroidism. Amiodarone could also influence thyroid function independently of iodine. Moreover, direct cytotoxic effects of amiodarone and its metabolite, resulting in the destruction of thyroid tissue and the release of thyroid hormones, may be the cause of hyperthyroidism. The consequences of amiodarone treatment can be observed during the treatment (usually 36 months after the onset), but also up to two years after its discontinuation [7].

Among our patients, the shortest time of amiodarone therapy that led to thyroid impairment was seven days, the longest — four years and six months. In patient 3, discontinuation of the antiarrhythmic agent had led to hyperthyroidism 10 months later. Similar discrepancies of duration of amiodarone treatment in relation to thyroid impairment ranging from 12 to 33 months of amiodarone treatment, and a mean of seven months after its cessation were observed by other authors as well [8, 9].

We observed different types of thyroid dysfunction. Patients 2, 3, 4, 5, and 6 presented with clinical and subclinical hypothyroidism. In case 2, subclinical hypothyroidism initially seemed to be transient and directly related to the pharmacological action of amiodarone, but the patient remains dependent on levothyroxine substitution. Patient 3 developed two episodes of hypothyroidism with an intermediate period of hyperthyroidism. In case 4 we also observed episodes of hypothyroidism with interspersed periods of hyperthyroidism. Initially, the Wolff-Chaikoff effect was clearly observed. After transient increase of TSH with normal fT3 and fT4, spontaneous remission occurred. The next episode of hypothyroidism required levothyroxine. In cases 5 and 6 hypothyroidism was diagnosed based on the result of a screening test for congenital hypothyroidism. At the time of screening, the patients remained on an intravenous infusion of amiodarone, which, taking into account the presence of the Wolff-Chaikoff effect, could have a significant impact on the obtained result. Due to an increase of TSH concentration observed in the control tests levothyroxine was administered.

According to the literature, transplacental transport of amiodarone varies between 10 and 12% and desethyloamiodarone between 20 and 22%. The concentration of amiodarone and its metabolite is much smaller than in the mother, but it would be enough to develop hypothyroidism, resulting from excess iodine, the Wolff-Chaikoff effect, and the lack of a fully developed escape phenomenon [10]. This risk is definitely higher before 36 weeks of pregnancy (the normal effect of Wolff-Chaikoff develops between 36 and 40 weeks). The frequency of this complication may reach 20%. This type of hypothyroidism is transient and requires administration of levothyroxine in less than 50% of cases [11, 10].

However, hypothyroidism in the prenatal or early postnatal period requires special attention due to the relationship between the level of thyroid hormones and the development of the nervous system. The first two weeks of life are critical [12]. It is estimated that children whose levothyroxine supplementation was included between 12 and 30 days of age have an IQ ratio approximately 15.7 higher compared to children whose treatment was included after 30 days of age [13]. However, according to data, subclinical hypothyroidism, which is a consequence of the amiodarone therapy, rarely leads to abnormal development of the nervous system. A mild developmental disorder is also observed in children receiving amiodarone and being in biochemical euthyreosis, which points to a direct neurotoxic effect of amiodarone on the brain and the consequences of possible hypoxia episodes associated with severe cardiac condition.

Three patients (1, 3, and 4) developed AIT. Its clinical presentation may be atypical. This seems to be related to antiadrenergic action of amiodarone. To confirm the diagnosis, it is mandatory to detect increased levels of T3 and fT3 in correlation to decreased TSH levels. Abnormal thyroid function test may be detected although patient remains clinically euthyroid.

Due to various mechanisms leading to hyperthyroidism during amiodarone treatment, we can distinguish two main types of AIT. Type 1, associated with the use of excess iodine for the synthesis of hormones by autonomic thyroid tissue; and type 2, resulting from the destruction of thyroid tissue and releasing hormones. In some cases, differentiation between type 1 and type 2 is difficult, then we recognise type 3 — mixed.

In the differential diagnosis, we can use a number of parameters, although it is difficult and often does not lead to diagnosis of hyperthyroidism of only type 1 or type 2. A tool that is considered to be most useful is Colour Flow Doppler Sonography of the Thyroid (CFDS). Based on CFDS features, 80% of cases can be classified as type 1 or 2 AIT [4, 14]. Other markers are: current or previous thyroid disease, level of iodine supply, level of thyroid antibodies, radioactive iodine (RAI) uptake, pertechnetate uptake, technetium-99 methoxyisobutylisonitrile (99mTc-MIBI), response to treatment, risk of subsequent hypothyroidism, and spontaneous remission of AIT [3, 14–16].

Our patients who had developed hyperthyroidism presented symptoms of both type 1 and type 2 AIT. In Patient 1, towards type 1 indicated stage II goitre and

ultrasound image suggesting an autoimmune disease. No history of pre-existing thyroid disease, undetectable autoantibodies, and correct thyroid vascularity suggested type 2. In Patient 3 ultrasound image and history of pre-existing thyroid disease were consistent with type 1. Undetectable antibodies and hypothyroidism subsequent to hyperthyroidism treatment indicated type 2. In Patient 4 detectable autoantibodies and pre-existing thyroid disease indicated type 1, but normal ultrasound thyroid indicated type 2. The combination of the above-mentioned features allowed us to diagnose mixed type AIT.

Our observations confirm the results in the literature. Among the few paediatric cases of AIT described to date the authors also described mixed type AIT [8, 17]. Available data and our own observations indicate difficulty and importance of differentiation of type of AIT for successful treatment .

Based on the mechanism of AIT, we may implement goal-directed therapy. For AIT type 1 this is a thyroid hormone synthesis inhibitor (drug of choice — methimazole, dosage up to 40–60 mg/day). In adults it is often combined with the iodine intake inhibitor potassium perchlorate (adult dosage 1 g/day) or sodium perchlorate used for a period of 4–6 weeks [14]. There are no data regarding children. Type 2 AIT should be treated with glucocorticosteroids due to its anti-inflammatory and membrane-stabilising effects (0.5–0.7 mg/kg/day of prednisone, up to 30 mg/day) [14, 17]. Often the initial diagnosis changes as a result of the lack of response to the initially applied treatment, targeted at a specific type of AIT [14, 17]. Each of our patients required treatment with both drugs, which confirms the mixed aetiology of AIT.

Such observations also allow us to conclude that in a life-threatening clinical scenario combined therapy is most beneficial, even in the absence of a clear diagnosis of the type of AIT. In accordance with new recommendations, after 4–6 weeks of treatment with a thyrostatic drug without effect, steroids should be introduced to the therapy [14]. Besides typical treatment, AIT requires additional pharmacotherapy and procedures.

Alternative methods of treatment of AIT (used in adult patients — data supporting usage in paediatric patients are lacking) include: lithium carbonate, radioactive iodine therapy, plasmapheresis, total thyroidectomy, and embolisation of the thyroid artery [18–20]. According to the latest recommendations, complete thyroidectomy or radioactive iodine therapy as a radical treatment is indicated in hyperthyroidism, regardless of its type, allowing rapid achievement of euthyreosis and possible re-inclusion of amiodarone into the treatment, especially in type 1 AIT [21, 14]. The special role of total thyroidectomy, performed in patients with a severe condition due to cardiac causes and not responding to pharmacological treatment of hyperthyroidism, without first obtaining euthyroidism, is underlined [14]. Radioactive iodine therapy as an alternative method is recommended 6–12 months after discontinuation of amiodarone due to decreased iodine uptake. However, there are reports in the literature that it is effective and justified not only in cases of normal or increased radioiodine uptake, but also in a situation when radioiodine uptake is lowered [18]. Few data indicate effectiveness of rhTSH-aided radioiodine therapy [4, 21]. However, the latest recommendations do not recommend this procedure [14].

Close follow-up of amiodarone-treated patients is also a very important issue. T3 and fT3 are parameters not only reflecting thyroid condition, but also prognostic factors of treatment. T3 and fT3 correlate better with clinical status and therefore are crucial in diagnosis and treatment of amiodarone-induced thyrotoxicosis. During AIT treatment, changes in fT3 concentrations are observed, in contrast to the steady status of fT4 [22]. Modification of treatment should be based on T3 and fT3 concentration levels in correlation with the patient's clinical status.

In children with complex congenital heart defects, thyroid dysfunction as a side effect of the treatment of amiodarone administrated due to various forms of refractory cardiac arrhythmias requires specific guidelines for diagnosis, treatment, and monitoring [22, 23]. The main issue is hyperthyroidism, which may lead to potentially life-threatening thyroid storm.

Hypothyroidism is usually not a serious condition and requires supplementation of levothyroxine. However, in very young children (below three years old) hypothyroidism could significantly impair psychosomatic development and should be diagnosed and treated at once. According to the recommendations, close thyroid function assessment including autoantibody assay and ultrasound of the gland is required before, every six months, and until two years after amiodarone treatment cessation [16]. We postulate that in very young children treated with amiodarone, the assessment of thyroid function should be done much more frequently with the aim of preventing impairment of their development.

To summarise, our data indicate that in paediatric patients treated with amiodarone, monitoring of thyroid function is indicated, due to the risk of thyroid dysfunction, which often occurs asymptomatically or atypically but may significantly deteriorate the development of the child and the results of cardiological treatment. Moreover, the results of our study underline that AIT in children may have atypical, mixed-identified form including characteristics of both types of AIT, and it

requires immediate and composed treatment to prevent the exacerbation of heart dysfunction.

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Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

The first authorship of A.F. and A.W. is of equal rank.

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