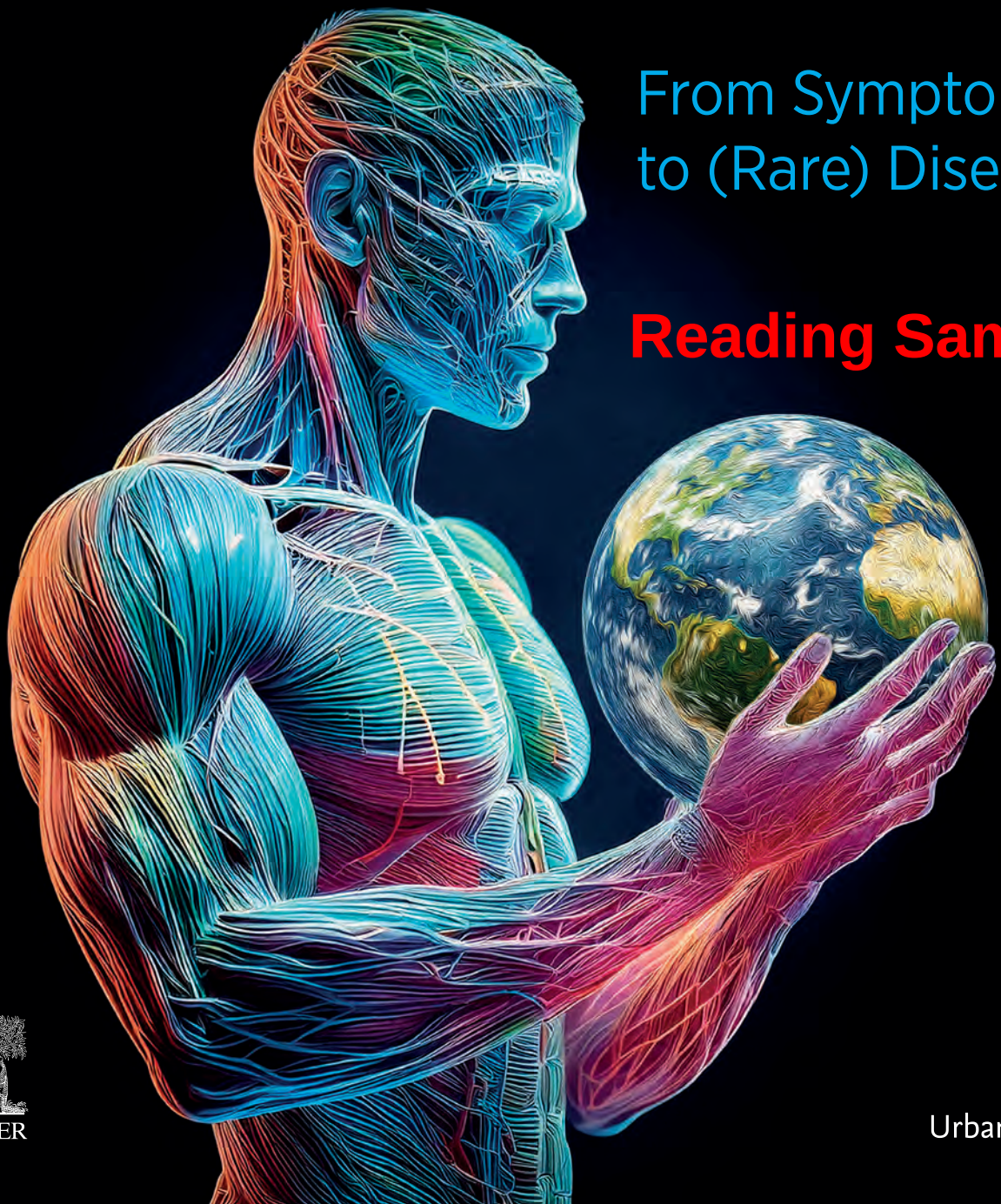
Martin Mücke Rupert Conrad (Eds.)

eBook included

Evolving Atlas of Clinical Syndromes

From Symptoms to (Rare) Diseases

Reading Sample



ELSEVIER

Urban & Fischer

Table of contents

CHAPTER

1 5-Oxoprolinase Deficiency

Synonym

Oxoprolinase deficiency

Classification

ICD-10: E72.8
ICD-11: 5C50.5
GARD: 5681
UMLS: C0268525
MedDRA: N/A
MeSH: C535322
Orpha: 33572
OMIM: 260005
SCTID: 26132002

FACTS

- **Male-to-female ratio** in
  – children: equal distribution
  – adults: equal distribution
- **Prevalence:** N/A
- **Incidence:** N/A
- **Ethnicity:** no predilection
- **Age of onset:** variable (from newborn to adulthood; often identified via urinary organic acid analysis)
- **Median:** N/A
- **Range:** N/A
- **Inheritance pattern:** autosomal recessive
- **Geographical distribution:** worldwide

DEFINITION

5-Oxoprolinase deficiency is due to biallelic mutations in the *OPLAH* gene and presents with 5-oxoprolinuria.

HISTORICAL DATA

The first patients with 5-oxoprolinase deficiency were reported in 1981—two brothers, aged 16 and 11 years, and an unrelated woman.

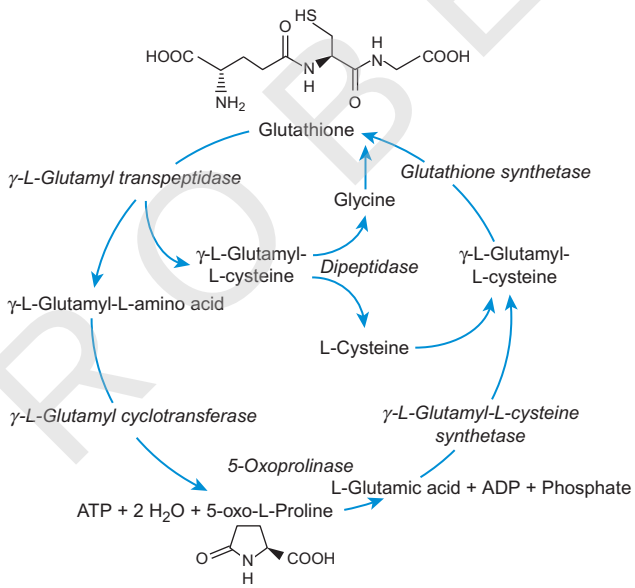


Fig. 1.1 The γ-glutamyl cycle. [L143]

SYMPTOMS

Several patients identified with biallelic *OPLAH* mutations have shown psychomotor (weakness) or developmental disability. However, these clinical features frequently are an indication to perform organic acid analysis and may reflect an ascertainment bias.

DIAGNOSIS/DIAGNOSTIC CRITERIA

- 5-Oxoprolinuria (5-oxoproline [= pyroglutamic acid] is part of the pattern of urinary organic acids)
- Decreased 5-oxoprolinase activity (in leukocytes/ fibroblasts)
- Normal glutathione status/normal erythrocyte glutathione levels
- No hemolytic anemia

DIFFERENTIAL DIAGNOSIS

- 5-Oxoprolinuria due to glutathione synthetase deficiency (mutations in the *GSS* gene)
- Secondary 5-oxoprolinuria

ETIOLOGY

Biallelic mutations in the *OPLAH* gene result in 5-oxoprolinase deficiency.

PATHOGENESIS

5-Oxoprolinase catalyzes the ATP-dependent cleavage of 5-oxoproline. Deficiency of the enzyme results in the accumulation of 5-oxoproline in body fluids.

TREATMENT

Symptomatic, not focused on 5-oxoprolinase or 5-oxoprolinuria.

PROGNOSIS

The existence of a causal relationship between an *OPLAH* defect/5-oxoprolinase deficiency and disease has not been proven.

RESOURCES

https://www.vademetab.org/
https://www.iembase.org/

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CHAPTER

2 22q11.2 Deletion Syndrome

Synonyms

- *Shprintzen syndrome*
- *DiGeorge syndrome*
- *22q11 deletion syndrome (22q11DS)*
- *CATCH-22*
- *Sedlačková syndrome*
- *Velofacial hypoplasia*
- *Conotruncal anomaly face syndrome*
- *Cayler cardiofacial syndrome*
- *Autosomal dominant Opitz G/BBB syndrome*
- *DiGeorge sequence*
- *Microdeletion 22q11.2*
- *Monosomy 22q11*
- *Takao syndrome*
- *Velocardiofacial syndrome*

Classification

ICD-10: Q93.81, D82.1
ICD-11: LD44.N0
GARD: 10299
UMLS: C0012236
MedDRA: 10012979
MeSH: D004062
Orpha: 567
OMIM: 192430, 188400, 125520
SCTID: 767263007

Organ Systems

- Cardiovascular system
- Craniofacial
- Endocrine system
- Nervous system
- Lymphatic system (blood and immune system)
- Skeletal system
- Urinary system
- Visual system
- Auditory system
- Digestive tract

FACTS

- **Male-to-female ratio** in
  – children: 1:1
  – adults: 1:1
- **Prevalence:** 1:2,000–14,000
- **Incidence:** N/A
- **Ethnicity:** no predilection
- **Age of onset:** congenital
- **Median:** N/A
- **Range:** N/A
- **Inheritance pattern:** autosomal dominant (90% de novo cases)
- **Geographical distribution:** worldwide

DEFINITION

22q11.2 deletion syndrome (22q11.2 DS) is a common congenital multisystem syndrome, the most common cause of cleft palate, and the most common chromosome microdeletion syndrome. 22q11.2 DS frequently presents with conotruncal cardiac anomalies, immune-related problems, thyroid dysfunction, hypocalcemia, palatal and other craniofacial defects, intellectual impairments and developmental delays, psychotic features, vision and auditory impairments, dysphasia and dysphagia, and gastroenterologic problems but is highly variable and without a well-defined set of distinguishing clinical features.

HISTORICAL DATA

Czech physician, Eva Sedlácková, originally described a syndrome of velar hypoplasia, hypernasal speech, and facial stigmata in 1955, subsequently associating intellectual disability and cardiac anomalies. An independent description was made by American pediatric endocrinologist, Angelo M. DiGeorge, in 1965. The same constellation of features was termed "*velo-cardio-facial syndrome*" in 1978 by American speech-language pathologist, Robert J. Shprintzen. In 1967, American pediatric cardiologist, Glen G. Cayler, had described an association of "*congenital facial paresis and heart disease*". This presentation was also referred to as Takao syndrome, in honor of the Japanese pediatric cardiologist, Atsuyoshi Takao. John M. Opitz described a variety of midline anomalies. In 1981, it was reported that DiGeorge syndrome could be caused by a deletion in chromosome 22. Through the 1990s, additional studies indicated that DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, autosomal dominant Opitz G/BBB syndrome, and

Cayler cardiofacial syndrome exhibited clinical and genetic overlap, all being associated with a microdeletion on the long arm of chromosome 22 at band 11.2. By the early 2000s, it had become accepted that these conditions represented a single condition.

SYMPTOMS

At least 180 clinical findings have been described in association with 22q11.2 DS, including:

- **Cardiovascular:**
  - aberrant subclavian artery
  - aortic arch abnormalities
  - internal carotid artery abnormalities
  - pulmonary atresia
  - tetralogy of Fallot
  - truncus arteriosus
  - ventricular septal defect
- **Psychiatric:**
  - aggression
  - attention deficit and hyperactive disorder
  - autistic features
  - bipolar disorder
  - blunt or inappropriate affect
  - depressive features
  - obsessive-compulsive features
  - paranoia
  - psychotic features
  - schizoaffective disorder
  - schizophrenia
- **Ophthalmologic:**
  - accommodative esotropia
  - amblyopia
  - esophoria
  - exotropia
  - posterior embryotoxon
  - sclerocornea
  - small optic discs
  - strabismus
  - tortuous retinal vessels
- **Craniofacial:**
  - bifid uvula
  - bulbous nasal tip
  - dysphagia
  - dysphasia
  - dysmorphic external ears
  - eyelid hooding
  - hypertelorism
  - hypoplastic alae nasi
  - laryngotracheoesophageal anatomic and functional anomalies
  - long facies
  - low-set ears
  - malar flattening
  - microcephaly
  - micrognathia
  - middle ear abnormalities
  - narrow palpebral fissures
  - nasolacrimal duct agenesis
  - palatal anatomic and functional defects
  - retrognathia
  - pharyngeal hypotonia
  - Pierre Robin syndrome
  - short philtrum
  - square nasal root
  - velopharyngeal incompetence
- **General / Endocrine:**
  - growth hormone deficiency
  - hypocalcemia
  - hypoparathyroidism, secondary to parathyroid hypoplasia or agenesis
  - hypo- or hyperthyroidism
  - short stature
- **Neurologic:**
  - auditory impairment
  - asymmetric facies while crying
  - developmental delay
  - early-onset Parkinson disease
  - hypotonia
  - intellectual impairment
  - seizures
- **Immunologic / Hematologic:**
  - autoimmune disease
  - autoimmune hemolytic anemia
  - frequent, severe, and longer duration of infections
  - increased bleeding risk
  - increased incidence of allergies
  - increased platelet size
  - increased risk for some malignancies
  - T-cell immunodeficiency
  - thrombocytopenia, neutropenia, hemolytic anemia
  - thymic aplasia
- **Urologic / Gastroenterologic:**
  - cryptorchidism
  - gastroenterologic anatomic and functional abnormalities
  - hypospadias
  - inguinal hernia
  - renal defects
- **Musculoskeletal:**
  - musculoskeletal defects
  - scoliosis
  - slender hands and long and tapering fingers
  - umbilical hernia

DIAGNOSIS/DIAGNOSTIC CRITERIA

- Diagnosis is based on clinical presentation and finding of a 1.5 or 2.54 megabase pair deletion at 22q11.2 encompassing the 480 kilobase pair critical region. A deletion range of 0.7–3 megabase pairs is also reported.

- Rarely, some patients with clinical findings consistent with 22q11.2 DS do not have an identified deletion; in these patients, it is customary to use one of the synonyms that best reflects the patient's presentation.
- Unbalanced translocations, instead of deletions, are very rarely seen involving the same locus and critical region and are accepted as diagnostic of 22q11.2 DS.
- Great phenotypic variability is seen, including intra-familiar and between individuals with identical genotypes.
- Elevated plasma proline and aortic arch anomalies each may suggest 22q11.2 microdeletion.

DIFFERENTIAL DIAGNOSIS

- 4q21.3, 10p13-14, 11q23-ter associated conditions
- Alagille syndrome
- Distal chromosome 22q11.2 deletion syndrome
- CHARGE syndrome
- Interrupted aortic arch
- Goldenhar syndrome
- Kabuki syndrome
- Maternal diabetes or retinoic acid exposure
- Nezelof syndrome
- Opitz GBBB syndrome (X-linked)
- Smith–Lemli–Opitz syndrome
- Tetralogy of Fallot with absent pulmonary valve
- Tetralogy of Fallot with pulmonary atresia
- Transposition of the great arteries
- Truncus arteriosus
- VATERL

ETIOLOGY

A contiguous gene syndrome, 22q11.2 DS is associated with a 1.5 or 2.54 megabase pair microdeletion bordered by low copy number repeats. In 90% of cases, the deletion arises *de novo* from a non-allelic meiotic recombination, with autosomal dominant inheritance responsible for 10% of cases. Somatic and germline mosaicisms have been documented.

PATHOGENESIS

The deletion causes embryonic abnormalities of neural crest cell migration and branchial arch development. The 22q11.2 DS critical region includes about 40 genes involving the parathyroid glands, thymus, central nervous system, and conotruncal region of the heart. Conotruncal cardiac defects develop secondary to malformations in cardiac outflow structures. Some craniofacial features, including palatal defects and auditory impairment; hypocalcemia; and conotruncal cardiac defects; and psychiatric pathology, including intellectual impairment, may be associated with loss of the *TBX1* gene. Psychiatric pathology and intellectual impairment may also be related to absence of the *COMT* gene. Deletion of the *GP1BB* gene, reducing platelet surface expression of GPIb-IX-V, is associated with thrombocytopenia with increased platelet size. Genotype–phenotype correlations generally have been elusive in this highly heterogenous condition.

TREATMENT

There is no specific treatment for 22q11.2 DS. Treatment continues throughout an individual's life and addresses specific problems, in consideration of the patient's overall clinical presentation. Imaging studies and laboratory monitoring of immune and thyroid function and complete metabolic panel and blood counts are appropriate. As with other congenital anomaly disorders, defects and other constitutional issues should be addressed as early as possible to reduce developmental impacts, morbidity, and risk to life. While the clinical picture varies greatly between patients, treatment may include:

- Medical management of immune-related problems, thyroid function, and hypocalcemia
- Surgical repair of cardiac defects
- Surgical amelioration of palatal defects and other craniofacial deformities
- Management of vision and auditory impairments
- Speech therapy for dysphasia and dysphagia
- Management of developmental delays
- Management of gastroenterologic problems
- Management of psychiatric problems, especially psychotic features
- Special educational services for intellectual disabilities
- Screening for early-onset Parkinson disease

PROGNOSIS

- Prognosis depends on severity of presentation, which ranges from life-limiting to being so mild that some patients remain undiagnosed.
- Absence of major cardiovascular defects, immunocompromised status, neurologic, and psychiatric involvement are associated with normal life expectancy.
- Patients with serious psychiatric illness or intellectual disabilities may have poor functional and socioeconomic outcomes.

COMMENTARY

- 22q11.2 DS encompasses a staggering breadth of possible presentations, requiring extreme caution in initial workup and longitudinal monitoring with timely interventions when indicated.
- Despite the manifold potential physical problems associated with 22q11.2 DS, psychotic illness is the most therapeutically challenging predictor of psycho-socioeconomic outcomes.
- It has been observed that informing families their child has an eponymous syndrome may be less distressing than advising them their child has a "deletion syndrome".

- Shprintzen syndrome should not be confused with Shprintzen–Goldberg syndrome, which is an unrelated systemic connective tissue disorder involving mutations in the *SKI* gene.

RESOURCES

https://medlineplus.gov/genetics/condition/22q112-deletion-syndrome/
https://rarediseases.info.nih.gov/diseases/10299/index

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CHAPTER

3 Abetalipoproteinemia (ABL)

Synonyms

- *Bassen–Kornzweig syndrome*
- *MTP deficiency*

Classification

ICD-10: E78.6
ICD-11: 5C81.1
GARD: 5
UMLS: C0000744
MedDRA: 10083851
MeSH: D000012
Orpha: 14
OMIM: 200100, 615558, 605019
SCTID: 767263007

Organ Systems

- Digestive tract
- Liver
- Nervous system
- Visual system
- Lymphatic system (blood and immune system)
- Skeletal system
- Muscular system
- Cardiovascular system

FACTS

- **Male-to-female ratio** in
  - children: N/A
  - adults: N/A
- **Prevalence:** common in groups with consanguineous marriages
- **Incidence:** 1 per million
- **Ethnicity:** increased incidence in Ashkenazi Jews
- **Age of onset:** infancy
- **Median:** N/A
- **Range:** N/A
- **Inheritance pattern:** autosomal recessive
- **Geographical distribution:** worldwide

DEFINITION

Inherited disorder of fat malabsorption and transport due to impaired formation of beta-lipoproteins with fat-soluble vitamin deficiency and acanthocytosis.

HISTORICAL DATA

The American physicians Frank Albert Bassen and Abraham Leon Kornzweig first described red blood cell acanthocytosis, atypical retinitis pigmentosa, and ataxia in a patient in 1950. Jampel and Falls observed low serum cholesterol in affected patients in 1958. Salt (1960) reported the absence of beta-lipoproteins in the serum, and the syndrome was called "abetalipoproteinemia".

SYMPTOMS

- Gastrointestinal: steatorrhea, diarrhea, vomiting, abdominal distension and pain, hepatomegaly, steatosis, transaminitis
- Neurologic: spinocerebellar degeneration, ataxia, dysmetria, dysarthria
- Ophthalmologic: retinitis pigmentosa, nystagmus, ptosis, strabismus, anisocoria, ophthalmoplegia
- Hematologic: acanthocytosis, prolonged international normalized ratio, absence of apoB-containing lipoproteins, bleeding diathesis, low plasma lipids and fat-soluble vitamins
- Musculoskeletal: lordosis, kyphoscoliosis, pes cavus, muscle weakness

DIAGNOSIS/DIAGNOSTIC CRITERIA

- Low levels of blood lipids including triglycerides and cholesterol
- Absence of apoB-containing lipoproteins including chylomicrons and very low-density lipoproteins
- Low levels of fat-soluble vitamins (vitamins A, E, K and D)
- Presence of abnormal spiculated red blood cells (acanthocytosis)
- Biallelic loss-of-function mutations in the *MTTP* gene

Diagnosis is confirmed by molecular genetic testing of the *MTTP* gene.

DIFFERENTIAL DIAGNOSIS

Other familial hypobetalipoproteinemia disorders including:

- Homozygous familial hypobetalipoproteinemia and chylomicron retention disease
- Pancreatic insufficiency including cystic fibrosis, biliary atresia
- Intolerance to milk lipids

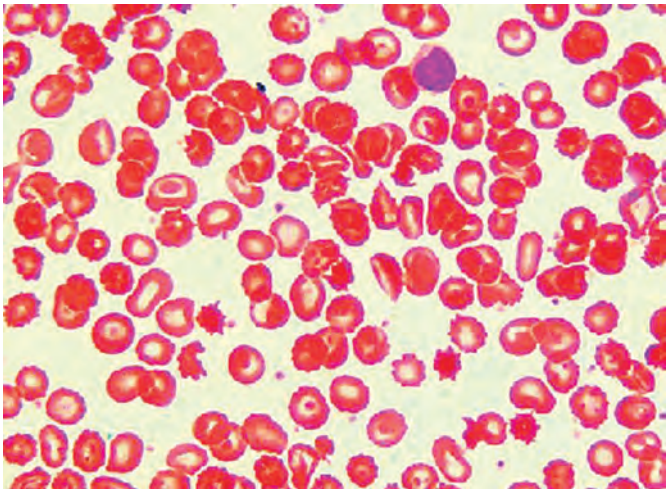

Fig. 3.1 Peripheral blood smear from a 5-month-old male patient shows acanthocytosis of red blood cells. [H488-001]

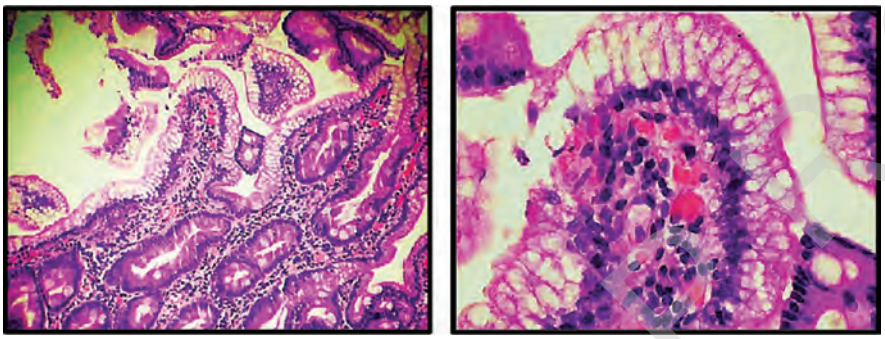

Fig. 3.2 Hematoxylin and eosin staining of duodenal biopsy shows normal villi with lipid laden enterocytes. [H488-001]

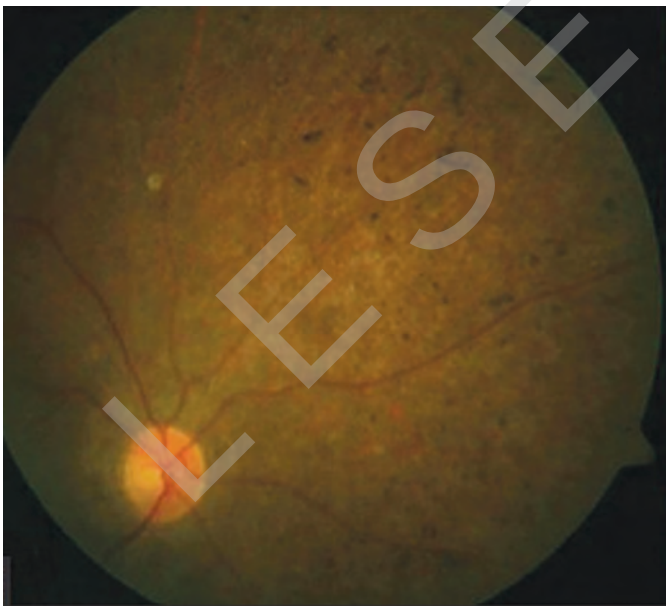

Fig. 3.3 Fundus photograph of a patient with abetalipoproteinemia and atypical pigmentation of the retina. [H601-001]

- Inflammatory bowel disease
- Intestinal lymphangiectasia
- Mechanical defects of the small bowel
- Gluten-sensitive enteropathy
- Friedreich ataxia
- Refsum disease
- Spinocerebellar ataxia
- Ataxia with isolated vitamin E deficiency

ETIOLOGY

Abetalipoproteinemia (ABL) is an autosomal recessive disorder due to mutations in the *MTTP* gene. Microsomal triglyceride transfer protein (MTP) is essential for the assembly of apoB-containing lipoproteins that transport fat in the blood.

PATHOGENESIS

Patients with ABL cannot synthesize apoB-containing lipoproteins and therefore are unable to absorb dietary fat and fat-soluble vitamins. Transport of endogenous lipids is also defective. In the absence of treatment, ABL is a progressive disease that causes severe multi-organ dysfunction. Neurologic abnormalities typically begin in the first or second decade of life due to vitamin E deficiency. Ophthalmologic symptoms result from vitamin A and E deficiency. Most untreated individuals are legally blind by age 40. Bleeding diathesis from vitamin K deficiency has been reported. Hepatomegaly and steatosis develop from triglyceride accumulation.

TREATMENT

Dietary recommendations:

- Adequate caloric intake while restricting total fat to less than 10–15% (5–15 grams/day) of total daily caloric requirement
- 1–2 teaspoons of oils rich in polyunsaturated fatty acids is advised to ensure adequate intake of essential fatty acids (EFA)
- Consumption of long chain fatty acids is not recommended.

Vitamin supplementation:

- Vitamin E 100–300 IU/kg/day
- Vitamin A 100–400 IU/kg/day
- Vitamin D 800–1,200 IU/day
- Vitamin K 5–35 mg/week

PROGNOSIS

The prognosis is good provided restrictions of dietary fat content and supplementation of fat-soluble vitamins are adequate.

COMMENTARY

Patients with ABL often present in infancy with failure to thrive and steatorrhea. Due to the rarity of this condition, the diagnosis may not be made at this stage. The complete absence of plasma apoB-containing lipoproteins, low plasma cholesterol and acanthocytosis are diagnostic features of ABL and further substantiate the diagnosis. It is critical that ABL is diagnosed early for appropriate treatment and management to avoid multi-organ damage.

RESOURCES

https://rarediseases.org/rare-diseases/abetalipoproteinemia/
https://rarediseases.info.nih.gov/diseases/5/abetalipoproteinemia
https://www.ncbi.nlm.nih.gov/books/NBK532447/
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CHAPTER

4 Acatalasemia

Synonyms
- *Takahara disease*
- *Acatalasia*

Classification
ICD-10: E80.3
ICD-11: 5C57.1
GARD: 363
UMLS: COCO268419, C2931868
MedDRA: 10086141
MeSH: D020642
Orpha: 926
OMIM: 614097
SCTID: 267454002

Organ Systems
- Liver
- Blood

FACTS
- **Male-to-female ratio** in
  – children: not known
  – adults: 0.98
- **Prevalence:** 40 per million in Hungary, 50 per million in Switzerland, and 800 per million in Japan
- **Incidence:** no new data
- **Ethnicity:** no data
- **Age of onset:** 11–69
- **Median:** unknown
- **Range:** unknown
- **Inheritance pattern:** autosomal recessive
- **Geographical distribution:** worldwide

DEFINITION

Acatalasemia is a rare condition characterized by an inherited deficiency of catalase enzyme which is due to mutations in the catalase gene.

HISTORICAL DATA

The condition was detected by Takahara in 1946; in 1952 he reported on nine cases among Japanese patients. Later, acatalasemia was also detected in other countries such as China, Korea, Israel, Peru, Canada, Austria, and Germany.

Large-scale screenings using biochemical methods were performed in Japan (1968), Switzerland (1961), and Hungary (1992). These studies found 114 acatalasemics in America, Asia, and Europe

SYMPTOMS

Acatalasemia is generally asymptomatic. It may be associated with oral ulceration, gangrene, diabetes mellitus, atherosclerosis, vitiligo, schizophrenia, Parkinson's disease, tumors, and microcytic anemia. In acatalasemia, catalase activity in the blood (less than 5%) and in other tissues (8–16%) such as liver, pancreas, kidney, lung, and spleen is reduced.

DIAGNOSIS/DIAGNOSTIC CRITERIA

- **First step:** determination of blood catalase. For those methods measuring the decrease in hydrogen peroxide concentration the range of catalase deficiency for acatalasemic homozygotes is 0.5–5.3%, and for hypocatalasemic heterozygotes it is 52.1–61.6%.
- **Second step:** detection of known catalase gene mutations.
- **Third step:** When the known catalase gene mutations cannot be not found, a search for new catalase gene mutations leading to a decrease in enzyme catalase activity should be performed.

DIFFERENTIAL DIAGNOSIS

- People with less than 61.6% of blood catalase may indicate heterozygous hypocatalasia; confirm by genetic testing.
- When these can be excluded, a search for new mutations can be started. The catalase gene mutations should be responsible for decreased catalase synthesis which yields an inactive catalase protein.
- Decreased blood catalase without catalase gene mutations might be due to an unknown regulatory mechanism.

ETIOLOGY

Inherited acatalasemia is caused by catalase gene mutations. They might yield no or truncated catalase protein without enzyme activity.

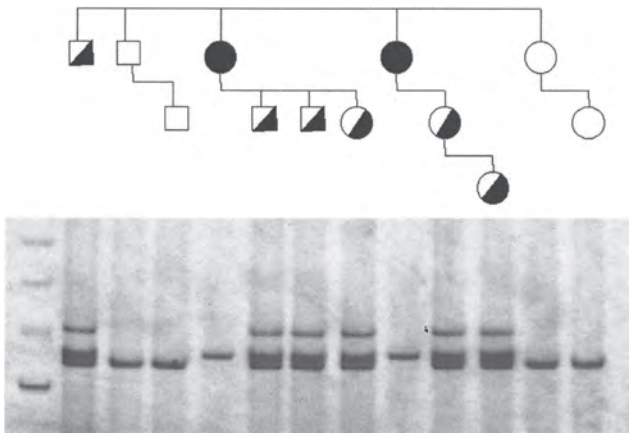

Fig. 4.1 Pedigree (top) and PCR-heteroduplex analysis (bottom) of an acatalasemic family in Hungary (black: homozygotes; half-filled: heterozygotes; blank: normocatalasemics). [F1002-002]

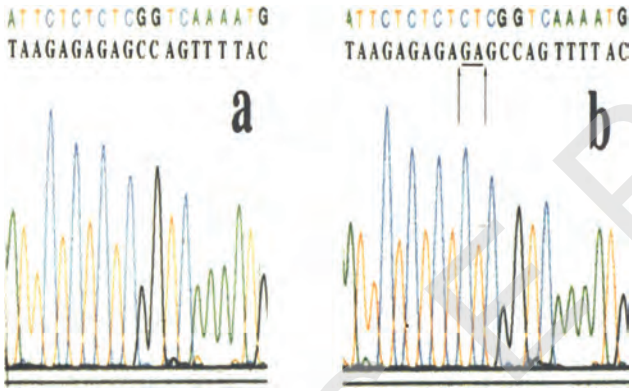

Fig. 4.2 Nucleotide sequencing of exon 2 of the catalase gene. Left: wild type; right: mutated gene. The arrows show a GA insertion of exon 2 at position 138 for type 1 of the Hungarian acatalasemia. [F1002-002]

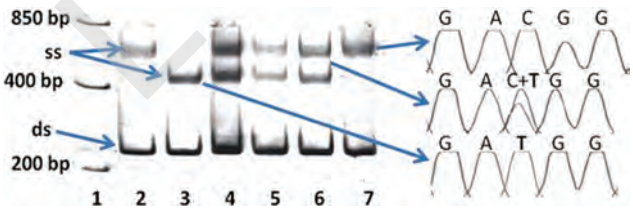

Fig. 4.3 Screening of catalase gene mutations in exon 9 for +22348C to T. The middle part shows PCR-heteroduplex analyses with the lanes 2 molecular weight markers, lanes 2,7 CC homozygotes, lanes 4, 5, 6, 7 CT heterozygotes, and lane 3 TT homozygote. On the right: nucleotide sequencing with CC (top), CT (middle) and TT (bottom) genotypes (ss: single-stranded DNA, ds: double-stranded DNA. [H471-001]

By 2018, 15 acatalasemic mutations have been reported: 1 in Swiss acatalasemics, 2 in Japanese acatalasemics, 2 in North American acatalasemics, and 10 in Hungarian acatalasemics.

PATHOGENESIS

The enzyme catalase decomposes high and toxic concentrations of H_2O_2 into oxygen and water. Physiologic H_2O_2 for signaling is generally not affected by catalase. Low activity of catalase in acatalasemia may cause an increase in concentrations of H_2O_2 which lead to oxidative damage to cells, proteins, DNA, and skin pigments. In acatalasemia, the lifelong exposure to increased H_2O_2 concentrations may damage the oxidation-sensitive and catalase-poor pancreatic beta cells. This may explain the increased frequency of diabetes in patients with inherited catalase deficiency. The symptoms of acatalasemia might be caused by the oxidative damage resulting from different catalase gene mutations.

TREATMENT

It is recommended that patients with inherited catalase deficiency avoid situations that are associated with an increased production of free radicals, mainly of hydrogen peroxide. For example, the treatment of tumor lysis syndrome with the enzyme uricase may produce large amounts of hydrogen peroxide.

Some methods for increasing the production of catalase in animal tissue samples have been reported, including overexpression of catalase, catalase delivery to peroxisomes and immunotargeting.

PROGNOSIS

- Acatalasemia patients in Japan, Switzerland, and Hungary can live a normal life.
- Acatalasemia patients have a higher risk for chronic, age-related diseases and acute conditions which generate high concentrations of hydrogen peroxide. They are more prone to diabetes mellitus, especially to its type 2 form. Compared to the general population, the onset of type 2 diabetes in acatalasemia patients occurs more than 10 years earlier.
- Autopsies of one acatalasemic and three hypocatalasemic patients revealed more atherosclerosis than typical for their age.
- 85.1% of the acatalasemia patients suffered from chronic disease such as diabetes, oral gangrene, schizophrenia, vitiligo, laryngeal tumor, Parkinson's disease, and atherosclerosis.

COMMENTARY

For 8 homozygous acatalasemic and 316 heterozygous patients, genetic testing revealed 15 different DNA mutations, including splicing of intron 4, stop codons in exon 2, T deletion in exon 4, and missense mutations in exons 2, 3 and 9. These mutations yielded

decreased blood catalase activity of 0.5–5.0% for homozygotes and 52.1–61.6% for heterozygotes.

The susceptibility to symptoms and diseases in acatalasemia patients is not due to a specific catalase gene mutation, but might be caused by the chronic, lifelong increase of hydrogen peroxide levels in these catalase-deficient patients.

RESOURCES

https://rarediseases.info.nih.gov/diseases/363/acatalasemia
https://medlineplus.gov/genetics/condition/acatalasemia/
https://pubmed.ncbi.nlm.nih.gov/24522161/
https://www.guidetopharmacology.org/GRAC/DiseaseDisplayForward?diseaseId=1249

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CHAPTER

5 Acrofacial Dysostosis Weyers Type (WAD, MIM 193530)

Synonyms

- *Weyers syndrome II*
- *Weyers acrodental dysostosis*
- *Curry–Hall syndrome*
- *Acrodental dysostosis, Weyers type*

Classification

ICD-10: Q75.4
ICD-11: LD25.2
GARD: 497
MedDRA: N/A
MeSH: C536695
OMIM: 193530
Orpha: 952
UMLS: C0457013

Organ Systems

- Skeletal system
- Teeth
- Cardiovascular system
- Nails

FACTS

- **Male-to-female ratio** in
  - children: equal distribution
  - adults: equal distribution
- **Prevalence:** unknown, but considered very rare
- **Incidence:** unknown, but considered very low
- **Ethnicity:** no predilection
- **Age of onset:** neonatal
- **Median:** N/A
- **Range:** N/A
- **Inheritance pattern:** autosomal dominant (heterozygous EVC2 variants)
- **Geographical distribution:** worldwide

DEFINITION

Weyers acrofacial dysostosis (WAD, MIM 193530) or Curry–Hall syndrome is a very rare autosomal dominant disorder that affects the development of the teeth, nails, and bones. The disease is present from birth, affecting both sexes. So far, only a few affected families have been reported worldwide.

HISTORICAL DATA

In 1952, German pediatrician Helmut Weyers reported on radiological findings in three infants with postaxial polydactyly and anomalies of the lower jaw, dentition, and oral vestibule similar, but milder than those peculiar for Ellis–van Creveld syndrome (EvC, MIM 225500). Weyers proposed to name this condition acro-facial dysostosis and also suggested an autosomal dominant model of inheritance.

SYMPTOMS

- WAD patients usually present with:
  - mild short stature (around the 5th percentile),
  - hands and feet postaxial polydactyly type A,
  - fusion of the 5th and 6th metatarsals and metacarpals
  - mild brachydactyly.
- In addition, micrognathia with osseous clefts of the mandibular symphysis, small mouth with multiple labial frenula, and dental anomalies (hypodontia, conical shape of the permanent teeth, irregularly shaped, or absent incisors) can be present.
- Dysplastic and dystrophic nails are common. Cardiovascular malformations have been reported in only two families with a dominant pedigree, while a double epiglottis was reported once.

DIAGNOSIS/DIAGNOSTIC CRITERIA

WAD diagnosis is based on clinical findings, family history and genetic studies. Causative variants have been identified in *EVC2* (exon 22). However, a more extended allelic heterogeneity has not yet been excluded and, therefore, it is recommended to extend the analysis to *EVC*. If no point mutation is identified, it is advisable to scan *EVC* and *EVC2* for exonic rearrangements by multiplex ligation probe amplification analysis or chromosomal microarray. Recently, WAD diagnosis has been implemented by the use of next-generation sequencing approaches, such as the skeletal ciliopathies panel.

Diagnosis is confirmed by molecular analysis identifying heterozygous pathogenic variants in *EVC2* (exon 22).

DIFFERENTIAL DIAGNOSIS

- WAD and EvC are allelic disorders, and WAD is considered in differential diagnosis with EvC.
- WAD is intended also in differential diagnosis with five other types of acrofacial dysostosis:
  - Nager type (MIM 154400)
  - Rodriguez lethal type (MIM 201170)
  - Miller syndrome (MIM 263750)
  - Catania type (MIM 101805)
  - Palagonia type (MIM 601829)
- Cranioectodermal dysplasia (MIM 218330, 613610, 614099, 614378) should be also considered in differential diagnosis with WAD.

ETIOLOGY

WAD is due to heterozygous pathogenic variants in *EVC2*. It has also been linked to variants in *EVC*, but this association has not been con-

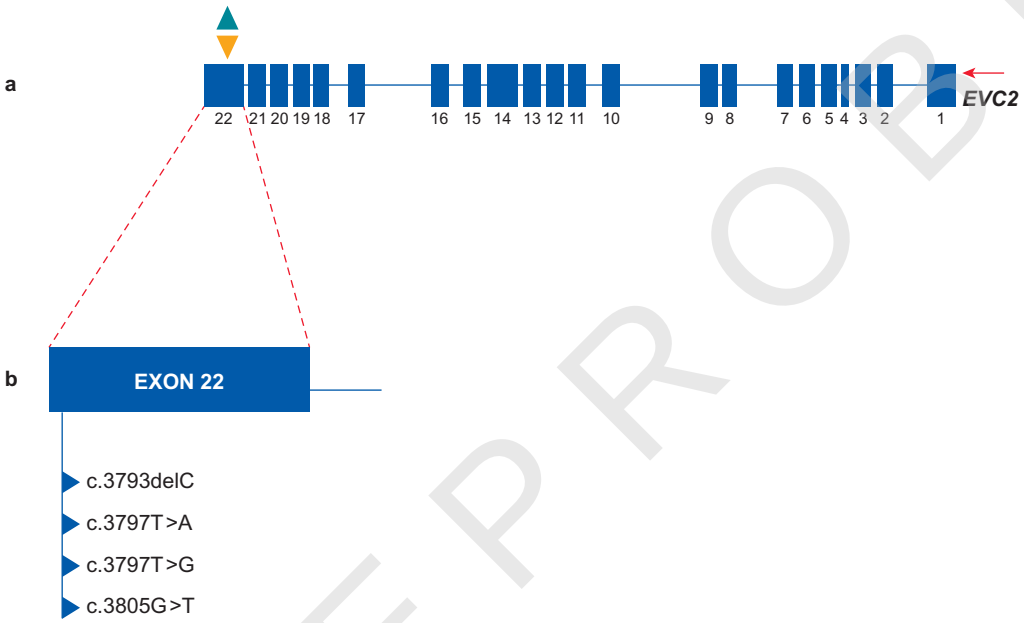

Fig. 5.1 Distribution of the *EVC2* pathogenic variants detected in Weyers patients. Panel **a** illustrates the exon composition of *EVC2* gene with the type of variants found in exon 22 shown above. Code: Nonsense variants are represented by blue triangles and microdeletions by orange inverted triangles. Panel **b** indicates the position of Weyers dominant variants clustering in exon22 of *EVC2* (elaborated from Ruiz-Perez VL, et al. Nat Genet 2000; 24: 283–286). [H484-001/L231]

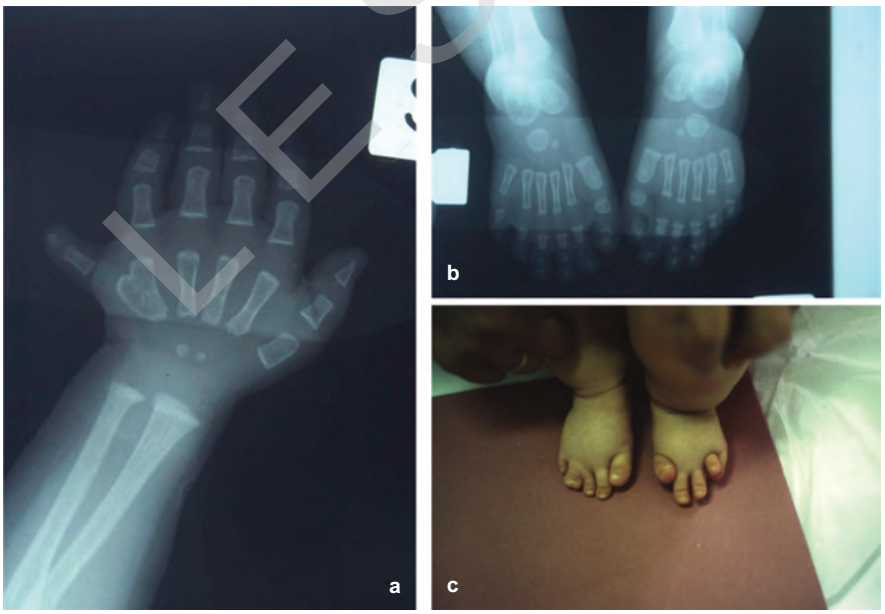

Fig. 5.2 Radiographs and a photo of a Weyers patient showing: **a** postaxial polydactyly of the hand ; **b** postaxial polydactyly of the feet, **c** monolateral postaxial polysyndactyly of the right foot. [P1480]

firmed. Thus far, four causative *EVC2* pathogenic variants have been identified in WAD patients, clustering in the last coding exon of the gene (exon 22) and leading to a truncated protein lacking the C-terminus. The *EVC* and *EVC2* genes are located close to each other in a head-to-head configuration and may be functionally related. It was shown in the mouse that Evc and Evc2 proteins form a complex that interacts with Smo and, by regulating Sufu/Gli3 dissociation and Gli3 trafficking in primary cilia, controls Hedgehog (Hs) signaling pathway.

PATHOGENESIS

Localization of the Evc and Evc2 proteins to the EvC zone, a distinct compartment at the base of primary cilia, is critical for their function in Hh signaling. Stability and localization of the Evc/Evc2 complex is regulated by the C-terminus of Evc2. WAD mutated alleles encode Evc2 truncated proteins that lack the C-terminal amino acids, resulting in aberrant localization of the Evc/Evc2 complex that—rather than being restricted to the EvC zone—is distributed along the entire ciliary membrane. These mutant proteins function as a dominant inhibitor of Hh signaling, explaining the dominant mode of inheritance seen in Weyers families.

TREATMENT

Management of WAD requires both regular follow-up and a multidisciplinary approach involving pediatrician, general physician, plastic surgeon, dermatologist, and dental surgeon. Extra fingers or toes as well as syndactyly are often surgically removed shortly after birth or in infancy. Dental treatment includes esthetic improvement and functional rehabilitation of supernumerary and congenitally missing teeth.

Taking into account that cardiovascular malformations have been reported in a few patients, a careful echocardiographic examination would be appropriate in children with suspected diagnosis of WAD, and if necessary, appropriate surgical treatment followed by a periodic cardiac follow-up.

PROGNOSIS

The prognosis is generally benign as WAD rarely causes severe life-threatening malformations and WAD patients have good health and normal life expectancy.

COMMENTARY

An accurate diagnosis of WAD through the identification of the causative variant should not only be considered in the clinical evaluation of the condition, but also in the genetic interpretation towards a more appropriate genetic counseling and risk assessment.

RESOURCES

https://www.orpha.net/en/disease/detail/952
https://www.omim.org
https://accessanesthesiology.mhmedical.com/content.aspx?bookid=2674&sectionid=220520161
https://pubmed.ncbi.nlm.nih.gov

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Howard TD, Guttmacher AE, McKinnon W, Sharma M, McKusick VA, Jabs EW. Autosomal dominant postaxial polydactyly, nail dystrophy, and dental abnormalities map to chromosome 4p16, in the region containing the Ellis–van Creveld syndrome locus. Am J Hum Genet 1997; 61:1405–12.

Roubicek M, Spranger J. Weyers acrodental dysostosis in a family. Clin Genet 1984; 26: 587–90.

Ruiz-Perez VL, Ide SE, Strom TM, Lorenz B, Wilson D, Woods K, et al. Mutations in a new gene in Ellis–van Creveld syndrome and Weyers acrodental dysostosis. Nat Genet 2000; 24: 283–6.

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CHAPTER

6 Acromesomelic Dysplasia (AMD)

Classification

ICD-10: Q77.8 / Q78.8
ICD-11: LD24.9
GARD: 6UMLS: C5235036
MedDRA: 10083866
MeSH: C535658
Orpha: 93437 – Acromesomelic dysplasia
OMIM: 602875, 200700, 201250, 228900, 609441, 619636
SCTID: 279082008

FACTS

- **Male-to-female ratio:** not predicted
- **Prevalence:** < 1 per million
- **Incidence:** < 1 per million worldwide; clusters reported in Pakistan and India
- **Ethnicity:** any, but most cases are reported from Pakistan, Brazil, Morocco and India (Karnataka). AMD has a higher incidence in populations with consanguineous marriages in both Pakistan and India, e.g., some areas of Punjab, Balochistan, and Khyber Pakhtunkhwa where cousin marriages are very common. Similarly, states locating in the Southern region of India (Karnataka, Tamil Nadu, Andhra Pradesh, and Telangan) also have higher incidence rates of AMD and other skeletal disorders.
- **Age of onset:** neonatal, early childhood
- **Median:** N/A
- **Range:** N/A
- **Inheritance pattern:** autosomal recessive
  Geographical distribution: worldwide, with some clusters of AMD cases being found in some specific regions, including Pakistan, India, Iran, Morocco, Brazil, Poland, St. Helena, and China.

DEFINITION

Acromesomelic dysplasia (AMD) is a heterogeneous collection of congenital, highly rare, and progressive skeletal abnormalities characterized by a special form of short stature called short-limb dwarfism with acromelia and mesomelia of the limbs. AMD actually has abnormal consequences for the development of bones and cartilage, resulting in the shortening of fingers, toes, hands, feet, forearms, and hind limbs.

Keeping in view the radiological and phenotypic variations observed in patients of different populations, acromesomelic dysplasia is categorized into **six subclasses**:

1. Acromesomelic dysplasia Maroteaux type (AMDM, OMIM: 602875)
2. Acromesomelic dysplasia Grebe type (AMDG, OMIM: 200700)
3. Acromesomelic dysplasia Hunter–Thompson type (AMDH, OMIM: 201250)
4. Acromesomelic dysplasia DuPan type (AMDDu, OMIM: 228900)
5. Acromesomelic dysplasia Demirhan type (AMDD, OMIM: 609441)
6. Acromesomelic dysplasia, PRKG2 type (AMDP, OMIM: 601591)

HISTORICAL DATA

- **AMDM** was named after its discoverer Maroteaux in 1971, who reported a male affected individual having dwarfism with a height below 120 cm and a dolichocephalic skull.
- **AMDG** was named for Grebe, who reported two sibs in 1955, complaining the shortening of metacarpals and carpals. In addition, they had a trapezoid configuration to the middle phalanx of the index finger and also radial deviation in that finger.
- **AMDH** was first reported by Hunter and Thompson in a 27-year-old woman in 1976. She had a short stature, short extremities, and short digits.
- **AMDDu** was named for Martin du Pan, who identified an isolated case of a boy having brachydactyly associated with bilaterally absent fibulae.
- **AMDD** was named for Demirhan, when he reported a 16-year-old Turkish girl from a multiply consanguineous family, who was suffering from genital anomalies in addition to bone deformities.
- **AMDP:** In 2020, a new acromesomelic dysplasia known as acromesomelic dysplasia, PRKG2 type, was characterized in Moroccan and Indian girls by Díaz-González and colleagues.

SYMPTOMS

AMD is characterized by shortened long bones including those of the forearms and lower legs due to their growth inhibition. This disease typically appears during the first year of life. There is a disproportionate growth of the forearms, lower legs, hands and feet as compared to the rest of the body.

Some of the hallmarks of AMD are short stature, abnormal bone shape, progressive degeneration, osteoarthritis, progressive joint deformities, pain, stiffness and tenderness of bones and cartilage. AMD-affected infants can have a birth weight in the normal range but abnormal facial characteristics that are apparent at birth, including an abnormally small pug nose, macrocephaly, frontal bossing, a

slightly flattened midface, occipital prominence, broad hands and feet, and thoracic kyphosis or lumbar hyperlordosis. AMD patients also have scoliosis and a reduced mobility as potential complications. Scoliosis can affect posture and spinal functioning. The reduced mobility mainly affects the joint function and overall physical ability of the body.

AMD has remarkable psychosocial effects on the daily activities of affected individuals, such as mental health issues (stress, anxiety, and depression). People with AMD may face emotional challenges that can seriously affect their self-esteem and quality of life; and for these reasons they may experience limitations in physical functioning.

DIAGNOSIS/DIAGNOSTIC CRITERIA

- Dwarfism with acromelia, mesomelia and deformation of limbs, hands, fingers, feet and toes on **physical examination**.
- The diaphyseal and epiphyseal regions of the long bones are abnormally developed and fused with each other. Abnormal fusion of the growing ends of phalanges, metacarpals and metatarsals in the fingers, toes, hands, and feet on **radiological examination**.
- Autosomal recessive inheritance pattern.

AMD diagnosis is based on thorough clinical evaluation, patient history, advanced imaging techniques, and molecular analysis. In most cases, AMD is diagnosed in the early postnatal period. However, identification of the principal phenotypes is the key criterion. The patient's detailed family history ranging from his parents to other relatives is very important. The radiological examination shows abnormal growth plates and disproportionate bones in the limbs, which confirms the abnormal development and premature fusion of the regions where the diaphyses of the long bones meet their epiphyses. Molecular analysis is very useful in examining the DNA of the affected individual and his parents. The results are used to find the mutant allele on a chromosome and its transmission from parents onto the affected offspring.

Next-generation sequencing of *NPR2*, *GDF5*, *BMPR1B*, and *PRKG2* is recommended for definitive diagnosis.

DIFFERENTIAL DIAGNOSIS

Achondroplasia: There are about 350 rare skeletal dysplasias that cause short stature. However, some of them may be confused with achondroplasia. For example, hypochondroplasia and thanatophoric dysplasia also show features of rhizomelic dwarfism, caused by similar genetic defects as achondroplasia, with different pathogenic variants in *FGFR3* leading to different levels of FGFR3 activation; hence, both are included in the differential diagnosis. It is usually very difficult to distinguish between achondroplasia and hypochondroplasia because most of their radiological and clinical features have been found to be overlapping. Affected individuals appear normal at birth; however, they have underdeveloped arms and legs, and stocky or chunky bodies as compared to their normal peers. This condition is caused by *FGFR3* variants residing on chromosome 4p16.3. There is less height difference than in achondroplasia. In addition, about 10% of cases have mild intellectual disability (ID).

Thanatophoric dysplasia (TD) is a lethal skeletal deformity that causes short-limb dwarfism in the perinatal period. This genetic defect is caused by *FGFR3* pathogenic variants. There are two clinically distinct forms of TD, both being characterized by micromelia. Individuals with type I TD have bowed femurs, while type II individuals have straight femurs with uniform presence of moderate-to-severe cloverleaf skull deformity/craniosynostosis ("Kleeblattschädel"). Infantile hypotonia, macrocephaly, frontal bossing, flat facies with ocular proptosis, brachydactyly, and micromelia are the common features present in both forms of TD. Most infants with TD die shortly after birth due to respiratory insufficiency.

SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans) is another skeletal dysplasia caused by *FGFR3* gene variants. Affected individuals develop extensive areas of acanthosis nigricans with severe neurological impairments in the early childhood stage. Research on individuals with SADDAN has shown that *FGFR3* gene variants cause severe endochondral bone growth impairments, like those observed in TD type I (generally incompatible with survival into adulthood). Bone deformities include femoral bowing, apex posterior tibial, and fibular bowing and curved "ram's horn" deformities of the clavicles. Moreover, acanthosis nigricans can also be seen in those with other *FGFR3*-caused genetic abnormalities. Hence, the progressive skin changes caused by the underlying medical condition are thought of as a long-term complication rather than a specific hallmark of SADDAN.

Pseudoachondroplasia is a genetic and clinical skeletal dysplasia, which may also cause diagnostic confusion. It is caused by *COMP* gene variants residing on chromosome 19p13.1-p12 with autosomal dominant pattern of inheritance. Clinical features include cervical instability and scoliosis with increased lumbar lordosis and significant lower extremity bowing. Affected individuals can acquire hip, knee, and elbow flexion contractures with precocious osteoarthritis. Radiological findings include metaphyseal flaring and delayed epiphyseal ossification.

Ellis-van Creveld syndrome (EVC): a rare genetic abnormality characterized by short-limb dwarfism, polydactyly with nails and teeth abnormalities. EVC needs to be distinguished from other short-rib polydactyly syndromes (SRP) and related skeletal dysplasias, particularly Jeune and Verma–Naumoff syndromes. Important distinguishing features: the presence of teeth in the neonatal stage, hypoplastic nails, fused lips with gingiva (lip tie or lip frenulum attachment), and cardiac anomalies.

- **Prenatal differential diagnosis:**
  - **Short-rib polydactyly syndromes (SRP):** EVC is a type of short rib-polydactyly (SRP) group, autosomal recessive disorders with short ribs, short limbs, polydactyly, and visceral organs irregularities. During prenatal differential diagnosis, the other SRP types including Saldino–Noonan, Majewski, and Verma–Naumoff also need to be considered. The SRP type-III (Verma–Naumoff), can be difficult to differentiate radiographically.
  - **Jeune syndrome:** Both EVC and Jeune syndrome are characterized by short ribs and skeletal deformities, but the latter has a distinguishing feature of renal cysts, while teeth and nail abnormalities are only present in EVC.

  - **Other skeletal dysplasias** including achondroplasia, chondrodysplasia punctata, and Morquio syndrome.
- **Postnatal differential diagnosis:**
  - **Jeune syndrome:** The key differential diagnosis is based on the absence of neonatal teeth, hypoplastic nails, and lip and gingival fusion, which is helpful in differentiating Jeune syndrome from EVC.
  - **McKusick–Kaufman syndrome:** EVC and McKusick–Kaufman syndrome share polydactyly as a common feature, but the genital and intestinal abnormalities are present only in the latter.
- **Important differentiating features:**
  - Neonatal teeth and nail dystrophy/hypoplasia: distinguishing features of EVC.
  - Lip and gingival fusion: another characteristic feature of EVC which can be helpful in distinguishing it from other related disorders.
  - Cardiac defects: Congenital heart defects (particularly endocardial cushion defects) are common in EVC.
  - Polydactyly: This is the key feature of both EVC and other SRPs, but the type of its presentation (e.g., postaxial) can be helpful in differentiating EVC from other types.

ETIOLOGY

Alterations in four genes, i.e., *GDF5*, *NPR2*, *BMPR1B* and *PRKG2*, have been implicated to cause various forms of AMD:

- *GDF5* (OMIM: 601146) is located on the long arm of chromosome 20q11.22. It encodes a protein called growth differentiation factor 5 (formerly called cartilage-derived morphogenetic protein-1, CDMP1). Mutations in this gene can result in the phenotypes of Grebe, Hunter–Thompson and Du Pan dysplasia.
- *NPR2* (OMIM: 108961) has been mapped to chromosome 19p13.3, encoding natriuretic peptide receptor B (NPR-B), a receptor for C-type natriuretic peptide (CNP). Mutations in *NPR2* are the causative sources of Maroteaux-type acromesomelic dysplasia.
- *BMPR1B* (OMIM: 603248), located on chromosome 4q22.3, encodes a protein called bone morphogenetic protein receptor, type 1B (BMPR1B). Alterations in *BMPR1B* are responsible for causing Demirhan-type acromesomelic dysplasia.
- *PRKG2* (OMIM: 601591) has been mapped to chromosome 4q21.21, encoding type II cGMP-dependent protein kinase. Recently, variants in this gene have been reported to cause a new type of acromesomelic dysplasia, called PRKG2-type acromesomelic dysplasia.

PATHOGENESIS

The pathogenic mechanism of AMD lies in the fact that each of the four genes (*GDF5*, *NPR2*, *BMPR1B,* and *PRKG2*) involved in displaying the phenotypes of a specific acromesomelic dysplasia type in their mutated forms, encode a protein that is essential for normal development of cartilage and bones. Any mutation that occurs in these genes will hinder their normal function by producing an insufficient or malfunctioned protein product which ultimately will not fulfil the requirements for the normal development of bones. Because of this haploinsufficiency or malfunctioning of the protein, the phenotypes of the disease will happen to develop.

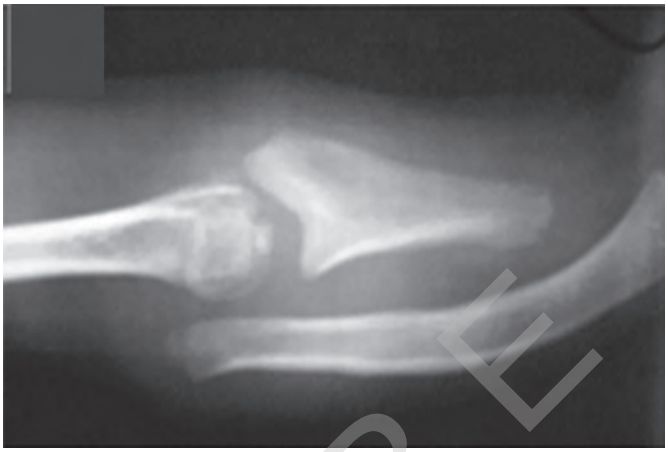

Fig. 6.1 Radiograph of the upper limb: The radius is malformed, and the radial head is displaced upward out of the elbow joint. [H600-003]

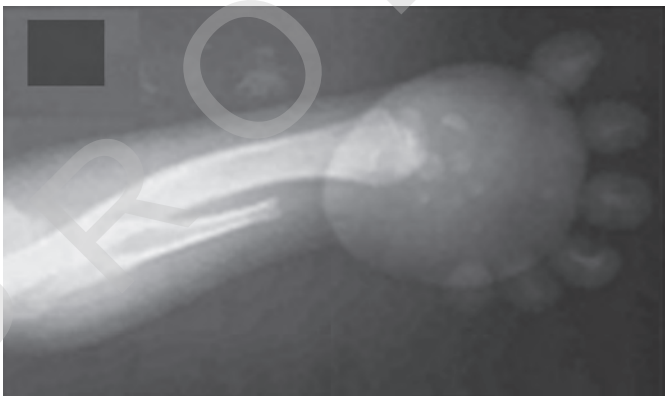

Fig. 6.2 The pruned ulna with sharp distal edges. The carpal bones are distorted and hypoplastic, and the metacarpals are completely missing. The distal phalanges are present, while the proximal and middle phalanges are absent. [H600-003]

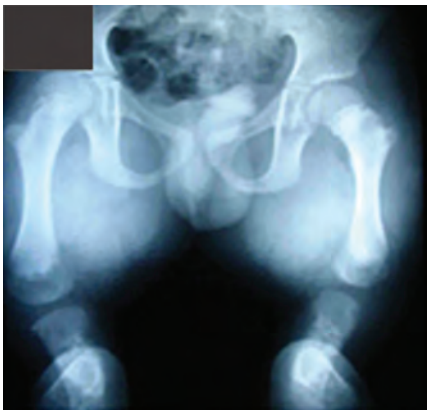

Fig. 6.3 The femoral and tibial bones of the lower limb are short in the absence of the tibial plateau. The fibulas are completely absent. [H600-003]

The *NPR2* gene mutations result in slowing down the proliferation and reducing the differentiation of chondrocytes or consequently result in their death. In normal conditions, the NPR2 protein increases chondrocytes proliferation by elevating cGMP levels and thus activates the cGMP-dependent protein kinase PRKG2. NPR2 is receptor that acts as guanylyl cyclase and converts GTP to cGMP in response to the natriuretic peptide signals. Hence, the *NPR2* mutations lead to an impairment of its ability to produce cGMP and thus produce decreased cGMP levels, which in turn result in the deactivation of the cGMP-dependent protein kinase PRKG2. Thus, in the *NPR2* mutants, chondrocyte differentiation is inhibited leading to the appearance of abnormal phenotypes (skeletal abnormalities). *NPR2* mutations also disrupt the growth plate development, resulting in short stature and skeletal dysplasia. As stated earlier, *NPR2* mutations reduce the cGMP activity (a signaling molecule involved in growth plate processes), and decrease the number and size of proliferating and hypertrophic chondrocytes.

GDF5 mutations also result in a decreased affinity for its receptors (BMPR1B and BMPR2). It disrupts the normal signaling cascade initiated when GDF5 binds to its receptors. Moreover, the GDF5 signaling cascade involves the activation of downstream signaling molecules (Smads), which have a fundamental role in regulating chondrocyte differentiation. *GDF5* mutations disrupt the phosphorylation and activation of Smads, and thus ultimately interfere with their ability to promote chondrocyte differentiation.

Biallelic and monoallelic *NPR2* and *GDF5* mutations can both contribute to short stature. Both genes play a fundamental role in bone development and growth. In case of haploinsufficiency, a single gene copy is not sufficient, hence it also causes disease in its heterozygous form. In addition to its role in bone development and growth, *GDF5* is also involved in cartilage formation. Hence, when a single copy of these genes is disrupted due to mutation, it can disrupt the growth process, resulting in a shorter stature phenotype.

TREATMENT

Depending on the AMD type and the patient's symptoms, various treatment plans are used:

- **Physical therapy** aims to relieve specific symptoms of AMD. For example, the abnormal curvature of the spine may be normalized by specially planned exercises. Similarly, **braces or casts** may be used to relieve stress/pressure on the lower back region.
- In severe cases, **corrective surgery** is recommended.
- **Recombinant human growth hormone** (rhGH) is used to support muscle and bone growth in children and adolescents. But it is a long-term strategy and does not properly cure the disease since it helps patients grow just a couple of centimeters.
- Some pain relievers and osteoporosis medications are also used to treat AMD.
- Several **genome/gene-editing strategies** have been used for several rare diseases with varied levels of success in order to correct or replace mutated genes. Specific nucleases, including, transcription activator-like effector nucleases (TALEN), meganucleases, zinc finger nucleases (ZFN), and the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) complex, are able to add, replace, and remove the DNA fragments to correct the mutated genes in genomes. Mutations in *NPR2*, *GDF5*, and *BMPR1B* cause different forms of AMD, and gene editing approaches have a lot of potential to address the mutations that cause these different forms of AMD. However, more research is required to develop efficient and effective strategies. The complexity of bone and cartilage development and the varying genetic basis of AMD make it even more challenging to develop a universal gene editing approach.
- The recognition of **chaperone effects** has been one of the most exciting achievements by molecular biologists in recent years. The endoplasmic reticulum (ER) has a remarkable peculiarity of retaining the mutant proteins within it by a quality control mechanism that recognizes imperfect folding of these mutant proteins. Chaperones are involved in several activities including accelerating the correct protein folding, guiding the way of correctly folded proteins through the biosynthetic steps in ER and Golgi bodies, and retaining the unfolded or misfolded proteins. While research is ongoing to discover potential treatments for AMD, including molecular chaperones, there are currently no definitive studies available specifically focusing on chaperones for AMD.
- **Limb-lengthening surgery** is sometimes considered as a treatment option for AMD patients in order to improve their height and limb proportions. Patients may gain some height, but the procedure is complex and associated with potential complications and long-term effects.
- **Corrective surgeries** for spinal deformities, such as scoliosis, kyphosis, and lordosis, usually involve realignment of the spine, reduction of curvature, and stabilizing the spine with metal hardware (rods and screws). These procedures are aimed for pain relief, functional improvement, and restoration of proper alignment. Surgery can significantly reduce deformity and improve quality of life but may be associated with long-term complications including nerve damage, increased pain, hardware malfunction, and reduced spinal flexibility.
- **Long-term management strategies** include pain management (activity adjustment/modification, medication) and assistive devices such as braces and splints that can provide support and mobility.

PROGNOSIS

The signs and symptoms of AMD generally worsen over time. However, life expectancy of affected individuals is usually normal, though there is no chance of a full recovery yet. Patients will have to endure the sufferings associated with the disease throughout life. Many bones, especially of the hands and feet, are affected by the abnormal development of bone and cartilage in the body. Over time, they may appear more disproportionate, and even the joints may not be spared. The long-term effects of AMD include arthritis, abnormal curvature of the spine, shortened limbs, and short stature.

- **AMDG** as the most severe form of AMD can severely affect the patients' quality of life. Affected individuals have a lower life expectancy and increased morbidity rates.
- **AMDH** is considered the second most severe type of AMD, characterized by severe dwarfism, affecting, in particular, physical stature (standing height). Both quality of life and survival rates of the individuals are severely affected.
- The quality of life of individuals with **AMDDu** (Du Pan syndrome) is severely impaired but their survival is normal.
- Patients with **AMDD** can live a long life but their quality of life is significantly reduced by the negative impact on physical function and mental health.
- **AMDM** is not a life-threatening condition. Affected individuals have severe short stature, which affects their quality of life, but they have a normal intellect and a normal lifespan, with survival rates similar to those of the general population.
- **AMDP** (or AMD PRKG2 type) causes severe dwarfism and limb shortening. The patients suffer from limited physical functioning. Their survival rate is not severely affected, but their quality of life is.

Early diagnosis and intervention are essential to improving functional outcomes in individuals with AMD so that a more targeted and effective management can be ensured. These strategies include timely orthopedic interventions, e.g., surgery, specified rehabilitations to optimize limb mobility and minimize other skeletal complications. Early interventions are also helpful to prevent or mitigate complications, improve quality of life and thus increase the survival rate.

COMMENTARY

Acromesomelic dysplasia is an abnormal condition of the human appendicular skeleton, but the axial skeleton remains normal, and the affected individuals have a normal intellect. The disease is hereditary and follows an autosomal recessive mode of inheritance. The height of the patient is variable, depending upon the type of AMD. In AMDM, the average adult size is 120 cm; in AMDG and AMDH it is 100 cm and 100–130 cm, respectively. This apparent shortening in height is caused by the fusion, hypoplasia and deformation of bones comprising the appendicular skeleton.

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https://en.wikipedia.org/wiki/Acromesomelic_dysplasia
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CHAPTER

7 Acute and Transient Psychotic Disorders (ATPD)

Synonyms

- *Brief psychotic disorder*
- *Non-affective acute remitting psychosis*
- *Reactive psychosis*
- *Acute remitting psychosis*
- *Brief psychotic episode*

Classification

ICD-10: F23
ICD-11: 6A23
GARD: N/A
UMLS: C0751466
MedDRA: N/A
MeSH: D001523
Orpha: N/A
OMIM: N/A
SCTID: N/A

Organ Systems

- Nervous system

FACTS

- **Male-to-female ratio** in
  – children: N/A
  – adults: approx. 1:1
- **Prevalence:** estimated prevalence ≈ 5–10 % among first-episode psychoses
- **Incidence:** 1.4–6.7 per 100,000
- **Ethnicity:** no mid-30s
- **Age of onset:** 35.6
- **Median:** 34.5
- **Range:** 15–64
- **Inheritance pattern:** familial aggregation possible; no single-gene inheritance identified
- **Geographical distribution:** worldwide

DEFINITION

Acute and transient psychotic disorders (ATPD) are characterized by the sudden onset of florid psychotic symptoms—often following stress—with complete remission within weeks or months.

HISTORICAL DATA

In the late 19th century, Magnan and followers (Legrain and Saury) developed the concept of *bouffée délirante aiguë* under the aegis of the theory of degeneration. They contrasted transient delusional states characterized by sudden onset and fleeting polymorphic symptoms *(délire d'emblée)* with more persistent and uniform psychotic disorders leading to mental deterioration *(délire chronique à évolution systématique)*.

- Cycloid psychosis (Germany)
- Reactive (psychogenic) psychosis (Scandinavia)
- *Schizophrenieähnliche Emotionspsychose* (schizophrenia-like emotion psychosis; Switzerland)
- Atypical psychosis (Japan)

SYMPTOMS

- The clinical picture is often polymorphic, with rapidly fluctuating affect and perception, and typically lacks persistent negative symptoms.
- Delusions, hallucinations, incomprehensible or incoherent speech, perplexity, misidentification or impaired attention, catatonia-like features and emotional turmoil.
- The symptomatology may be highly variable in both type and intensity (daily or even faster) and involves rapidly changing delusions, hallucinations, and emotional states such as intense feelings of happiness and ecstasy or overwhelming anxiety and irritability (i.e., polymorphic psychotic disorder).
- Symptoms must not be culturally sanctioned or attributable to substance use.

DIAGNOSIS/DIAGNOSTIC CRITERIA

- **WHO ICD-10 ATPD:** acute onset < 2 weeks; polymorphic, schizophrenia-like and predominantly delusional symptoms; association (or not) with acute stress; duration < 1 or 3 months.
- **WHO ICD-11 ATPD:** acute onset < 2 weeks; polymorphic psychotic symptoms; duration < 3 months.
- **DSM-5:** brief psychotic disorder (APA): delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior; duration 1 day to 1 month; association (or not) with marked stress, onset < 4 weeks postpartum.

Neuroimaging and laboratory tests are performed mainly to exclude organic causes.

DIFFERENTIAL DIAGNOSIS

- Schizophrenia
- Schizophreniform disorder
- Manic episode
- Bipolar affective disorder
- Substance-induced psychosis
- Psychosis due to brain diseases or general medical conditions
- Simulation psychosis

ETIOLOGY

- Unknown brain alterations.
- Neurophysiological and metabolic (i.e., bilirubin, TNF-α, IL-6, and TGF-β) changes have uncertain clinical significance.
- Family morbidity risk is lower than for schizophrenia and bipolar disorder.
- Psychosocial risk factors are more common in developing countries and migrant and minority populations.

PATHOGENESIS

Patients with ATPD would have an increased emotional reactivity, which renders them less likely to cope with life events in keeping with the vulnerability–stress model.

Social adversities would lead to dopamine dysregulation or interact with a vitamin D deficit in immigrants to the northern hemisphere (the latitude et).

TREATMENT

- Many individuals end up in hospital owing to altered behavior, impaired insight, and aggressive and/or suicidal acts.
- In the absence of controlled trials and specific guidance, atypical antipsychotics are usually prescribed for acute symptoms and relapse prevention (the guidelines for first-episode psychosis recommend at least 1-year treatment at lowest doses after symptom remission).
- Electroconvulsive therapy proves effective in selected cases with polymorphic psychotic symptoms.
- Psychotherapeutic support is useful in cases with brief reactive psychosis.

PROGNOSIS

In longitudinal studies at least 50% of patients, especially those with polymorphic symptoms, do not develop longer-term illness. Good premorbid adjustment, abrupt onset, female gender, age over 30 years, and remission within 4 weeks are variables associated with a favorable course and outcome. Suicide is the major cause of premature death.

COMMENTARY

Diagnosis may prove difficult owing to the lack of pathognomonic symptoms and the high risk of recurrences with varying transition rates mainly to schizophrenia and major affective disorders.

RESOURCES

https://icd.who.int/browse10/2010/en#/F23
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https://id.who.int/icd/entity/284410555
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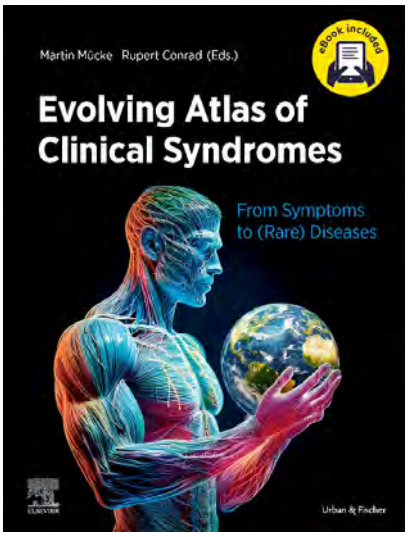

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