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CO-INCIDENCE OF TURNER SYNDROME AND DUCHENNE MUSCULAR DYSTROPHY – AN IMPORTANT PROBLEM FOR THE CLINICIAN

WSPÓŁISTNIENIE ZESPOŁU TURNERA I DYSTROFII MIĘŚNIOWEJ DUCHENNE'A – WAŻNY PROBLEM DLA KLINICYSTY

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Abstract

Introduction: *Turner syndrome is a relatively common chromosomal disorder which affects about one in 2000 live born females. Duchenne muscular dystrophy is an X-linked recessive disorder affecting 1:3600 live born males. Considering the above, the coexistence of these two diseases may occur only anecdotally.*

Case presentation: *Here, we report a 4½ year-old female with classical 45,X Turner syndrome who also had Duchenne muscular dystrophy caused by a point mutation in the dystrophin gene (c.9055delG). The patient showed the typical phenotype of Turner syndrome including distinctive dysmorphic features (short neck, low posterior hairline, wide position of nipples), aortic coarctation and feet lymphedema. Besides, she presented with an unusually early beginning of muscular dystrophy symptoms with infantile-onset motor developmental delay, intellectual disability and early calf muscular hypertrophy.*

Conclusion: *The coexistence of an X-linked recessive disorder should be considered in women affected by Turner syndrome presenting with additional atypical clinical features.*

Key words: Turner syndrome, Duchenne muscular dystrophy, monosomy X chromosome, DMD

Streszczenie

Wstęp: *Zespół Turnera jest stosunkowo częstą aberracją chromosomową, która dotyka około 1:2000 żywo urodzonych noworodków płci żeńskiej. Dystrofia mięśniowa Duchenne'a jest chorobą o dziedziczeniu recesywnym sprzężonym z chromosomem X występującą z częstością około 1:3500 żywo urodzonych noworodków płci męskiej. Biorąc pod uwagę powyższe dane, dystrofia mięśniowa Duchenne'a może wystąpić u dziewczynek z zespołem Turnera, niemniej współistnienie tych dwóch jednostek chorobowych jest niezmiernie rzadkie.*

Prezentacja przypadku: *W pracy przedstawiamy 4½ letnią dziewczynkę z klasycznym zespołem Turnera 45,X, u której wystąpiły również objawy dystrofii mięśniowej Duchenne'a wywołane mutacją punktową w genie dystrofiny (c.9055delG). Pacjentka od okresu noworodkowego prezentowała charakterystyczne dla zespołu Turnera cechy dysmorfii (krótka szyja, nisko schodząca linia włosów na karku, szerokie rozstawienie brodawek sutkowych) jak również koarktację aorty oraz obrzęk limfatyczny stóp. U dziewczynki obserwowano równocześnie wczesny początek objawów dystrofii mięśniowej manifestujący się między innymi opóźnieniem rozwoju psychomotorycznego oraz wczesnym wystąpieniem przerostu mięśni łydek. U pacjentki stwierdzono również niepełnosprawność intelektualną.*

Wnioski: *Współwystępowanie chorób sprzężonych z chromosomem X należy zawsze brać pod uwagę u dziewczynek z zespołem Turnera jeśli występują dodatkowe, nietypowe dla podstawowego rozpoznania, objawy kliniczne.*

Słowa kluczowe: zespół Turnera, dystrofia mięśniowa Duchenne'a, monosomia chromosomu X, DMD

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INTRODUCTION

The coincidence of Turner syndrome (TS) and X-linked recessive disorders is extremely rare, the most frequently ones that have been reported being Duchenne muscular dystrophy (DMD; OMIM#310200) and hemophilia A and B (OMIM# 306700 and OMIM# 306900 respectively). Based on the incidence of the two disorders, the coexistence of DMD and TS may occur with a frequency of $4x10^{-8}$. So far, a few cases of DMD in a Turner syndrome patient have been documented [for example 1-4], however, not all of these have been analyzed cytogenetically and molecularly. Previously reported cases had considerable variability in the phenotype, with respect both to the features of TS and DMD.

CASE PRESENTATION

The girl was born at 36 weeks of gestation by spontaneous delivery with an APGAR score of 8, weight of 2.470 kg (3rd percentile) and height of 53 cm (25 rd percentile). Apart from the previous history of two miscarriages, no pregnancy or family history is available, as the child was abandoned by the mother in the neonatal period.

In the neonatal period the typical dysmorphic features of TS were present: short neck, low posterior hairline, arched palate, low positioning of ears, wide position of nipples, feet lymphedema and dysmorphic feet with hipoplastic nails (Fig. 1). The patient presented with generalized hypotonia and had problems with sucking. Image studies revealed the presence of a horseshoe kidney and mild aortic coarctation. Laboratory tests showed abnormal liver tests (AST 300 U/l, ALT 92 `U/l), increased creatine phosphokinase (CPK 3781 IU/l) and subclinical hypothyroidism.

From the age of 6 months, the progressive increase in both CPK (20451 IU/l) and liver tests (AST 450 U/l; ALT 348 U/l) were observed. Metabolic screening using GC/MS and Tandem MS methods showed no pathology. At the age of 1.5 years the patient was evaluated for significant developmental delay. The girl was able to sit, crawl, roll from her abdomen to her back, but could not stand or walk. She used palmar grasp for catching small objects. She communicated using simple signals like crying and laughing, and had good eye contact with her caregivers. At the age of 3 years she was able to stand supported, but not walk. She articulated incomprehensible words.

At the last observation at the age of 4.5 years her weight was 10 kg, height 88.5 cm (5-10th percentile on TS growth charts). On physical examination apart from typical TS features it was noted that she had convergent strabismus and muscular hypertrophy at the calves. She was able to sit but could stand up only with support or by performing Gowers' sign. She could walk but quickly tired and could not climb stairs. She presented with a waddling gait. Her head was drooping back due to the weakening of the flexor neck muscles. The few blurred words she spoke were difficult to understand but she could follow simple instructions. Moreover, she was hyperactive and had episodes of aggression. She was not able to report physiological needs.

NEUROMUSCULAR STUDIES

At the age of 14 months, a biopsy of her quadriceps femoris muscle was performed. Histopathological analysis showed myopathy with features of muscular dystrophy and significant decrease in dystrophin expression. The electromyography (EMG) of the upper and lower limb muscles was consistent with the myogenic character of the lesions. Her nerve conduction examination study was within the range of norm.

GENETIC ANALYSIS

Cytogenesis analysis of metaphase chromosomes prepared from cultured peripheral blood lymphocytes was performed according to standard procedures using GTG banding technique. The girl's karyotype was 45,X. The dystrophin gene was assessed initially by MLPA (Multiplex Ligation-dependent Probe Amplification) analysis in search for deletions/duplications followed by Sanger sequencing of all the coding exons of the gene.

A frame-shift point mutation c.9055delG (p.Asp3019Thrfs*2) was detected in the exon 60. The origin of the mutation (de novo vs. familial) could not be established as the patient was adopted into a foster family.

DISCUSSION

We report an extremely rare case of the coexistence of classical 45,X Turner syndrome and Duchenne muscular dystrophy caused by point mutation c.9055delG in the dystrophin gene. Even though a few similar cases have already been reported, no genotype-phenotype correlation has yet been performed with respect to the clinical course of DMD.

Chelly et al. 1986 presented a 45,X female and early onset DMD [1]. The patient had difficulties standing up at the age of 2 years and 3 months. This was followed by a typical evolution of DMD disease. The diagnosis of DMD was confirmed

Table I. Comparison of clinical features of DMD in males and females with abnormal karyotype.

Tabela I. Porównanie obrazu klinicznego DMD u chłopców z przebiegiem DMD u dziewczynek z nieprawidłowym kariotypem.

Karyotype:	**46,XY** Classic form of DMD [5,6] *Klasyczny przebieg DMD [5, 6]*	**45,X** (present case) *Prezentowany przypadek*	**45,X** Chelly et al.[1]	**45,X/46,XX** Ferrier et al.[2]	**45,X/46,XX** Sano et al.[3]	**46,X,i(X)(q10)** Ou et al.[4]
Mutation in DMD gene	Deletions (60-70%), duplications (5-10%), small mutations (25-35%)	Point mutation c.9055delG	Deletion of no known size	Molecular analysis not available	Molecular analysis not performed	Deletion exons 46-47
Mutacja w genie DMD	*Delecje (60-70%), duplikacje (5-10%), mutacje punktowe (25-35%)*	*Mutacja punktowa c.9055delG*	*Delecja o nieznanej wielkości*	*Analiza molekularna była niedostępna*	*Nie wykonano analizy molekularnej*	*Delecja eksonów 46-47*
Age at 1st manifestation of clinical symptoms suggestive of DMD (not laboratory indicators)	3-4 years	1 years 6 months	2 years 3 months	6 years	6 years	4 years
Wiek pojawienia się pierwszych objawów klinicznych sugerujących DMD (bez wskaźników laboratoryjnych)	*3-4 lata*	*1 rok 6 m-cy*	*2 lata 3 m-ce*	*6 lat*	*6 lat*	*4 lata*
Motor development in first 3 years sitting walking	normal/or delayed	delayed 18 months 36 months	delayed 12 months 19 months	normal 8 months 20 months	normal	normal 10 months 15 month
Rozwój ruchowy w pierwszych 3 latach siadanie chodzenie	*prawidłowy /opóźniony*	*Opóźniony 18 m-cy 36 m-cy*	*Opóźniony 12 m-cy 19 m-cy*	*Opóźniony 8 m-cy 20 m-cy*	*Prawidłowy*	*Prawidłowy 10 m-cy 15 m-cy*

(+) Present; (-) Not present; N/A: Not available

(+) Objaw obecny; (-) Objaw nieobecny; D/N: Dane niedostępne

Table I. Cont
Tabela I. Cd.

Waddling/abnormal gait *Kołyszący/ nieprawidłowy chód*	+ +	+ +	N/A D/N	- -	+ +	+ +
Calf hypertrophy /or pseudohypertrophy (age) *Przerost/przerost rzekomy mięśni łydek (wiek)*	+ +	+ (4 ½) + (4 ½)	N/A D/N	+ (7 ½) + (7 ½)	+ +	+ (4) + (4)
Gower's sign (age) *Objaw Gowersa (wiek)*	+ +	+ (4 ½) + (4 ½)	N/A D/N	+ (7 ½) + (7 ½)	+ +	+ +
Age at loss of ambulation *Wiek unieruchomienia*	10-13 years *10-13 lat*	Not yet at 4 ½ years *Nadal chodzi* *w wieku 4½ lat*	9 years *9 lat*	N/A D/N	Not yet at 21 years *Nadal chodzi* *w wieku 21 lat*	N/A D/N
Intellectual disability *Niepełnosprawność intelektulana*	+ or – + *lub* -	+ +	- -	- -	- -	- -

(+) Present; (-)Not present; N/A: Not available
(+) Objaw obecny; (-) Objaw nieobecny; D/N: Dane niedostępne

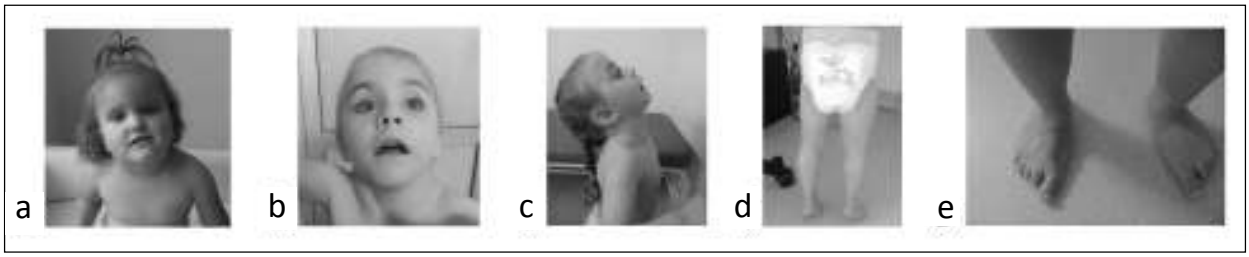

Fig. 1. Phenotype of the patient.
(A) Frontal view of the patient at the age of 18 months. (B) Frontal view of the patient at the age of 4.5 years. (C) Drooping head back at the age of 4.5 years. (D) Calf muscular hypertrophy at the age of 4.5 years. (E) Dysmorphic feet (broad feet with short toes and long hallux) at the age of 4.5 years.

Ryc. 1. Fenotyp pacjenta.
(A) Pacjentka w wieku 18 miesięcy. (B) Pacjentka w wieku 4,5 roku. (C) Opadanie głowy w wieku 4,5 lat. (D) Przerost mięśni łydek w wieku 4,5 lat. (E) Dysmorficzne stopy (szerokie stopy z krótkimi palcami i długim paluchem).

by the detection of a deletion in the dystrophin gene. Ferrier et al. 1965 described a girl with mosaic 45,X/46,XX karyotype, who presented with symptoms of muscular dystrophy at the age of 6 years [2]. She had difficulty climbing stairs, she tired more easily on exercise and fell down more often than before. Clinical signs progressed slowly. DMD diagnosis was based on clinical features, including: muscular weakness with pseudohypertrophy at the calves, increased serum CPK levels and results of muscular biopsy, but the diagnosis could not be confirmed molecularly, because the causative gene was not yet known. Sano et al.1987 described another girl with mosaic 45,X/46,XX karyotype and relatively late clinical presentation of DMD [3]. Her motor development was normal until she was 5 years of age when she started having difficulty running fast. Later she also presented with a slow evolution of DMD. As in the previous case, the diagnosis of DMD was based on clinical features. Ou et al. 2010 described a girl with 46,X,i(X)(q10) karyotype [4]. She started walking on time but fell down easily. She never ran or jumped. At the age of 4 years she presented with typical features of DMD. A more detailed clinical description of the above listed cases is provided in Table I.

From the review of the previously published cases and our patient it appears that girls with chromosome X monosomy have a severe course of the disease, even when compared to the typical course of the disease in males [5, 6]. Not only does the disease affect early motor development with problems of standing and walking, but it also progresses more rapidly. On the other hand girls with a mosaic karyotype have a milder form of the disease, while the girl with isochromosome X had an intermediate course of the disease. It cannot be excluded, however, that also the type of dystrophin gene mutation affects the phenotype. The latter cannot be tested in the cohort analyzed, as only 2 out of 6 patients had molecular evaluation of the DMD gene performed.

Intellectual disability is reported in 30-50% of the children with DMD, and its presence does not depend on socio-economic conditions, education or the severity of symptoms and disease duration [7]. Nonetheless, some authors [8] described heterogeneity in the intelligence level among children with DMD and pointed out the importance of non-verbal intelligence. Our patient presented with moderate intellectual disability but it is hard to assess to what extent it results from the somatic disease(s) vs. the fact that the patient was raised in an orphanage until the age of 1½ years.

CONCLUSION

We suppose that the very early onset of clinical features of DMD is the consequence of the coexistence of classical TS in the same patient. Chromosome X monosomy results in more severe and rapidly progressing DMD even when compared to the typical course of the disease in males. Conversely, the course of DMD disease is milder in females with chromosome X mosaicism.

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List of abbreviations:

DMD: Duchenne muscular dystrophy; TS: Turner syndrome; GCMS: Gas Chromatography/Mass Spectometry; Tandem MS: Tandem Mass Spectometry; MLPA: Multiplex Ligation-dependent Probe Amplification; CPK: creatine phosphokinase

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Competing interests:
The authors declare that they have no competing interests.
Authors' contribution:
EK conceived of the study, participated in its design and coordination and drafted the manuscript; JZ and JP carried out the molecular genetic studies; MCK and AM performed clinical evaluations of the patient; JW coordinated clinical aspects of the study, participated in its design and coordination and helped to draft the manuscript; JL helped with genetic evaluations and drafting of the manuscript; BSL-Z participated in its design and coordination, helped with data analyses and drafting the manuscript. All of the authors read and approved the final manuscript.

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