Cleidocranial Dysplasia

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USC Advanced Periodontology 2017
What is it?

AKA: Cleidocranial dysostosis / Marie-Sainton syndrome

• A condition that primarily affects the development of the bones and teeth

• Skeletal dysplasia characterized by delayed closure of the cranial sutures, hypoplastic or aplastic clavicles, and multiple dental abnormalities.

• Occurs in approximately 1 per million individuals worldwide
Defining characteristics

- Underdeveloped or absent collarbones (clavicles)
  - Shoulders are narrow and sloping
  - Can be brought unusually close together in front of the body
  - Shoulders can be made to meet in the middle of the body.
- Delayed closing of the spaces between the bones of the skull (fontanels) is also characteristic of this condition.
- Hearing loss and be prone to sinus and ear infections
- Some young children with this condition are mildly delayed in the development of motor skills such as crawling and walking, but intelligence is unaffected.
Persistently open skull sutures with bulging calvaria

Hypoplasia or aplasia of the clavicles permitting abnormal facility in apposing the shoulders

Wide pubic symphysis

Vertebral malformation

Dental anomalies

Short middle phalanx of the fifth fingers
• 3 to 6 inches shorter than other members of their family,

• Short, tapered fingers and broad thumbs; short forearms; flat feet; knock knees; and scoliosis

• Wide, short skull (brachycephaly); a prominent forehead; wide-set eyes (hypertelorism); a flat nose; and a small upper jaw
Decreased bone density (osteopenia) and may develop osteoporosis.

Women with cleidocranial dysplasia have an increased risk of requiring a cesarean section when delivering a baby, due to a narrow pelvis preventing passage of the infant's head.
Dental Abnormalities

- Up to 94% of persons with CCD have dental findings
- Delayed loss of the primary teeth
- Delayed eruption of the secondary teeth
- Unusually shaped, peg-like teeth
- Misalignment of the teeth and jaws (malocclusion)
- Supernumerary teeth (70%), sometimes accompanied by cysts in the gums.
Diagnosis/Testing

- Clinical and radiographic findings
- Imaging of the cranium, thorax, pelvis, and hands.
- \textit{RUNX2 (CBFA1)} is the only gene in which mutation is known to cause CCD.
- Molecular genetic testing of \textit{RUNX2} detects pathogenic variants in 60%-70% of individuals with a clinical diagnosis of CCD.
Clinical Diagnosis

• Affects most prominently those bones derived from intramembranous ossification, such as the cranium and the clavicles, although bones formed through endochondral ossification can also be affected

• Abnormally large, wide-open fontanels at birth that may remain open throughout life
  • Forehead is broad and flat; the cranium is brachycephalic

• Mid-face retrusion

• Abnormal dentition

• Clavicular hypoplasia, resulting in narrow, sloping shoulders that can be apposed at the midline

• Hand abnormalities such as brachydactyly, tapering fingers, and short, broad thumbs
Chest x-ray demonstrates clavicular hypoplasia

*Hand x-ray of a male age 2.5 years with cleidocranial dysplasia*

Note pseudoepiphyses at the bases of the second and third metacarpals.

Cone-shaped epiphyses are seen involving most predominantly the third and fourth middle phalanges.

The phalanges appear abnormally formed, particularly the middle phalanges of the second through fifth digits.
Skeletal survey that includes:

- Anteroposterior (AP) and lateral projections of the skull and thorax
- AP of the pelvis
- Lateral of the lumbar spine; and
- AP of the long bones, hands, and feet.

Sequence analysis, followed by deletion/duplication analysis

Chromosomal microarray (CMA) to evaluate for microdeletions or microduplications that involve RUNX2.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variant in the family

Can be diagnosed by ultrasound examination in the offspring of an affected parent as early as 14 weeks' gestation
Genetic Testing

On occasion individuals with CCD have cytogenetically visible complex chromosome rearrangements [Purandare et al 2008].

**RUNX2 (CBFA1)** is the only gene in which mutation is known to cause CCD.

Evidence for locus heterogeneity. Although not all cases clinically diagnosed as CCD have pathogenic variants in **RUNX2**, there is little additional evidence for locus heterogeneity.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Test Method</th>
<th>Mutations Detected</th>
<th>Mutation Detection Frequency by Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUNX2</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>about 60%</td>
</tr>
<tr>
<td></td>
<td>Deletion / duplication analysis</td>
<td>Large microdeletions involving RUNX2 and contiguous gene(s)</td>
<td>10%</td>
</tr>
</tbody>
</table>
Inheritance

Inherited in an autosomal dominant pattern

In some cases, an affected person inherits the mutation from one affected parent. Other cases may result from new mutations in the gene. These cases occur in people with no history of the disorder in their family.
Management

**Dental:** Early referral to a dental clinic familiar with CCD allows for timely planning of necessary procedures.

- Prosthetic replacements, removal of the supernumerary teeth
- Surgical repositioning of the permanent teeth
- Combination of surgical and orthodontic measures for actively erupting and aligning the impacted permanent teeth
- Speech therapy
Aggressive treatment of sinus and middle ear infections

If the cranial vault defect is significant, the head needs protection from blunt trauma; helmets may be used for high-risk activities.

Surgical cosmesis for depressed forehead or lengthening of hypoplastic clavicles can be considered.

If bone density is below normal, treatment with calcium and vitamin D supplementation is considered. Preventive treatment for osteoporosis should be initiated at a young age.
References


Craniosynostosis

Jae Kim
1st Yr Orthodontic Resident.
Definition Craniosynostosis

- A birth defect in which sutures in your baby's skull close prematurely, before your baby's brain is fully formed.
- Craniosynostosis can affect one or more sutures in your baby's skull. In some cases, craniosynostosis is associated with an underlying brain abnormality that prevents the brain from growing properly.
Symptoms

- A misshapen skull, with the shape depending on which of the cranial sutures are affected
- An abnormal feeling or disappearing "soft spot" (fontanel) on your baby's skull
- Slow or no growth of the head as your baby grows
- Development of a raised, hard ridge along affected sutures
- Increased pressure within the skull (intracranial pressure)
- The signs may not be noticeable at birth, but they become apparent during the first few months of your baby's life.
Sutures that close

- Coronal sutures
- Sagittal sutures
- Unilateral of either coronal or lamboidal sutures
- Metopic suture
- There are many different types of craniosynostosis.
- The term given to each type depends on what sutures are affected.
Types of Synostosis

- **Sagittal synostosis (scaphocephaly).** Premature fusion of sagittal suture
  - Long and narrow.
  - Most common type
- **Coronal synostosis (anterior plagiocephaly).** Premature fusion of a coronal suture
  - Flatten forehead
  - Raised eye socket
  - A deviated nose and slanted skull.
- **Bicoronal synostosis (brachycephaly).** Both of the coronal sutures fuse prematurely,
  - A flat, elevated forehead and brow.
Causes

- Classified as nonsyndromic or syndromic. Nonsyndromic craniosynostosis is the most common type of craniosynostosis, and its cause is unknown.

- However, syndromic craniosynostosis is a complication caused by certain genetic syndromes, such as Apert syndrome, Pfeiffer syndrome and Crouzon syndrome, which can affect your baby’s skull development.
Complications

- Increased pressure inside the skull (intracranial pressure). Their skulls don't expand enough to make room for their growing brains.

- If untreated,
  - Blindness
  - Seizures
  - Brain damage
  - Death, in rare instances

- If mid-face is affected,
  - Upper airway obstructions, compromising your baby's ability to breathe
  - Permanent head deformity
  - Problems with speech and language development
  - Poor self-esteem
Diagnosis

- Physical exam
  - Feel the skull for suture ridges and look facial deformities
- Imaging studies
  - CT scan of skull
  - Look for suture closure
  - Cephalometry to measure precise dimensions of skull
- Genetic testing
  - Scan for possible underlying syndrome
Treatments

- Vary from no tx to surgeries and drugs
- No treatment
  - If mild condition: one suture closed.
- Treatment usually involves surgery to separate the fused bones
- Surgery: To relieve pressure on the brain and create room for the brain to grow. Also to improve esthetics. This is typically done before 6 months of age
  - Traditional surgery
  - Endoscopic surgery
  - If syndromic, regular follow up visits after surgery to monitor growth and intracranial pressure.
Surgery
Endoscopic Surgery

Endoscopic Sagittal Synostosis Repair
- Skin incisions
- Outline of bone removal
- Midline bone removal and bone wedge resections
- Completed bone removal
- Helmet therapy

Other repairs
- Coronal Synostosis
- Metopic Synostosis

Source: Neurosurg Focus ©2005 American Association of Neurological Surgeons
Outcome

BEFORE

AFTER
Dental Complications

- Lack of cleaning skills, poor oral hygiene, and high carb diet
- Higher risk of developing oral diseases: dental cavities, periodontal disease and malocclusions.
- Depending on the syndrome associated with craniosynostosis, oral complications may vary.
  - Example: supernumerary teeth, anodontias, maxilla hypoplasia
Dental Treatment

- Surgery and Orthodontic treatment to resolve malocclusion
- Prosthodontic and periodontic treatment as needed.
- Behavior management, oral hygiene instructions
- Preventive care
- Frequent recalls
Questions?
Goldenhar Syndrome

Lubna Hamadah
Goldenhar Syndrome

- Was first reported by Dr Maurice Goldenhar in 1952
- Other names:
  - oculo-auriculo-vertebral syndrome by Gorlin in 1960
  - Considered as a variant of Cranio facial Microsoma but also present with **Epibulbular dermoids** and **vertebral anomalies**
Clinical Features

- Unilateral or bilateral
- Range from mild to severe
- Hemifacial microsomia,
- Bilateral or unilateral ear anomalies (preauricular tags and pits, ear dysplasia, anotia, microtia),
- Hearing loss (conductive and/or sensorineural),
- Ocular defects (epibulbar dermoids, microphthalmia, coloboma of upper eyelid)
- Orofacial clefts and vertebral abnormalities
Goldenhar’s Features

Fig. 1. Case 1. Note epibulbar dermoids in lower outer quadrants, ptosis in glabellar area. Coloboma of left upper lid repaired prior to picture.

Goldenhar’s Features

Fig. 2. Case 1. Ear tags were present bilaterally

Other Organs that can be involved

- There is a high rate of associated anomalies of other organs/systems up to 69.5%
- 27.8% most commonly congenital heart defects
- Renal and cerebral malformations
- Can be associated with mental retardation
Why it Happens?

- Mostly unknown
- Occur sporadically, autosomal recessive and dominant inheritance are described in literature
- Genetic and non-genetic factors, in line with a oligogenic or even a multifactorial etiology
- Anomalies on 22q11, may contribute to or increase the risk of OAVS

Current Explanation

- Malformations primarily involving the structures derived from the 1st and 2nd branchial arches and the intervening first pharyngeal pouch and branchial cleft, in particular the ear, mouth, mandible, eye and cervical spine.

- It has been proposed that the presence of rare and common genetic variation, of variable penetrance and effect, combined with environmental factors, may affect specific tissue interactions that occur between the cranial neural crest cells and the endoderm, mesoderm and ectoderm, and the way they connect during their migration in establishing the foundations of craniofacial morphogenesis, hence affecting the risk to OAVS.
Risk Factors

- **Intrauterine exposure to:**
  - Different drugs especially vasoactive medications (pseudoephedrine, Thalamide)
  - Cigarette smoking in the first trimester
  - Use of Cocaine

- Disturbance in vascular supply to cephalic neural crest cells could hinder embryonic development in the branchial arches and cause OAV spectrum
**Differential Diagnosis**

- Treacher Collin Syndrome
- Townes–Brocks syndrome
- CHARGE syndrome
- Mandibulofacial dysostosis
### Table 4  Differential diagnoses of OAVS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Main clinical features</th>
<th>Gene</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| Treacher Collins syndrome | Hypoplasia of the zygomatic bones and mandible  
OMIM 154500, 613717, 248390 | TCOFI    | 86   |
|                                                                           | External ear abnormalities frequently associated with hearing impairment  
                                                                           |          |      |
|                                                                           | Coloboma of the lower eyelid                                                             |          |      |
|                                                                           | Absence of the lower eyelashes                                                           |          |      |
|                                                                           | Preauricular hair displacement onto the cheeks                                           |          |      |
|                                                                           | Craniofacial involvement is generally symmetrical                                       |          |      |
| Townes–Brocks syndrome  | Imperforate anus  
OMIM 107480 | SALL1    | 89   |
|                                                                           | Dysplastic ears (overfolded superior helices and preauricular tags) frequently associated with sensorineural and/or conductive hearing impairment |          |      |
|                                                                           | Thumb malformations (triphalangeal thumbs, duplication of the thumb, preaxial polydactyly or hypoplasia of the thumbs) |          |      |
|                                                                           | Renal impairment with or without structural abnormalities                                |          |      |
| CHARGE syndrome  | Coloboma of the iris, retina-choroid, and/or disc  
OMIM 214800 | CHD7     | 90   |
|                                                                           | Unilateral or bilateral choanal atresia or stenosis                                     |          |      |
|                                                                           | Ear abnormalities (external ear malformation, ossicular malformations, Mondini defect of the cochlea and/or absent/hypoplastic semicircular canals) |          |      |
|                                                                           | Cryptorchidism in males and hypogonadotrophic hypogonadism in both males and females |          |      |
|                                                                           | Cardiovascular malformations                                                            |          |      |
|                                                                           | Orofacial clefts                                                                       |          |      |
|                                                                           | Tracheoesophageal fistula                                                                |          |      |
|                                                                           | Cranial nerve dysfunction                                                               |          |      |
| Branchio-oto-renal spectrum disorders  
(branchio-oto-renal and branchio-otic syndromes)  
OMIM 113650, 610896, 602588 | Malformations of the outer, middle and inner ear  
                                                                           | EYA1, SIX5 and SIX1 | 91   |
|                                                                           | Conductive, sensorineural, or mixed hearing impairment                                  |          |      |
|                                                                           | Branchial fistulae and cysts                                                            |          |      |
|                                                                           | Renal malformations ranging from mild renal hypoplasia to bilateral renal agenesis.   |          |      |
|                                                                           | Branchio-otic syndrome has the same features as branchio-oto-renal syndrome but without renal involvement. |          |      |
| Mandibulofacial dysostosis, Guion–Almeida—type  
OMIM 610536 | Oto-facial abnormalities (acrofacial dysostosis)  
                                                                           | EFTUD2   | 92, 93 |
|                                                                           | Oesophageal atresia                                                                     |          |      |
|                                                                           | Thumb anomalies                                                                         |          |      |
|                                                                           | Intellectual disability                                                                  |          |      |
|                                                                           | Zygomatic anomalies                                                                     |          |      |
|                                                                           | Microcephaly                                                                            |          |      |

OAVS, oculo-auriculo-vertebral spectrum.
Prognosis

- Hearing problems
- Weakness in moving the side of the face that is smaller
- Dental problems - the soft palate may move to the unaffected side of the face
- Tongue may be smaller on the affected side of the face
- Fusion of the bones of the neck
- Deglutition problem
- Facial asymmetry with facial paralysis
- Ear abnormalities (external ear)
Management

- Craniofacial team:
  Maxillofacial surgeon, Plastic Surgeon, Speech therapist and orthodontist.

- Primary goal: ensure that the patient’s vital functions are not hindered

- Secondary goal: aesthetics

- Goes under multiple surgeries

- Stem cell therapy has had some success in dealing with eye dermoids
Thank you
Facial Palsy

Reham Alsamman
Advanced Operative Program
Facial Nerve VII

The seventh cranial nerve (VII) that controls:

• Muscles of facial expression
• Taste sensations in the anterior 2/3 of the tongue.
• Parasympathetic fibers to lacrimal and salivary glands.
Facial Nerve VII

Brainstem > stylomastoid foramen > 5 extra-cranial branches

- Temporal branch
- Zygomatic branch
- Buccal branch
- Marginal branch
- Cervical branch
Facial Palsy

**Def:** is loss of facial movement because of facial nerve damage (central or peripheral).

**Congenital facial palsy** is a condition present at birth. In most cases the cause is uncertain. It could be lack of proper nerve and/or muscle development, or stretching of the muscles or nerves during the birth.

**Acquired palsy** caused by trauma to the facial nerve and muscle, infectious diseases as Lyme disease, stroke and head and neck tumors. It could occur sudden (Bell’s Palsy) or gradual (tumors).
House-Brackmann facial nerve grading system

- Grade I - Normal facial function in all areas
- Grade II - Slight Dysfunction, normal symmetry and tone at rest
- Grade III - Moderate Dysfunction, obvious but not disfiguring difference between two sides, normal symmetry and tone at rest
- Grade IV - Moderate Severe Dysfunction, obvious weakness and/or disfiguring asymmetry, but normal symmetry and tone at rest
- Grade V - Severe Dysfunction, only barely perceptible motion and asymmetry at rest
- Grade VI - Total Paralysis, no movement
Sign & Symptoms

- facial pain
- earaches, and sensitivity to sound
- altered/ loss of taste
- muscle twitching
- impairment of movement in the facial and platysma muscles
- impaired closure of the eye and mouth
- drooping of the brow and corner of mouth
- dry eye and mouth.
Bell’s Palsy

- The most common form of facial paralysis.
- Occur in all ages, with peak incidence in the 40s.
- Sudden, unilateral, peripheral facial paralysis
- Caused by inflammation of the facial nerve (HSV-1) at the geniculate ganglion (nerve compression)
- Bell’s phenomenon: on attempted closure the eye rolls upward
Diagnosis

History:

• Medical history: rash, fevers, or arthralgias, otitis media, exposure to influenza vaccine or new medications

• Onset: Sudden vs. Gradual

• Duration and rate of progression

• Recurrent

• Previous surgeries
Diagnosis

Physical examination

• Head and neck region
• Complete vs. incomplete
• Unilateral vs. bilateral
• Cerebellar signs
Diagnosis

- Neurological exam to test function of VII
- Blood tests (viral, bacterial infection)
- MRI, or CT scan (tumors and head injuries)
- Bell’s palsy is diagnosed by exclusion
### Differential Diagnosis

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CAUSE</th>
<th>DISTINGUISHING FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nuclear (peripheral)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Spirochete <em>Borrelia burgdorferi</em></td>
<td>History of tick exposure, rash, or arthralgias; exposure to areas where Lyme disease is endemic</td>
</tr>
<tr>
<td>Otitis media</td>
<td>Bacterial pathogens</td>
<td>Gradual onset; ear pain, fever, and conductive hearing loss</td>
</tr>
<tr>
<td>Ramsay Hunt syndrome</td>
<td>Herpes zoster virus</td>
<td>Pronounced prodrome of pain; vesicular eruption in ear canal or pharynx</td>
</tr>
<tr>
<td>Sarcoidosis or Guillain-Barré syndrome</td>
<td>Autoimmune response</td>
<td>More often bilateral</td>
</tr>
<tr>
<td>Tumor</td>
<td>Cholesteatoma, parotid gland</td>
<td>Gradual onset</td>
</tr>
<tr>
<td><strong>Supranuclear (central)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Demyelination</td>
<td>Additional neurologic symptoms</td>
</tr>
<tr>
<td>Stroke</td>
<td>Ischemia, hemorrhage</td>
<td>Extremities on affected side often involved</td>
</tr>
<tr>
<td>Tumor</td>
<td>Metastases, primary brain</td>
<td>Gradual onset; mental status changes; history of cancer</td>
</tr>
</tbody>
</table>
Bells Palsy
Facial nerve lesion

Stroke
Supranuclear lesion

Facial nerve lesion

Supranuclear lesion
Treatments

• **Spontaneous Recovery**: 80% of Bell’s palsy

• **Physiotherapy**: electrical stimuli, massage and facial exercise

• **Corticosteroids**: 10-day tapering course starting at 60 mg per day for adult and 2mg/kg for child.

• **Antiviral**: acyclovir 400 mg X5/ day for 7 days or valacyclovir 1 g X3/ day for 7 days.
Treatments

- **Botox injection**: relax the muscles, reduce twitching
- **Surgery**: nerve decompression, anastomosis and nerve graft
- **Psychological support**
- **Other**: Eye lubricants, Analgesics
Factors reducing the prognosis:

- Complete facial palsy
- No recovery by three weeks
- Age over 60 years
- Severe pain
- Ramsay Hunt syndrome (herpes zoster virus)
- Associated conditions—hypertension, diabetes, pregnancy
- Severe degeneration of the facial nerve
Reference


JEFFREY D. TIEMSTRA, MD, and NANDINI KHATKHATE, MD. Bell’s Palsy: Diagnosis and Management. Am Fam Physician. 2007 Oct 1;76(7):997-1002.

Thank You!
CBY 579 L

Dr Sabina Hameed

ADVANCED PERIODONTOLOGY RESIDENT

BDS (Lond.), MFDS RCS (Eng.)
TREACHER COLLINS SYNDROME
Edward Treacher Collins

English Surgeon and Ophthalmologist

1896- During his Tenure at the Royal London Ophthalmic Hospital published a book called Researches into the Anatomy and Pathology of the Eye.

The success of his research helped identify Treacher Collins syndrome as but a specific disease that afflicted certain family lines, not just a random occurrence with mutations of the skull.
AKA:

• Franceschetti-Zwahlen-Klein Syndrome
• Mandibulofacial dysostosis (MFD1)
• Treacher Collins-Franceschetti syndrome
• Zygoauromandibular dysplasia
Incidence

1/10,000 and 1:50,000 live births
Signs and Symptoms

- **Variable**: V mild to severe life threatening complications (restriction of airway)

- Malformations of the 1st and 2nd Branchial arches leading to underdeveloped facial bones, particularly the cheek bones, and a very small jaw and chin (micrognathia).
Clinical Features

• EYES
• EARS
• MOUTH
• FACIAL BONES
• IQ
Dental Abnormalities

- Tooth agenesis
- Enamel Opacities
- Ectopic eruption of Upper Max Molars
Differential Diagnosis

Nager acrofacial dysostosis

Miller acrofacial dysostosis

Oculoauriculovertebral (OAV) spectrum:
  Hemifacial microsomia
  Goldenhar syndrome
Genetics

- Humans have 46 Chromosomes (23 pairs)
- Chromosome 5=
  - 181 million DNA Base pairs
  - 6% of total DNA, Approx 900 genes for making proteins
- Mutations in the following genes can cause TCS:
  - TCOF1
  - POLR1C
  - POLR1D
• “Treacher Collins-Franceschetti syndrome 1”

• TCOF1 gene mutations most common cause of TCS = 81 to 93% of all cases.

• HUMAN CHROMOSOME 5q32-33 (long (q) arm of chromosome 5 at position 32)

• Treacle
TCOF1 Gene Mutations and development of TCS
200 mutations in the TCOF1 gene

INSERT/DELETE a small number of base pairs in TCOF1

DECREASE in the amount of functional treacle in cells

rRNA Production REDUCED

APOPTOSIS of cells involved in the early development of facial bones and tissues

TCS
• POLR1C and POLR1D gene mutations cause an additional 2 percent of cases of TCS

• In individuals without an identified mutation in one of these genes, the genetic cause of the condition is unknown.

• The **proteins** produced from the TCOF1, POLR1C, and POLR1D genes all appear to play important roles in the **early development of bones and other tissues of the face**
Inheritance

AUTOSOMAL DOMINANT

AUTOSOMAL RECESSIVE
1 copy of the altered gene in each cell is sufficient to cause the disorder

Rare incomplete penetrance
Wide variability

40% of cases have a previous family history
60% of cases possibly arise from *de novo* mutations of *TCOF1*
AUTOSOMAL RECESSIVE

• TCS caused by mutations in the POLR1C gene

• Both copies of the gene in each cell have mutations.

• Parents each carry 1x copy of the mutated gene, but typically DON'T show signs and symptoms of the condition
Diagnostic Investigations

1) CT for evaluation of craniofacial abnormalities

2) Audiological evaluation for hearing impairment

3) DNA diagnosis
   Direct sequencing of TCOF1 detects mutations in about 90–95% of patients.
Identification & Management of TCS

1. Treacher Collins syndrome clinically suspected
   - Yes
     - TCOF1 mutation analysis
       - TCOF1 abnormality detected
         - Treacher Collins syndrome
           - Manage as Treacher Collins syndrome
             - Comprehensive craniofacial surgery, orthodontics, ophthalmology, otolaryngology, speech pathology
       - TCOF1 abnormality not detected
         - Treacher Collins facial appearance
           - Thumb defects
         - Treacher Collins syndrome unlikely
           - Manage as other syndrome e.g. Nager, Miller syndrome
   - No
Definition

• Zellweger syndrome is one of the Peroxisome Biogenesis Disorders (PBD).

• The peroxisome biogenesis disorders are divided into:
  • Zellweger Spectrum
  • Rhizomelic chondrodysplasia Punctua

• Zellweger spectrum is composed of three disorders
  • Zellweger Syndrome (severe form)
  • Neonatal adrenoleukodystrophy
  • Infantile Refsum Disease (least severe form)
Zellweger Syndrome

• Also referred as Cerebrohepatorenal syndrome

• Peroxisome biogenesis disorders have an incidence of 1:20,000 - 1:100,000 births

• Autosomal recessive disorder

• Deficiency of multiple peroxisome function
Characteristics

- Facial Features
  - High forehead, frontal bone
  - Underdeveloped eyebrow ridges
  - Broad nasal bridge

- Visual and hearing impairment

- Enlarged Liver and adrenal insufficiency

- Renal cysts

- Neurological impairment, including cognitive and seizures, gait (inability to move)

*D.I Crane et al*, 2014
Etiology

• It is caused by a defect in one of the *PEX* genes, that encode for the proteins *peroxins*, which are important for the biogenesis of peroxisomes (assembly and proliferation) that are involved in and catalyse a large number of metabolic functions.

• At the molecular level, ZW syndrome cells (Broslus et al 2001)
  
  • have peroxisome like structures indicating a defect in the synthesis of peroxisomal membrane
  
  • mislocalization of peroxisomal proteins in the cytoplasm because of a defect of the peroxisosmal targeting signal 1 or 2, involved in the import of membrane proteins to the peroxisome. (Sacksteder and Gould 2000)

• The link between the pathogenesis of the disease and the cellular mechanism is still limited, and research is still exploring the molecular, genetic, and multiorgan abnormalities of the Zellweger syndrome.

*D.I Crane et al*, 2014
Peroxisomes

• Are subcellular organelles that are bound by a single membrane, are ER-derived organelles of the endomembrane system. *(Wanders et al 2014)*

• It has been identified that 24 proteins involved in the biogenesis of peroxisomes, membrane bound and matrix proteins (all synthesised in the cytosol and transported to peroxisomes)

• Proteins are called *peroxins*, encoded by *PEX* Genes
Peroxisomes

• Metabolic Functions of Peroxisomes:

  • **Oxidation of very long fatty acids**, Beta chain fatty acids: C22, C24, C26, which happens only in the peroxisomes not in mitochondria. However, shorter fatty acids can be oxidised in the mitochondria.

  • **Oxidation of alpha fatty acids**

  • **Ether phospholipid biosynthesis and Bile acid synthesis**

  • **Detoxification of glyoxylate**

  • **Interacts with the mitochondria, because mitochondria is needed to metabolise the end products of the peroxisomal interactions**

  • **Peroxisomes lack citric acid cycle and respiratory chain, that are present in the mitochondria**
Peroxisomes

- Contain H2O2 producing oxidase and contain catalase enzyme which is an important antioxidant enzyme that converts H2O2 to H2O and O2.

- Mitochondrial dysfunction secondary to peroxisomal dysfunction has been implicated

- The neuropathology is ZS patients is because
  - of the high levels of VLCFA —> cytotoxicity
  - loss of beta oxidation VLCFA pathway —> loss of AA —> impacts a range of inflammatory in the brain
  - loss of plasmalogens (ether PL) —> loss of the anti oxidative stress function in brain

D.I Crane et al, 2014
Peroxisomes

- Peroxisomes are important for the brain development, the pathogenic factors implicated based on:
  - deficient peroxisomal metabolic pathways
  - accumulation of potentially toxic peroxisomal metabolic substrates
  - deficiency of peroxisomal synthetic products

_D.I Crane et al, 2014_
Molecular aspect

- 12 genes contribute for peroxisome biogenesis
- The zellweger spectrum patients are distributed among 11 complementation groups and their defect result in mutation in one of the PEX genes.
- Complementation 1 group one is the largest group, which includes more than half of all peroxisome defect patients
- This group includes defect in PEX1 gene, encodes an AAA protein, which is part of the Atpases family associated with various cellular activities.
  - A complete lack of PEX1 protein —> severe phenotypes
  - Residual amount of PEX1 protein —> milder forms of disease

(Brosius et al 2001)
### Table 5. Human PEX genes and peroxisome biogenesis disorders.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Complementation group [83]</th>
<th>Clinical phenotype</th>
<th>Peroxin motifs and functions</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>PEX1</td>
<td>CG1</td>
<td>ZS, NALD, IRD</td>
<td>AAA ATPase, matrix protein import</td>
<td>74, 84, 93</td>
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<td>PEX2</td>
<td>CG10</td>
<td>ZS, IRD</td>
<td>zinc RING, matrix protein import</td>
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<td>CG12</td>
<td>ZS</td>
<td>no known motif, peroxisome membrane synthesis</td>
<td>68, 97</td>
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<td>PEX5</td>
<td>CG2</td>
<td>ZS, NALD, IRD</td>
<td>TPR domain, matrix protein import, PTS1 receptor</td>
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<td>CG4</td>
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<tr>
<td>PEX7</td>
<td>CG11</td>
<td>RCDP</td>
<td>WD-40, matrix protein import, PTS2 receptor</td>
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<td>CG7</td>
<td>ZS, NALD</td>
<td>zinc RING, matrix protein import</td>
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<td>–</td>
<td>no known motif, peroxisome proliferation</td>
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<tr>
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<td>CG3</td>
<td>ZS, NALD, IRD</td>
<td>zinc RING, matrix protein import</td>
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<td>PEX19</td>
<td>CG14</td>
<td>ZS</td>
<td>farnesylation, peroxisomal membrane synthesis, putative PMP receptor</td>
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<tr>
<td>?</td>
<td>CG8</td>
<td>ZS, NALD, IRD</td>
<td>?, matrix protein import</td>
<td>8</td>
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</tbody>
</table>

CG, complementation group; ZS, Zellweger syndrome; NALD, neonatal adrenoleukodystrophy; IRD, infantile Refsum disease; RCDP, rhizomelic chondrodysplasia punctata; AAA ATPase, ATPases associated with various cellular activities; PMP, peroxisomal membrane protein; PTS1, peroxisomal targeting signal 1; PTS2, peroxisomal targeting signal 2; SH3, Src homology 3; TPR, tetratricopeptide repeat; WD-40, repeat containing approximately 40 amino acids with a central Trp-Asp motif.
Diagnosis

• Definitive diagnosis requires laboratory investigation to assess:

  • **Peroxisomal function**
    - Blood level of VLCFA and other metabolites, and erythrocytes plasmologens levels) *(Vreken et al 1998)*
    - adrenocorticotropic stimulation text *(Brendese et al 2014)*

  • **Enzymatic analysis by fibroblasts**
    - culture skin fibroblasts: catalase immunofluorescence microscopy *(Wanders et al 1995)*
    - peroxisomal alpha and beta oxidation activity and analysis of other enzymatic activities
Diagnosis

- Definitive diagnosis requires laboratory investigation to assess: Cont.

- **PEX gene mutation studies**
  - complementation analysis in cultured skin fibroblasts
  - Sanger sequencing of genomic DNA

*Ebberink et al.*, 2011
Treatment and Prognosis

• Treatment is mostly symptomatic and supportive.

• There is no cure for the syndrome because the metabolic and neurological abnormalities correction is limited after birth.

• Prognosis is poor, it has been believed that infants survive up to 6 months, but nowadays a cohort study by Berendse et al 2015, have shown that patients can survive into adulthood.
Thank you
Questions ?