CASE OF 7-YEAR-OLD GIRL WITH BLOOM SYNDROME

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INTRODUCTION

What is Bloom syndrome?

- very rare (1/48 000 births) disorder- about 275 cases reported
- more popular among Ashkenazi Jewish
- it’s caused by mutation in the **BLM gene** located on the long arm of the **15th chromosome (15q26.1)**
- BLM gene encodes helicase RecQ13

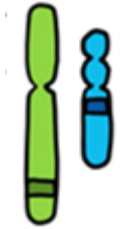


Fig.1- 15q26.1

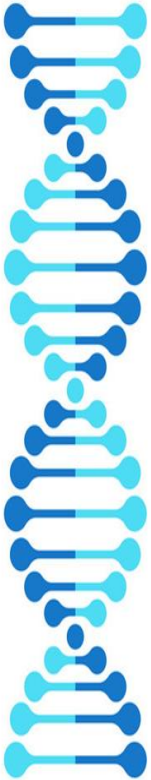


Fig.2- DNA

- Bloom syndrome is inherited as an **autosomal recessive trait**
- The BLM gene codes for a **RecQ helicase** that forms a complex with two other proteins, DNA topoisomerase IIIα and RMI. BLM heterozygotes are healthy and without any clinical features of the disorder

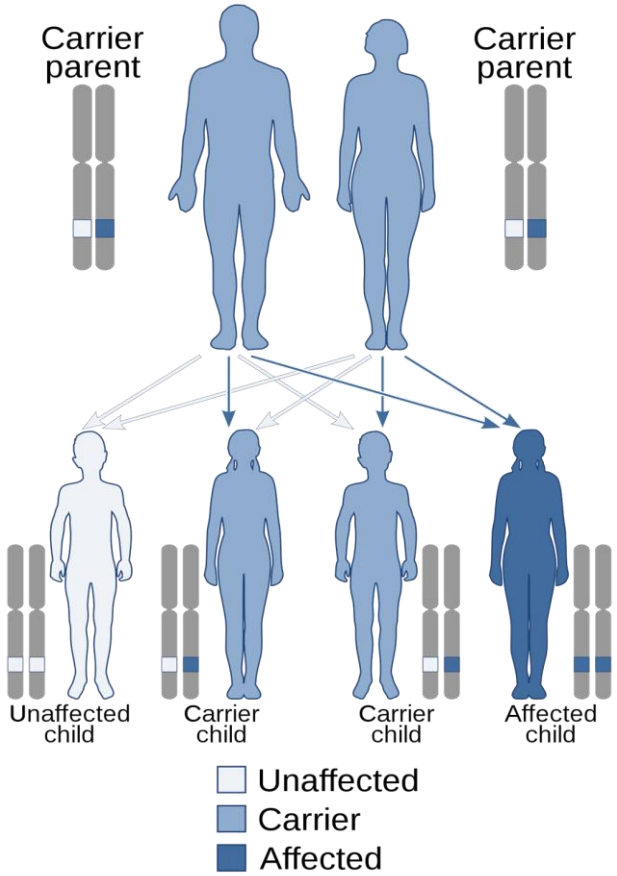


Fig.3- autosomal recessive trait

Signs and symptoms of Bloom syndrome

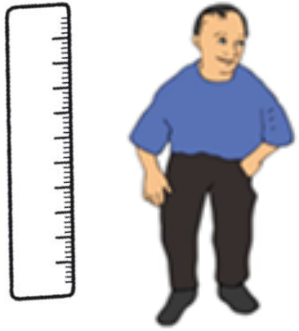


Fig.4- short stature

Fig.5- long, narrow face (dolichocephaly), micrognathism and prominent nose and ears

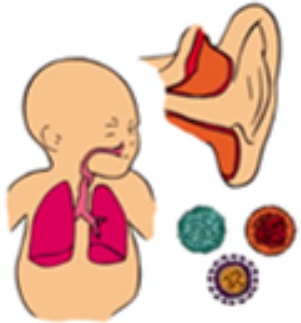


Fig.6- respiratory and digestive tract infections are linked to immunodeficiency occurring in this disorder

Fig.7- learning disabilities

Signs and symptoms of Bloom syndrome

Fig.8- rash on the skin that develops after the exposition to the sun, hyper-pigmented areas or cafe-au-lait spots

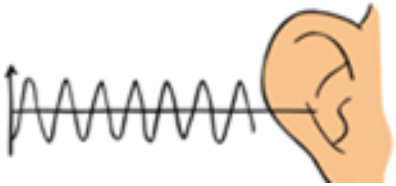
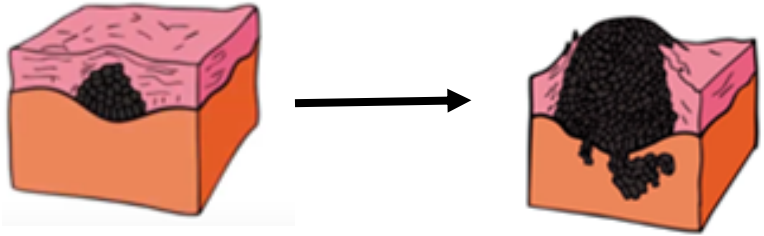


Fig.9- high-pitched voice

Fig.10- predisposition to diabetes

Due to mutation in gene encoding helicase RecQ13 patients with Bloom Syndrome are **150-300 times** more prone to develop cancer in early age, especially **leukemia** or **lymphoma**, and **adenocarcinoma** in adulthood comparing to the rest of the population.



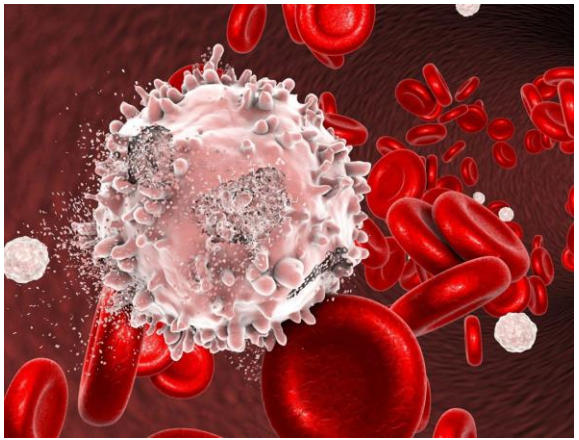


Fig.11&12- cancer development

CASE PRESENTATION

Admission

- January 2018- girl age 5 years and 9 months was admitted to Department of Paediatrics, Endocrinology, Diabetology with Cardiology Division, Medical University of Białystok to broaden the diagnostic process of her short stature (<3pc since birth)
- She was born at therm (39 weeks of pregnancy) with body mass 1580g (<5 pc) and length 44cm (SGA), 8 points in Apgar score
- Mother's height- 160cm (10-25 pc), father's height- 170 cm (10 pc)
- Medical history of the patient revealed hypothyroidism treated with L-thyroxine 25 μg.

Physical examination

- We observed substantial short stature (-5,25 SD) and body mass deficiency, dysmorphic features with long narrow face, micrognathism, cafe-au-lait spots on the skin of abdomen and right popliteal fossa, brachydactyly

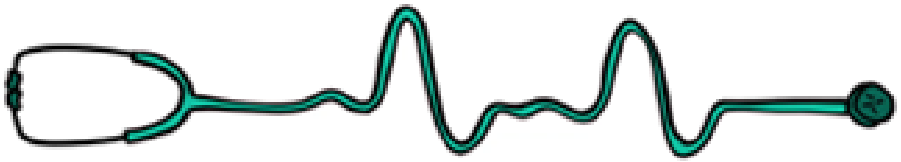
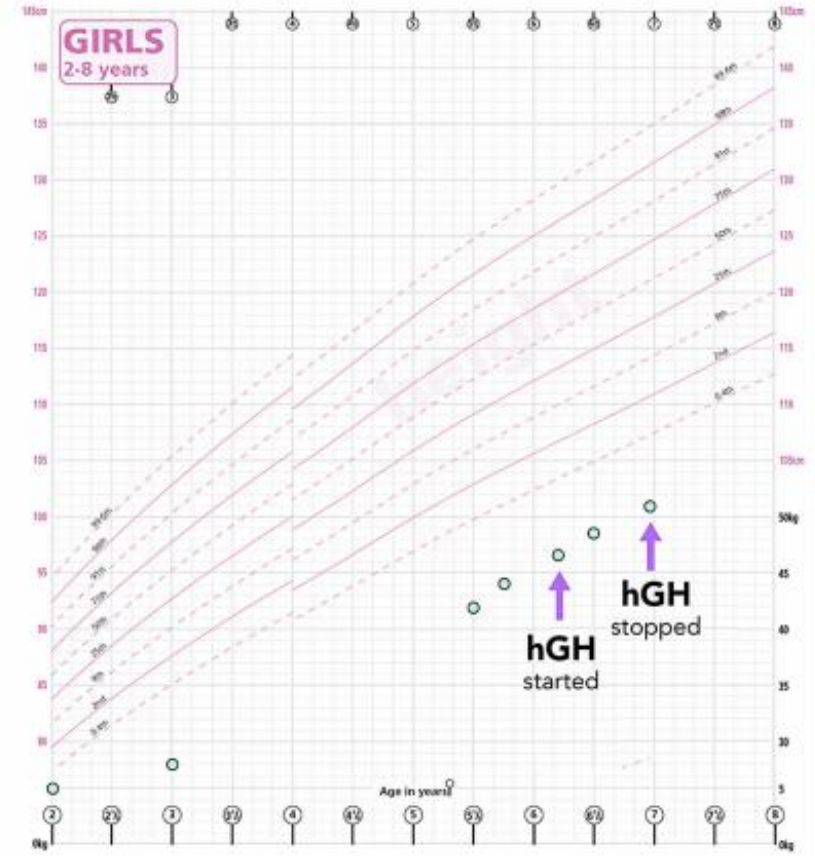


Fig.13- physical examination

a

b



Laboratory tests

- General parameters of blood count remained on normal level
- We observed growth hormone (GH) deficiency:

- Overnight Growth Hormone Frequent Sampling Test- GH max 8,92 ng/ml
- Glucagon Stimulation Testing GH max - 9,1ng/ml
- Arginine Test- 4,67 ng/ml

- IGF1 - 104 ng/ml (N=25.2-211 ng/ml)
- IGFBP3 - 5,4µg/ml (N=1.3-5.6 µg/ml)

Fig.14- laboratory tests

Laboratory tests

- Thyroid hormones concentration with supply of L-thyroxine was normal:

- TSH- 4.79 μlU/l (N=0.85-6.5 μlU/l)
- fT4- 1.5 ng/dl (N=0.9-1.7 ng/dl)

- Adrenal gland dysfunction was excluded:

- cortisol at 11pm- 43.6 nmol/l (N=67-473 nmol/l)
- cortisol at 8 am- 386.92 nmol/l (N=151-793 nmol/l)
- serum potassium- 4.66 mmol/l (N=3.5-5.1 mmol/l)
- serum sodium - 142 mmol/l (N=135-146 mmol/l)

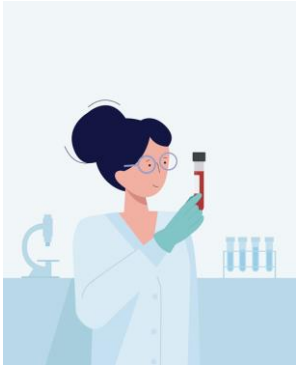


Fig.15- laboratory tests

Second admission

- August 2018- patient at the age of 6 years and 4 months was admitted to Department of Pediatrics and Pulmonary Diseases, Medical University of Białystok due to pneumonia resistant to treatment by amoxicillin / clavulanic acid (7 days), azithromycin (6 days) and clarithromycin (14 days)
- Fever up to 38.8 degrees for 5 days was observed, rhinitis, suffocating cough that has been protracted for a month
- Physical examination revealed redness of the throat, vesicular breath sounds above lung fields, in the lower right lung field at the front- wheezing and fine crackles

- X-ray of the thorax revealed bilateral numerous merging parenchymal densities
- Laboratory tests showed negative inflammatory markers, leucopenia, reduced parameters of the red blood cell system
- The concentration of complement components in the serum was normal, the concentration of IgA and IgM was reduced, the features of stimulation of CD4 and CD8 lymphocytes were observed in flow cytometry. Quantiferon test was negative. M. pneumoniae infection was excluded.

- Intravenous antibiotic therapy, inhaled glucocorticosteroids, inhalation of hypertonic salt, parenteral hydration, anti-reflux treatment and respiratory system rehabilitation with good effect were used.
- In control lung X-ray partial regression was obtained.
- The child was discharged home in good condition.

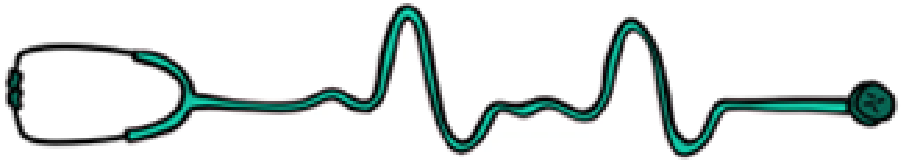
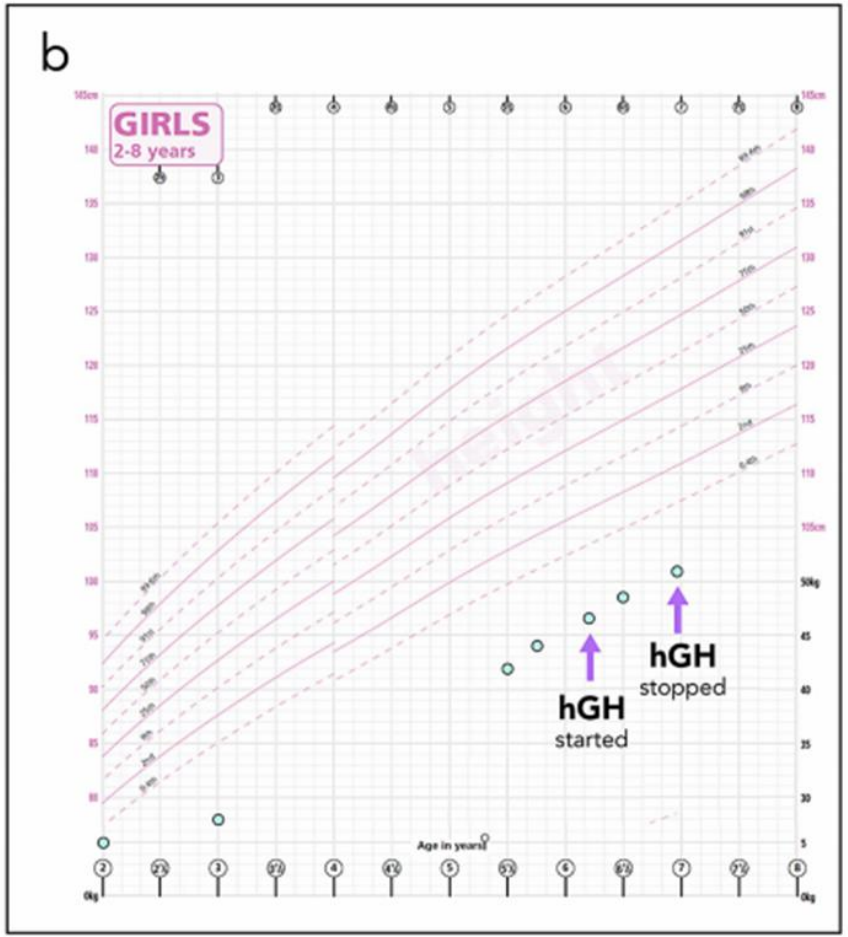


Fig.16- physical examination

- As genetic abnormality was suspected, the blood sample for genetic tests was collected and sent to laboratory.
- After a positive opinion of National Coordination Team for Growth Hormone Application the treatment with GH was initiated as for GH deficiency patients (initial dose of GH 0.54 U/kg/week). The growth rate of the patient after 9 months of the treatment was 5.4 cm/year.
- Nevertheless the treatment with GH had to be stopped due to genetic confirmation of Bloom syndrome and possible increased risk of cancer development.


b
GIRLS
2-8 years
hGH
started
hGH
stopped
Age in years

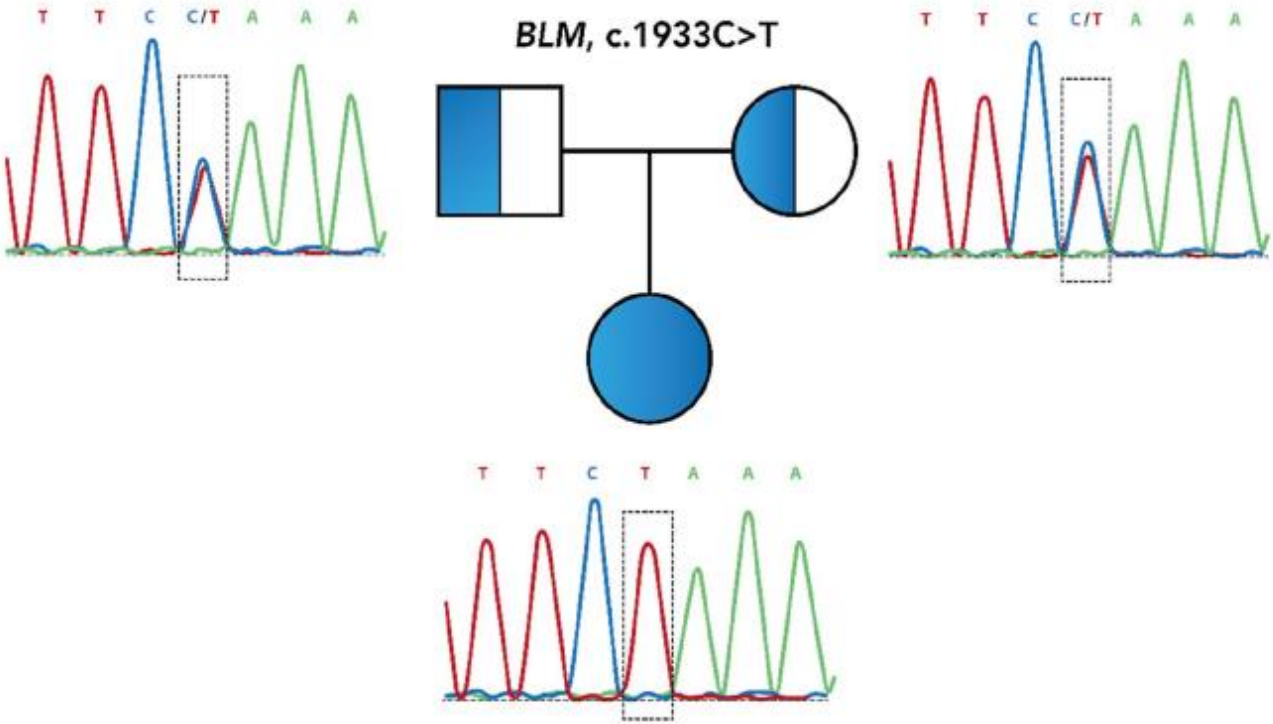


Fig. 2 Chromatograms and family pedigree. Genetic sequencing chromatograms and family pedigree demonstrating both parents were heterozygous and the proband was homozygous for the 91306246C>T, c.1933C>T, p.Q645* *BLM* gene variant

This BLM variant creates a stop codon leading to early termination of the protein (RecQ13 helicase) and is a recognised cause of Bloom syndrome.

CONCLUSIONS

- Rare genetic disorders such as Bloom syndrome should be taken into consideration while diagnosing children with short stature and concomitant dysmorphic features.
- Due to possible increased risk of cancer development in such patients standard GH therapy is contraindicated.

Thank you for your attention :)