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Case report 2

Alagille syndrome

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Learning outcomes

- the student is presented with a case report of children with microdeletion syndrome

- Alagille syndrome is a highly variable, autosomal dominant multisystem disease

- Alagille syndrome 1, ALGS1 (MIM # 118450), which is caused by a mutation in the *JAG1* gene on chromosome 20p12, with an incidence of 1:30,000 live births, 98% of patients with ALGS

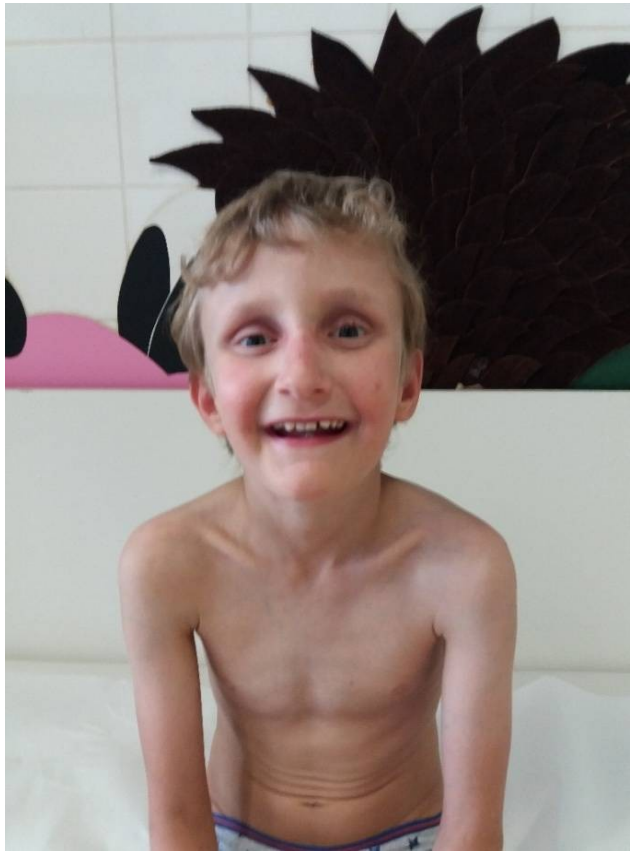
- Alagille syndrome 2, ALGS2 (MIM # 610205), which is associated with a mutation in the *NOTCH2* gene on chromosome 1p12 and represents a rarer form of disability (1: 70,000 live births), 1-2% of patients with ALGS

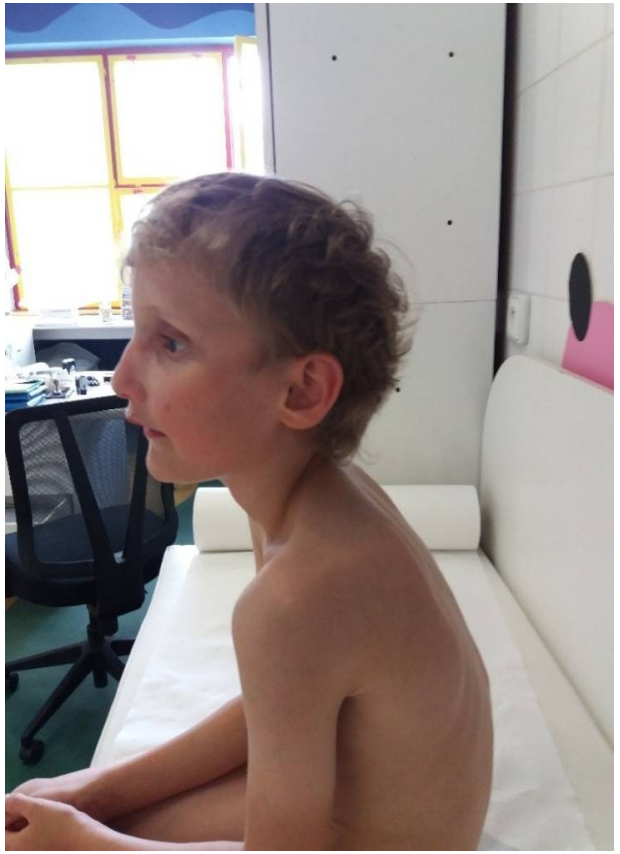
- we estimated that less than 7% of patients with Alagille syndrome have deletions of 20p12

- The basic symptom of the syndrome is a reduction of intrahepatic bile ducts in combination with 5 diagnostic features:
  - Cholestasis (jaundice with conjugated hyperbilirubinemia, ↑ GGT, ↑ Chol, ↑ TGL, 10-20% of patients with rapid progression of liver disease)
  - Congenital heart disease (most often peripheral pulmonary stenosis, Fallot's tetralogy, pulmonary atresia, atrial or ventricular septal defect)
  - Skeletal abnormalities (most often butterfly vertebrae, vertebral fusion, spina bifida occulta, hemivertebra, 12th rib anomalies)
  - Eye disorders (most often posterior embryotoxon - prominence of the Schwalbe´s ring at the interface of the iris and cornea)
  - Characteristic appearance of a triangular face with a wide forehead, deep set eyes, hypertelorism, lower set ears and a longer onion-shaped nose

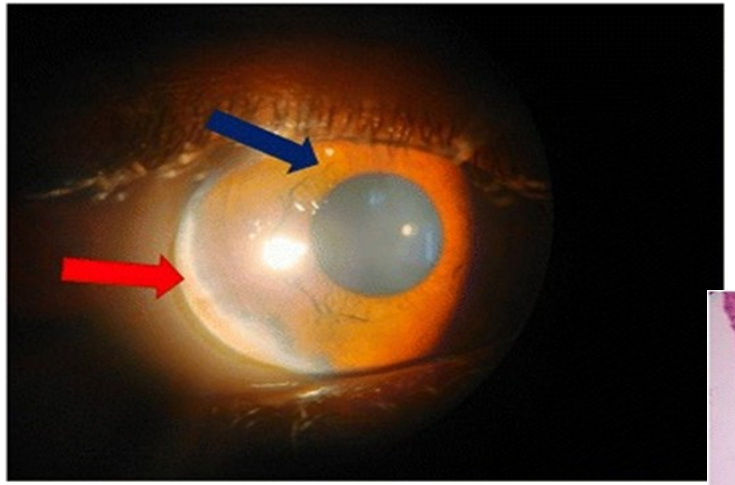
3 of these 5 major characters must be present to confirm the diagnosis

Patient with ALGS, typical face

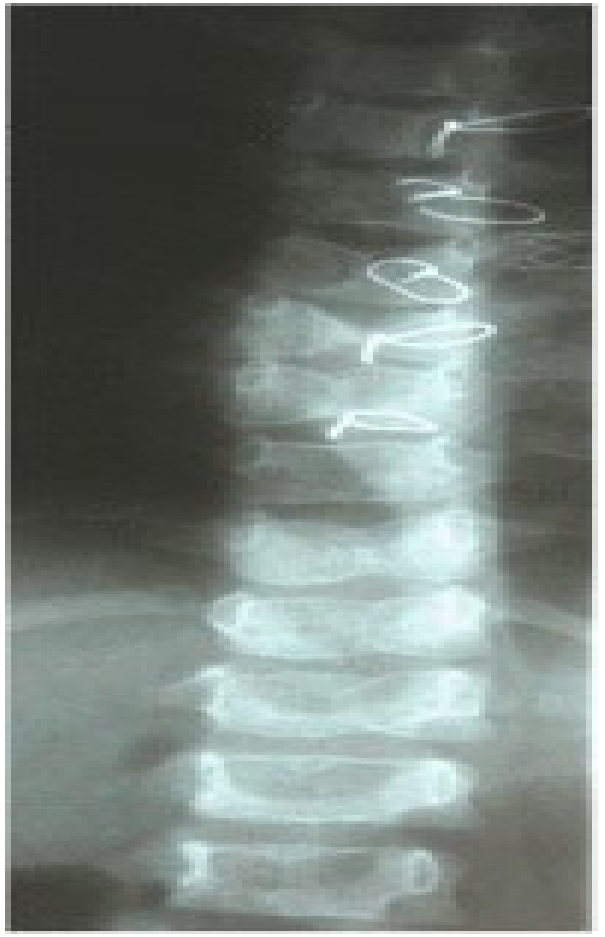




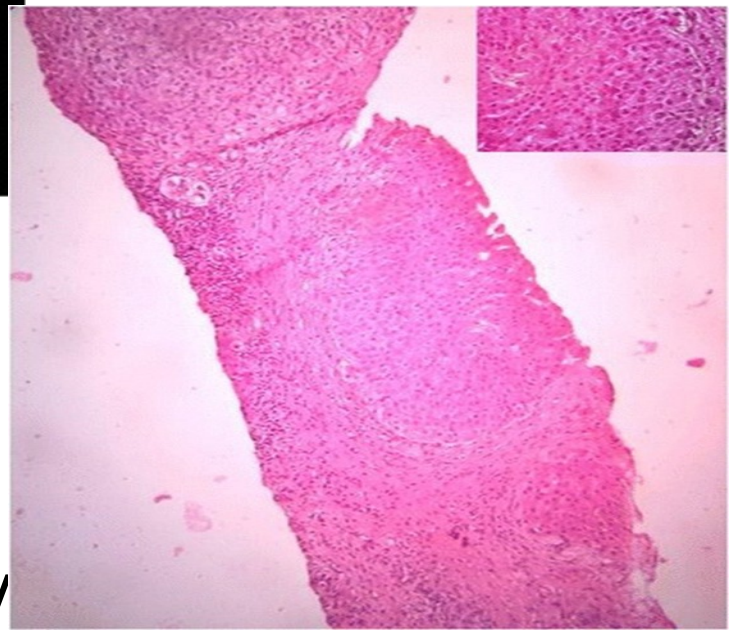
- posterior embryotoxon



- butterfly vertebrae



- bile duct paucity



- About 39% of patients suffer from kidney problems, most often renal dysplasia
- Growth retardation
- Pancreatic insufficiency (40%)
- Hypothyroidism
- Recurrent infections
- Mental retardation and learning disabilities usually in patients with deletion 20p12
- Alagille syndrome is a genetically heterogeneous disorder

- We present phenotype of 4 probands with ALGS1, whose involvement was confirmed by molecular genetic examination

- Method: **next generation sequencing technique** (MiSeq, Illumina) followed by direct sequencing of PCR products on a genetic analyzer. At the genomic DNA level, the coding region of the *JAG1* gene, including exon / intron boundaries, was sequenced. The obtained sequences were compared with the reference sequences of the *JAG1* gene NG_007496.1 and NM_000214.2. The analysis of the found variants was performed on the basis of the reference database (http://www.ncbi.nlm.nih.gov/projects/SNP).

Phenotype of patients with ALGS1

Table 1 Clinical features present in carriers of JAG1 mutations

Pacient	Diagnosis Age	Peculiar face	Cholestasis	Liver biopsy	Heart disease	Ocular anomalies	Skeletal anomalies	Renal anomalies	Others
1	16 month	yes	yes	intrahepatic bile duct paucity	peripheral pulmonary artery stenosis	no	butterfly vertebrae	no	learning disability
2	6 years	yes	yes	intrahepatic bile duct paucity	peripheral pulmonary artery stenosis	no	no	no	
3	7month	yes	yes	intrahepatic bile duct paucity	peripheral pulmonary artery stenosis	no	no	ren arcuatus	behavioral disorders
4	3 month	yes	yes	intrahepatic bile duct paucity	peripheral pulmonary artery stenosis	embryotoxon posterior	rib anomalies	cystic disease	hypothyroidism growth retardation

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Results of molecular genetic testing of the JAG1 gene

Table 2 Mutations in JAG1 found in patients with Alagille syndrome

Pacient	identified sequence variants	Mutation origin	Exon	cDNA	Protein	Mutation type
1	gene JAG1 (NM_000214.2):c.3189dupG in heterozygous state novel mutation, duplication	not investigated	25	c.3189dupG	p.Asn1064Glufs*45	frameshift
2	gene JAG1(NM_000214.2): c.2039delG in heterozygous state novel mutation, deletion	mother	16	c.2039delG	p.Gly680Alafs*63	frameshift
3	gene JAG1 (NM_000214.2):c.1913delG in heterozygous state novel mutation, deletion	father	15	c.1913delG	p.Cys638Leufs*105	frameshift
4	gene JAG1 (NM_000214.2):c.2230C>T p.(Arg744Ter) in heterozygous state substitution	de novo	18	c.2230C>T	p.Arg744Ter	nonsense

the c. nomenclature is based on the cDNA sequence NM_000214.2

Family screening

- The mother of proband No. 2 was monitored at the Department of Gastroenterology for unexplained hepatitis
- Molecular - genetic examination also confirmed ALGS1
- Cardiac examination revealed aortic valve insufficiency
- Another sibling - molecular-genetically ALGS1 excluded
- **Importance:** diagnosis and genetic counseling in the family

- The care of these patients is multidisciplinary
- It includes a pediatrician, hepatologist, cardiologist, ophthalmologist, nephrologist, endocrinologist, nutritional therapist, radiologist, geneticist and, in some cases, a transplant team.
- Molecular-genetic examination X classical scoring system
- Genetic testing in **unclear cases**

Take home message

- syndromological analyzes and syndromological diagnostics benefit from working together to share clinical and related laboratory findings

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2021