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Alström syndrome – a case report and literature review

Zespół Alströma – opis przypadku i przegląd literatury

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Summary:

Purpose: To report a case of Alström syndrome referred as bilateral macular degeneration.

Material and methods: A 52 years old man was diagnosed with an over 30 years history of progressive visual acuity worsening in both eyes, with the presence of night blindness and photophobia. Since childhood the right eye has been positioned in a divergent deviation. General history revealed: high grade obesity, dilated cardiomyopathy with mitral insufficiency, diabetes mellitus type 2, hepatic cirrhosis with elevated serum enzymes, systemic hypertension. Family history: one patient's brother died at the age of 2 years because of a congenital heart disease, and the second brother was diagnosed for the congenital organic heart disease. The basic ophthalmic examination was performed with additional diagnostic methods including: kinetic visual field examination, Amsler grid test, panel D-15 test, fundus photography, ERG, EOG and VEP.

Results: Best corrected visual acuity of both eyes was 0.1. Amsler grid and color vision tests were normal. Visual field revealed concentric contraction in both eyes. The funduscopy showed pale optic discs, atrophic maculopathy, golden appearance of peripheral and midperipheral fundus, coarser pigmentary changes with a „bone-spicule" configuration and arterioral narrowing. The red free pictures demonstrated the atrophy of internal retinal layers and the infrared pictures revealed the atrophy of the external layers of the retina in posterior pole of the fundus. The flash ERG showed reduced amplitude of photopic and scotopic b-wave. The multifocal ERG demonstrated the normal function of the central retina. EOG revealed decreased Arden ratio in both eyes; 1.68 in the right and 1.32 in the left. The pattern VEP revealed the P100 amplitude reduction by 80% and elongation of latency by 120% in the right eye and normal in the left eye. The flash VEP showed normal latency and amplitude reduction by 50% in both eyes.

Conclusions: Based on the results of performed tests the diagnosis of Alström syndrome was established. This rare congenital autosomal recessive condition is characterized by progressive cone-rod retinal dystrophy associated with obesity, sensorineural deafness, type 2 diabetes, congenital cardiac insufficiency secondary to dilated cardiomyopathy, systemic hypertension and kidney failure.

Słowa kluczowe: zespół Alströma, dystrofia czopkowo-pręcikowa siatkówki, kardiomiopatia rozstrzeniowa, otyłość, cukrzyca.
Key words: Alström syndrome, cone-rod retinal dystrophy, dilated cardiomyopathy, obesity, diabetes.

Alström syndrome is a very rare, hereditary genetic disorder first described by Carl Henry Alström in Sweden in 1959 (1). Currently about 450 individuals diagnosed with Alström syndrome are known worldwide. It is an autosomal recessive condition. The gene for Alström syndrome is on chromosome 2 in band 2p13. Mutations in this gene which is called ALMS1 lead to the production of an abnormal, nonfunctional version of the ALMS1 protein, which is necessary to maintain the integrity and the correct architecture of the cellular membranes (2-4). The defect in such a protein could account for the dysfunction involving many systems and/or sensory organs. Wide clinical variability is observed among affected individuals, including siblings. Alström syndrome is characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing impairment, dilated cardiomyopathy and the insulin resistance syndrome (5-9).

A case report

A 52 years old man was referred to our Retinal Diseases Out-Patient Clinic with an over 30 years history of progressive visual acuity worsening in both eyes with the presence of night blindness, photophobia and horizontal nystagmus. The patient was also complaining of visual field constriction, blurred and distorted vision affecting near and far vision. The symptoms affected activities of his daily life. General history and examination revealed: high grade obesity (Fig. 1), dilated cardiomyopathy with mitral valve insufficiency, diabetes mellitus type 2, hepatic cirrhosis with elevated plasma ALT, AST, GGT levels and systemic hypertension. Family history: one patient's brother died at the age of 2 years because of a congenital heart disease, and the second brother was diagnosed for the congenital organic heart disease.

The basic ophthalmic examination was performed with additional diagnostic methods including: kinetic visual field examina-

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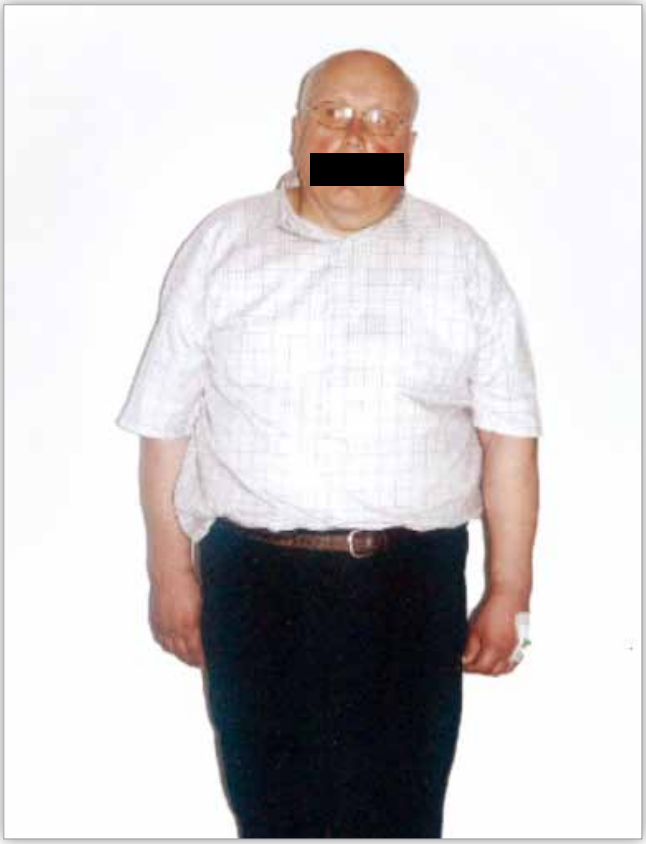

Fig. 1. A 52 years old man with Alström syndrome.
Ryc. 1. 52 letni mężczyzna z syndromem Alström'a.

tion, Amsler grid test, panel D-15 test, electroretinogram (ERG), electrooculogram (EOG) and visual evoke potentials (VEP).

Best corrected visual acuity in both eyes was 0.1. Amsler grid and color vision tests revealed no abnormalities. Kinetic visual field examination demonstrated a concentric contraction in both eyes (Fig. 2a, 2b).

The funduscopy revealed pale optic discs, atrophic "bull-eye" maculopathy (Fig. 3a, 3b), golden appearance of peripheral

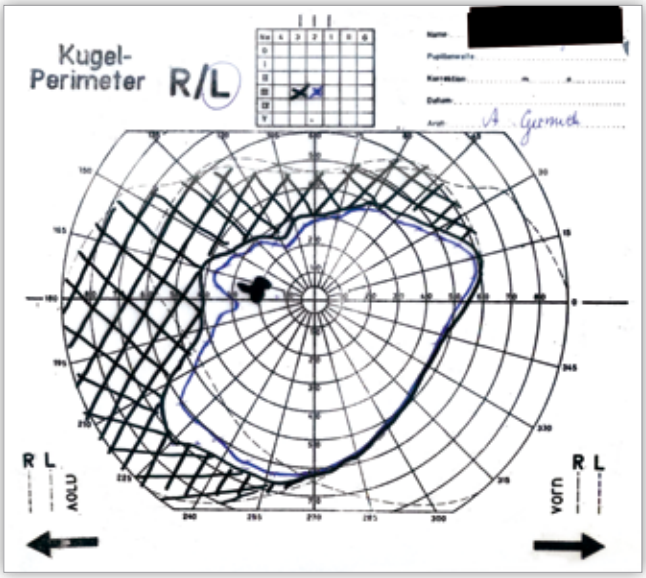

Fig. 2a. Kinetic visual field of the left eye.
Ryc. 2a. Kinetyczne pole widzenia oka lewego.

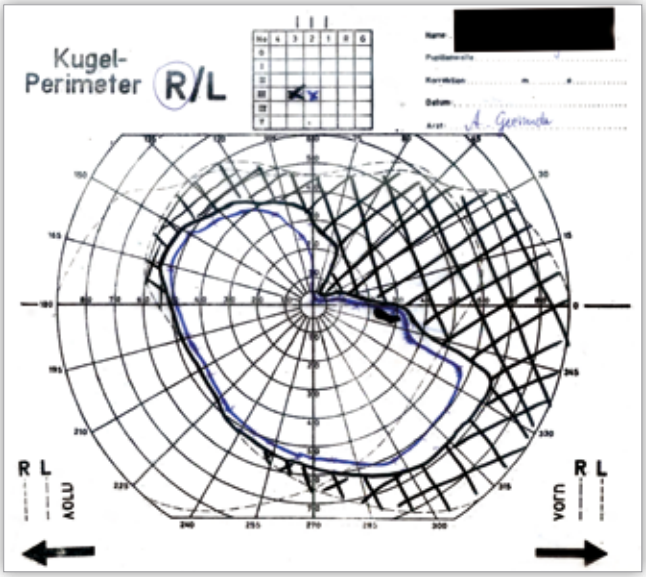

Fig. 2b. Kinetic visual field of the right eye.
Ryc. 2b. Kinetyczne pole widzenia oka prawego.

and midperipheral fundus, coarser pigmentary changes with a „bone-spicule" configuration with arteriolar narrowing (Fig. 4a, 4b).

Fig. 3a. Fundus retinography showing atrophic bull's eye maculopathy in the right eye.
Ryc. 3a. Makulopatie z zanikiem typu „bawole oko" – oko prawe.

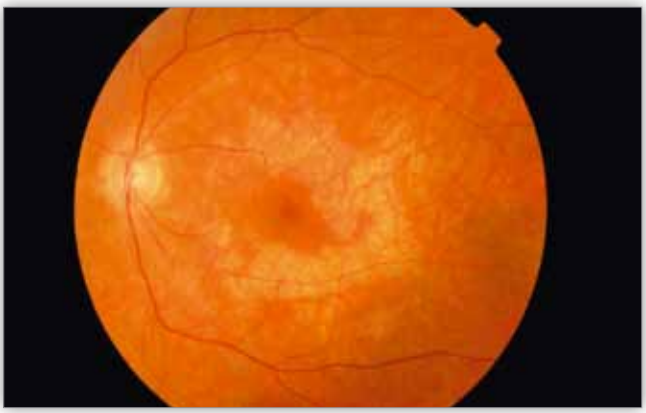

Fig. 3b. Fundus retinography showing atrophic bull's eye maculopathy in the left eye.
Ryc. 3b. Makulopatie z zanikiem typu „bawole oko" – oko lewe.

The red free pictures showed the atrophy of internal retinal layers and the infrared pictures revealed the atrophy of the external layers of the retina in the posterior pole of the fundus (Fig. 5a, 5b and Fig. 6a, 6b).

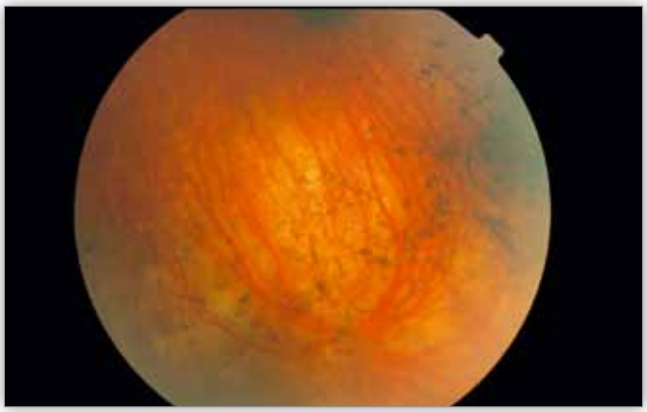

Fig. 4a. Picture of the midperiphery with "bone-spicule" pigmentary changes of the fundus of the right eye.
Ryc. 4a. „Komórki kostne" na dnie oka prawego.

Fig. 4b. Picture of the midperiphery with "bone-spicule" pigmentary changes of the fundus of the left eye.
Ryc. 4b. „Komórki kostne" na dnie oka lewego.

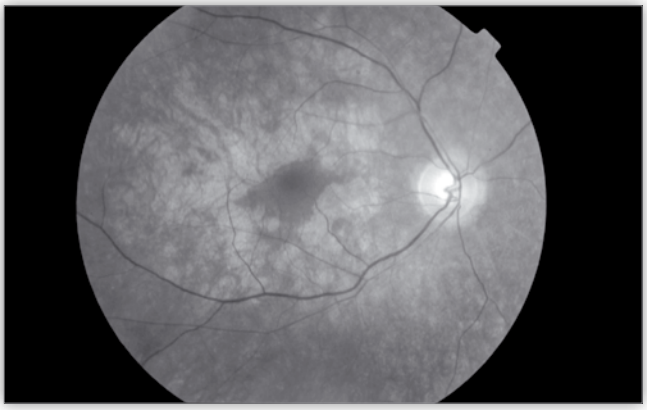

Fig. 5a. Red free picture of the fundus of the right eye.
Ryc. 5a. Obraz „czerwonej plamki" na dnie oka prawego.

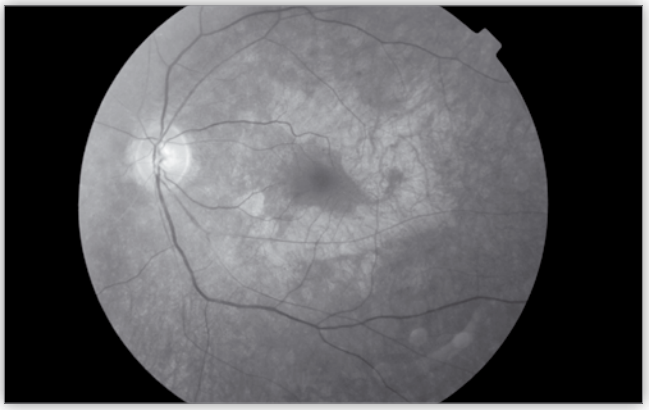

Fig. 5b. Red free picture of the fundus of the left eye.
Ryc. 5b. Obraz „czerwonej plamki" na dnie oka lewego.

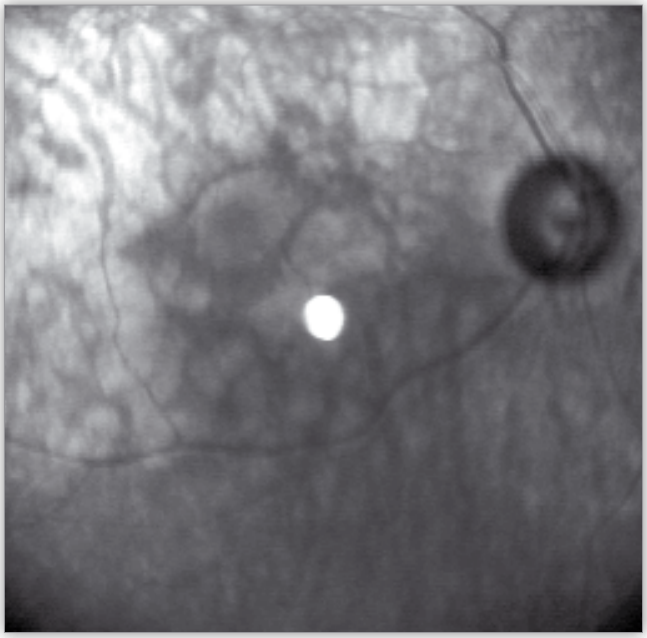

Fig. 6a. Infrared picture of the fundus of the right eye.
Ryc. 6a. Dno oka prawego w świetle bezczerwiennym.

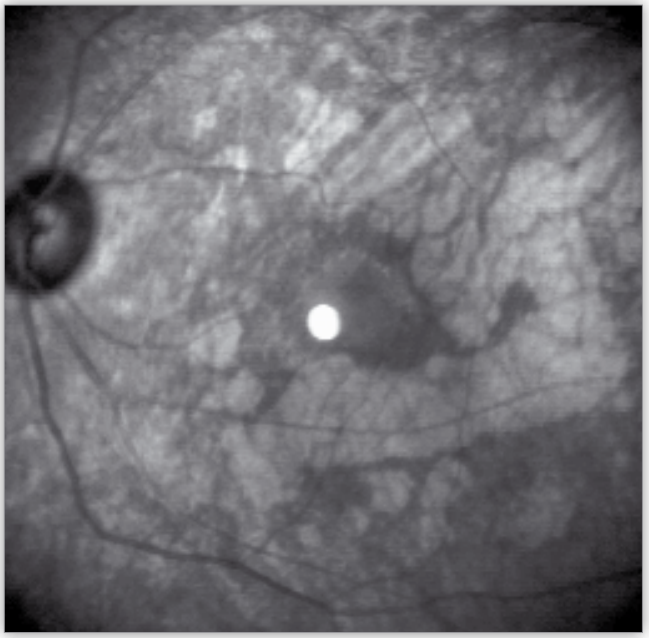

Fig. 6b. Infrared picture of the fundus of the left eye.
Ryc. 6b. Dno oka lewego w świetle bezczerwiennym.

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The flash ERG showed reduced amplitude of photopic and scotopic b-wave. The multifocal ERG demonstrated the normal function of the central retina. EOG revealed decreased Arden ratio in both eyes; 1.68 in the right and 1.32 in the left. The pattern VEP showed reduction of the P100 amplitude by 80% and elongation of its latency by 120% in the right eye and normal in the left eye. The flash VEP revealed normal latency and amplitude reduction by 50% in both eyes.

Discussion

The earliest sign of Alstöm syndrome is often visual impairment with photophobia and nystagmus as a result of a cone-rod dystrophy which occurs in 100% of affected patients within the first year of life (10,11). The retinal dystrophy progresses to include the rods, with visual acuity of 6/60 or less by age of ten years, increasing constriction of visual fields (8). An atrophic "bull's eye" maculopathy rarely occurs in Alström syndrome (5). The electroretinogram is absent or attenuated with better preserved rod than cone function. Rod function is preserved initially but deteriorates as the individual ages. Fundus examination in the first decade may be normal or may show a pale optic disc and narrowing of the retinal vessels with "bone-spicule" pigmentary changes (12). Posterior subcapsular cataract is common. In literature there is also a report on an Asian girl with bilateral congenital cone-rod dystrophy due to Alström syndrome who developed subretinal exudation resembling Coats' disease (13). Another of the early signs may be dilated cardiomyopathy (61%) and obesity (12,14,15). Multiple organ systems later can be affected, resulting in hearing impairment (81-88%), type 2 diabetes, heart failure, liver disease, pulmonary fibrosis and renal failure. In our patient however no hearing problems were noted. Additional features in some cases include hypothyroidism, male hypogonadism, short stature and mild to moderate developmental delay (25-30%) however the majority of patients are of normal intelligence (5,7,16,17). The complications of type 2 diabetes such as hyperlipidemia and atherosclerosis may be observed (6).

Alström syndrome is associated with ALMS1 gene. Molecular genetic testing of the ALMS1 gene is estimated to detect mutations in 25%-40% of individuals (3,4). In our patient we did not perform the genetic testing because they are not available on a routine way. The diagnosis of Alström syndrome is based on clinical findings but there is however considerable variation in the clinical picture (6,7,16,17). The differential diagnosis of Alström syndrome include: Bardet-Biedl syndrome, Leber's congenital amaurosis and achromatopsia (11,18-21). Bardet-Biedl syndrome shares some features of Alström syndrome. The major clinical features of Bardet-Biedl syndrome are rod-cone dystrophy, postaxial polydactyly, central obesity, cognitive impairment, hypogonadism, and renal dysfunction. A major difference between Alström and Bardet-Biedl syndrome is the timing of the onset of visual problems: in Alström syndrome, visual problems are usually apparent in the first two years of life; in Bardet-Biedl syndrome, the average age of onset of visual problems is later in the first life decade (11). Polydactyly, which is common in Bardet-Biedl syndrome, has not been described in Alström syndrome. Mental retardation is well described in Bardet-Biedl syndrome, while intellectual dysfunction is less common in Alström syndrome. Other differences include the relative infrequency of hearing problems, which are observed in less than 5% of cases and diabetes mellitus in 5-10% of patients with Bardet-Biedl syndrome. Mutations in twelve different genes are associated with Bardet-Biedl syndrome. Inheritance is autosomal recessive (11,18). Leber congenital amaurosis is a severe dystrophy of the retina without other organ system involvement, typically becomes evident in the first year of life. Reduced vision is accompanied by nystagmus, sluggish pupillary responses, photophobia, hyperopia, and keratoconus. The ERG is characteristically "nondetectable" or severely subnormal. Although the retina may appear normal in infancy, a pigmentary retinopathy reminiscent of retinitis pigmentosa is frequently observed later in childhood. Eight genes currently known to be associated with this disease: CRX, CRB1, GUCY2D, AIPL1, RDH12, RPGRIP1, RPE65, and CEP290. Leber congenital amurosis is inherited in an autosomal recessive manner, rarely in an autosomal dominant manner (19). Achromatopsia a disorder that affects only the retina and is characterized by reduced visual acuity, pendular nystagmus, photophobia, a small central scotoma, eccentric fixation, and reduced or complete loss of color discrimination. Nystagmus and photophobia develop shortly after birth. Visual acuity ranges from 20/200 or less in complete achromatopsia to 20/80 in incomplete achromatopsia (20). The diagnosis of achromatopsia is based on color vision testing, electrophysiologic examination. The fundus is usually normal. Mutations in three genes, CNGA3, CNGB3, and GNAT2, are associated with this disease. Inheritance is autosomal recessive (20,21,22).

In our case, the diagnosis of Alström syndrome has been made on the precise evaluation of disease's signs and symptoms. The ophthalmologists were the first who established the diagnosis of this rare condition. This rare congenital autosomal recessive syndrome is characterized by progressive cone-rod retinal dystrophy associated with obesity, type 2 diabetes, dilated cardiomyopathy, sensorineural deafness, systemic hypertension and kidney failure.

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