Long-term outcome of patients with alpha-mannosidosis – A single center study

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A B S T R A C T
Introduction: Alpha-mannosidosis (AM) is a rare autosomal recessive lysosomal storage disease which the natural history has not been exhaustively described yet. The aim of this study was to present the long-term follow-up of 12 Polish patients with AM, evaluate the clinical, biochemical, and molecular findings and progression of the disease.

Material and methods: The article presents a long-term (over 30 years) observational, retrospective, single-center study of patients with AM.

Results: The hearing loss, as one of the first symptoms, was detected in childhood (mean age of 2 years and 6 months) in 10 patients. The other symptoms include: recurrent infections (all patients), inguinal hernias (6 patients), craniosynostosis (1 patient). The mean age at AM diagnosis was 6 years while median was 4 years (age range: 1 year and 8 months – 12 years). The most commonly identified variant in the MAN2B1 gene was c.2245C>T, p.(Arg749Trp). The mean time of follow-up in our study was approximately 14 years (range: 1 year – 26 years). Following birth, children with AM grow slowly, finally reaching the 3rd percentile (or values below the 3rd percentile). Hearing loss was not progressive while a gradual exacerbation of intellectual disability with no developmental regression was observed in all patients. Ataxia was diagnosed in 6 patients in the second decade of life (age range 15-20 years).

Conclusions: Our study revealed the sensorineural hearing loss as one of the first noted symptom in AM which was congenital and non-progressive during the natural course of disease. A detailed anthropometric phenotype of AM patients was provided with observation of the growth decline during the long-term follow-up. Our study confirmed the existence of two distinguished clinical phenotypes of AM (mild and moderate), and also the lack of clear genotype-phenotype correlation.

1. Introduction

Alpha-mannosidosis ( # 248500; AM) is a rare autosomal recessive lysosomal storage disease (LSD) resulting from the deficiency of alpha-mannosidase (EC 3.2.1.24) responsible for degradation of N-linked oligosaccharides, associated with biallelic pathogenic variants in the MAN2B1 gene [1].

The natural history of AM has not been exhaustively described yet due to the rarity of disease and the lack of long-term follow-up of the patients. The first clinical description of AM was provided in 1967 year by the Swedish physician Öckerman [1]. Since then, few retrospective studies on the clinical course of AM had been performed [2-4].

According to Malm et al. (2008), three clinical phenotypes could be distinguished: type 1 – a mild form with very slow progression clinically recognizable after 10 years of age; type 2 – a moderate form with slower progression, clinically recognized before 10 years of age with development of ataxia in the 2nd decade of life; type 3 – a severe form with fatal outcome leading to an early death from primary central nervous system involvement [1].

In 2013, Beck et al. provided the results of the first multicenter...
longitudinal study on clinical data of 43 patients with AM (age range 1.4–42.1 years, mean age 19.8 years) [4]. They observed a spectrum of clinical presentation regarding the severity and disease progression. Hearing loss from an early childhood was seen in all patients, while ataxia and mental retardation were the prominent neurological findings. During study period (24 months) there was observed a slight progression of psychiatric symptoms and an impaired lung function in patients under the age of 18 years [4].

Currently, there is no effective treatment (besides of allogenic hematopoietic stem cell transplantation for some patients) for AM. However, the evaluation of velmanase alfa, which is a recombinant human alpha-mannosidase in development for enzyme replacement therapy (ERT) for AM, in phases I, II, III (and extension phase), showed promising results [5–7].

The aim of this study was to present the long-term follow-up of 12 Polish patients with AM, evaluate the clinical, biochemical, and molecular findings and progression of disease.

2. Material and methods

The article presents a long-term (over 30 years) observational, single-center study of patients with AM. Twelve patients who were diagnosed and followed-up at the Children's Memorial Health Institute (CMHI), Warsaw, Poland, were enrolled into the study.

The chart review of patients’ medical records concerning the following was performed:

(a) demographics (age, sex, ethnicity); (b) course of pregnancy and birth parameters; (c) first presented signs and symptoms; (d) results of clinical examinations – pure tone audiometry, clinical distortion product otoacoustic emission (detailed description in [8]); Evaluation of the degree of hearing loss based on ANSI (American National Standards Institute) and ISO (International Standards Organization) standards; (e) age at diagnosis; (f) results of biochemical analyses - thin-layer chromatography (TLC) of oligosaccharides in urine (detailed description in [9]), alpha-mannosidase activity in leukocytes; (g) results of molecular data – MAN2B1 gene pathogenic variants (see below); (h) anthropological assessment – the mean birth body height and weight were calculated. Two-tailed t-test was used to compare the mean values for birth body length and weight at birth between children with AM and the healthy population. Tendency of growth was presented as growth curves on percentile charts; (i) immunological assessment – analysis of the serum immunoglobulin (Ig) G, A, M, serum complement components C3 and C4, T and B lymphocyte subpopulations.

The diagnosis of AM was confirmed by the demonstration of reduced alpha-mannosidase activity in peripheral blood leukocytes. Sequence analysis of the MAN2B1 gene was performed either by targeted gene sequencing or whole exome sequencing (WES). The nomenclature of identified variants and patients’ genotype follows the Human Genome Variation Society guidelines (HGVS v 2.0, www.hgvs.org/mutnomen) and referral according to cDNA and protein sequences of MAN2B1 gene followed the Human Gene Mutation Database (HGMD, www.hgmd.cf.ac.uk).

Ethical approval was obtained from the Children's Memorial Health Institute Bioethical Committee, Warsaw, Poland.

3. Results

A total of 12 patients (9 males, 3 females) of Polish origin, from 9 families were enrolled into the study. A detailed characteristics of the study patients was presented in Table 1.

3.1. First signs and symptoms

The pregnancy course was uneventful in all the study patients. Birth length was significantly higher while body weight was comparable to the general Polish population.

Three patients passed the Newborn Hearing Screening Program (NHSP) and hearing loss was diagnosed in one of them (Pt 4). Audiological examinations revealed the hearing loss of moderate degree in 10 patients and severe hearing impairment in 2 patients (Pt 1 and 12). The hearing loss was detected in childhood (mean age of 2 years and 6 months) in all of them. Two other patients (Pt 3 and Pt 7) were diagnosed with normal hearing threshold level (Table 1).

The first symptoms, usually noted by the parents, were a delayed psychomotor development, including delayed development of speech. All the patients suffered from recurrent respiratory tract and middle ear infections (otitis media effusion, acute otitis) in the first years of life.

All of them presented with characteristic facial features: a large head with prominent forehead, rounded eyebrows, flattened nasal bridge. Ingual hernias were observed in 3 patients in a late infantile period (age range: 5 months – 1 year) and in the other 3 patients in childhood (age range: 4–8 years). One of the patients (Pt 3) was diagnosed with craniostenosis at the age of 1 year and 2 months. Hypogammaglobulinemia (decreased serum total IgG concentration) was noted in this patient before surgery with the need of intravenous immunoglobulins infusion (Table 1). Dilated cardiomyopathy was diagnosed in the other one patient (Pt 8) at 2 months of age (Table 1).

3.2. Diagnosis

The mean age at AM diagnosis was 6 years while median was 4 years (age range: 1 year and 8 months – 12 years). An urinary excretion of oligosaccharides by TLC as an initial screening procedure, was performed in 10 patients and demonstrated a high excretion suggesting AM, confirmed then by an enzymatic analysis of alpha-mannosidase in leukocytes (Table 1). Sequence analysis of the MAN2B1 gene was performed in all of them to confirm the biochemical diagnosis.

Two other patients (Pt 3 and Pt 7) were diagnosed first by WES (Table 1), and then confirmed by functional analysis (deficiency of alpha-mannosidase activity).

Among 10 patients who undergone molecular analysis, 6 various pathogenic (missense) variants in the MAN2B1 gene were identified. The most commonly identified variant was c.2245C > T, p.(Arg749Trp), accounting for 60% of all alleles. The frequency of other identified alleles was as following: p.(Thr785*) = 15%; p.(Leu565Pro) – 10%, p. (Gly215Asp) – 5%, p.(Glu751*) – 5%.

3.3. Follow-up

The mean time of follow-up in our study was approximately 14 years (range: 1 year – 26 years). One patient (Pt 10) died at 25 years of age due to chronic respiratory failure.

Following birth, children with AM grow slowly with no growth acceleration observed during the adolescence, finally reaching the 3rd percentile (or values below the 3rd percentile) for the general Polish population (Fig. 1). Narrow shoulders and convex chests were characteristic for the study group patients. Craniofacial analysis showed that the head circumference did not differ from healthy peers but has a tendency to be slightly shorter and broader than in general population. In some patients, shortening of the lower extremities' length was noted with normal trunk length which could contribute to the short stature of adolescent patients.

Hearing loss was not progressive – the hearing threshold level remained stable in all our patients (Table 1). A gradual exacerbation of intellectual disability with no developmental regression was observed in all patients.

One patient (Pt 5) was diagnosed with Sjögren syndrome (7 years of age) and then systemic lupus erythematosus (9 years of age). Ataxia was diagnosed in 6 (50%) patients in the second decade of life (age range 15–20 years) and its progression varied among patients – severe ataxia was observed in five patients (Pt 1, 4, 11, 12), while mild in the other one patient (Pt 2), see Table 1.
| Patient | Sex | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 | Patient 11 | Patient 12 |
|---------|-----|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| First signs and symptoms | | | | | | | | | | | | | |
| Hearing loss (Age at diagnosis) | | | | | | | | | | | | | |
| Severe (3 y) | Moderate (5 y) | No | Moderate (1 y) | Moderate (2 y) | Moderate (3 y) | No | Moderate (3 y) | Moderate (1.5 y) | Moderate (8 y) | Moderate (2 y) | Moderate (10 y) |
| Hernia (Age at diagnosis) | | | | | | | | | | | | | |
| Inguinal (5 mo) | Inguinal (5 mo) | No | Inguinal (1 y) | No | Bilateral inguinal (4 y) | No | Inguinal and umbilical (after birth) | No | No | Inguinal (8 y) | Inguinal (7 y) |
| Recurrent infections | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Mild hepatomegaly | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Yes | No | No | No | Yes |
| Facial features | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |
| Other | mild intellectual disability | Craniosynostosis (1-ataxia (3 y) y 2 mo) | | | | | | | | | | | |
| Diagnosis | Age at diagnosis | 3 y | 12 y | 1 y 8 mo | 3 y | 3.5 y | 6 y | 4 y | 3 y | 4 y | 10 y | 11 y | 10 y |
| Type of diagnosis | Biochemical + molecular | Biochemical + molecular | Biochemical (WES analysis) + biochemical | Biochemical + molecular | Biochemical + molecular + molecular | Biochemical + molecular + molecular | Biochemical + molecular + molecular | Biochemical + molecular | Biochemical + molecular | Biochemical + molecular |
| Thin-layer chromatography of oligosaccharides in urine | n.a. | + | n.a. | + | + | + | + | + | + | + | + | + |
| Enzymatic activity of alpha-mannosidase in leukocytes | 0.8 nmol/mg protein/h (73 ± 34) | 0.4 nmol/mg protein/h (55 ± 31) | 0.5 nmol/mg protein/h (63 ± 35) | 0.35 nmol/mg protein/h (55 ± 31) | 0.4 nmol/mg protein/h (24-204) | 1.1 nmol/mg protein/h (55 ± 31) | 0.5 nmol/mg protein/h (55 ± 31) | 16.1 nmol/L/h (> 1.35 nmol/mg protein/h (73 ± 34)) | 1.25 nmol/mg protein/h (73 ± 34) | 0.12 nmol/mg protein/h (n.a.) | 0.09 nmol/mg protein/h (n.a.) | |
| Genotype | c.2245C > T, p. (Arg749Trp)/c.2251G > A, p. (Glu751*) | c.2245C > T, p. (Arg749Trp)/c.2251G > A, p. (Glu751*) | c.2355G > A, p. (Thr785*) | c.2355G > A, p. (Thr785*) | c.2245C > T, p. (Arg749Trp)/c.2355G > A, p. (Thr785*) | c.2245C > T, p. (Arg749Trp)/c.2245C > T, p. (Arg749Trp)/c.2355G > A, p. (Thr785*) | c.2355G > A, p. (Thr785*) | c.2245C > T, p. (Arg749Trp) | c.2355G > A, p. (Thr785*) | c.2245C > T, p. (Arg749Trp) | c.2245C > T, p. (Arg749Trp) | c.2245C > T, p. (Arg749Trp) |
| Last follow-up | Follow-up | 6 y – mild intellectual disability, clumsiness; epilepsy – controlled with carbamazepine, moderate intellectual disability, sublethal ataxia; psychiatric disorder, ataxia 28 y – significant hearing loss, mild ataxia | 28 y – moderate hearing loss, severe ataxia | HSCCT18 y – moderate hearing loss, severe ataxia | 18 y – diagnosis of Sjogren syndrome, hearing loss, severe ataxia | 15 y – diagnosis of systemic lupus erythematosus, prednisonsone treatment; ataxia, toracic tests, normal IgGAM serum concentrations | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia | 10 y – normal IgGAM serum concentrations; normal cortisol, brain atrophy, chronic respiratory failure, tracheotomy, PEG implantation, no ataxia |
At the last follow-up, 8 out of 12 patients, underwent immunological analyses (Table 1). Besides of one patient (Pt 5), all of them had normal concentrations of the serum immunoglobulin (Ig) G, A, M, serum complement components C3 and C4, and normal T and B lymphocyte subpopulations. Pt 5 presented with changes secondary to SLE.

4. Discussion

The study presents the long-term outcome of 12 patients with AM diagnosed and followed in one referral center.

Like in the previous studies it was shown that children with AM are often born apparently healthy [2–4,10–13]. Interestingly, we found that patients’ birth length was significantly higher than general Polish population. The first signs and symptoms could be observed in the first years of life and include a slightly delayed psychomotor development, delayed speech, sensorineural hearing loss, hernias, recurrent respiratory tract and middle ear infections, and characteristic facial features [1–4,10–13].

A diagnostic algorithm for AM was recently proposed from an international working group [13]. It was stated that in patients below 10 years of age, the presence of hearing impairment and/or speech delay (which is probably partially secondary to hearing impairment) are the cardinal symptoms of AM. It was clearly illustrated also in our study. However, two patients with a mild form of disease were diagnosed with normal hearing threshold level.

In addition, we would like to highlight the usefulness of Newborn Hearing Screening Programs (NHSP) that could contribute to an early diagnosis of hearing loss and then AM. NHSP was introduced in Poland in 2002 year, aimed at early diagnosis and intervention in children with hearing loss.

We observed a quite high proportion of patients (58%) with hernias but this phenomenon has been found in many previous publications [2–4,10,13]. In some case descriptions, a murmur of the heart was mentioned in patients with AM, but so far, there are no reports on heart disease [1–4,10–13]. Our study for the first time revealed the presence of dilated cardiomyopathy in patient with AM.

Recurrent infections are an important hallmark of AM, however they are also present in other children with LSD or in otherwise healthy children in the first years of life [1]. The frequency of infections decreases towards the second decade of life. An impaired leukocyte chemotaxis and reduced phagocytosis were found in one reported patient in the literature [14]. Our study for the second time provided a more detailed assessment of the immunological system in patients with AM. Malm et al. in the group of 6 patients with AM found that postimmunization levels of antibodies were lower than in a healthy group [15].

Fig. 1. Growth curves for patients (A – males; B – females) with AM on references growth charts for healthy population.
Only one out of twelve patients had hypogammaglobulinemia. The other patient was diagnosed with Sjögren syndrome at 7 years of age and systemic lupus erythematosus (SLE) at 9 years of age. This is the second report in the literature about the coincidence of AM and SLE [16]. Thus, we can confirm the hypothesis that there might be an increased prevalence of autoimmune disorders in AM. In a mice model of AM it was observed a reduced complex-type N-glycan branching which induced an autoimmune disease similar to human SLE.

AM is considered a heterogeneous disorder in the form of clinical manifestation, its severity, as well as various progression rate [1–4]. Our study for the first time revealed that hearing loss in AM is non-progressive. Hearing loss is congenital, patients require audiological management and fitting with hearing aids since birth. Our study provided also a detailed anthropometric phenotype of AM patients. A growth decline was observed in the natural course of disease. There are symptoms that could appear in the 2nd decade of life (typically adolescence), including ataxia and signs of psychiatric disorder [13]. In our study ataxia was not observed in all patients, the progression was variable among patients, and not related with other features of the disease. However, there are also symptoms that could diminish with age, like hepatomegaly, recurrent infections.

In some cases, the clinical diagnosis of AM could be challenging [17]. Our study demonstrated that elevated urinary secretion of mannose-rich oligosaccharides is very suggestive for AM and constitute and initial screening test. Beck et al. also observed that oligosaccharide levels correlated with functional testing and may serve as biomarkers of disease severity, progression, and response to treatment [4]. However, nowadays this method is not routinely applied; it has been superseded by next-generation sequencing analyses.

Our study confirmed the hypothesis about no clear genotype-phenotype correlation in AM. Like in previous studies, the missense mutation c.2248C>T (p.Arg750Trp) was the most commonly reported [11]. It was suggested that c.2248C>T allele arose in eastern Europe and an east-to-west declining gradient across Europe was observed [11].

5. Conclusions
1. Our study revealed the sensorineural hearing loss as one of the first noted symptom in AM which was congenital and non-progressive during the natural course of disease.
2. A detailed anthropometric phenotype of AM patients was provided with observation of the growth decline during the long-term follow-up.
3. Our study confirmed the existence of two distinguished clinical phenotypes of AM (mild and moderate), and also the lack of clear genotype-phenotype correlation.

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Authors’ contributions
Project administration: Patryk Lipiński, Anna Tylki-Szymańska; Investigation: Patryk Lipiński, Agnieszka Różdżynska-Świątkowska, Katarzyna Iwanicka-Pronicka, Barbara Perkowski, Paulina Pokora, Anna Tylki-Szymańska; Supervision: Anna Tylki-Szymańska; Writing – original draft: Patryk Lipiński; Writing – review & editing: Patryk Lipiński, Agnieszka Różdżynska-Świątkowska, Katarzyna Iwanicka-Pronicka, Anna Tylki-Szymańska.

Declaration of Competing Interest
All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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