‘CATCH’ing the loose ends

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CASE 1

A 2 year 6 month old male child presented to emergency room with the complaints of fever for 9 days associated with cough and cold. History of refusal to walk and limping of right leg for 2 days.

First child to parents in a non consanguineous marriage (Medical parents)

LSCS(MSL grade 3) , Birth weight : 3.11kg

Shifted into NICU for respiratory distress

Found to have **PDA, SMALL ASD,VSD**

Spontaneous closure of ASD,VSD

Now on follow up with the cardiologist

3 months: 'Voice different ' shown to a pulmonologist

LARYNGEAL WEB, on follow up

1 year 6 months: Febrile seizure – Not evaluated

Development:

Delay in attaining milestones: Walking at 1 year 6months,
Now speaks in monosyllables

Examination:

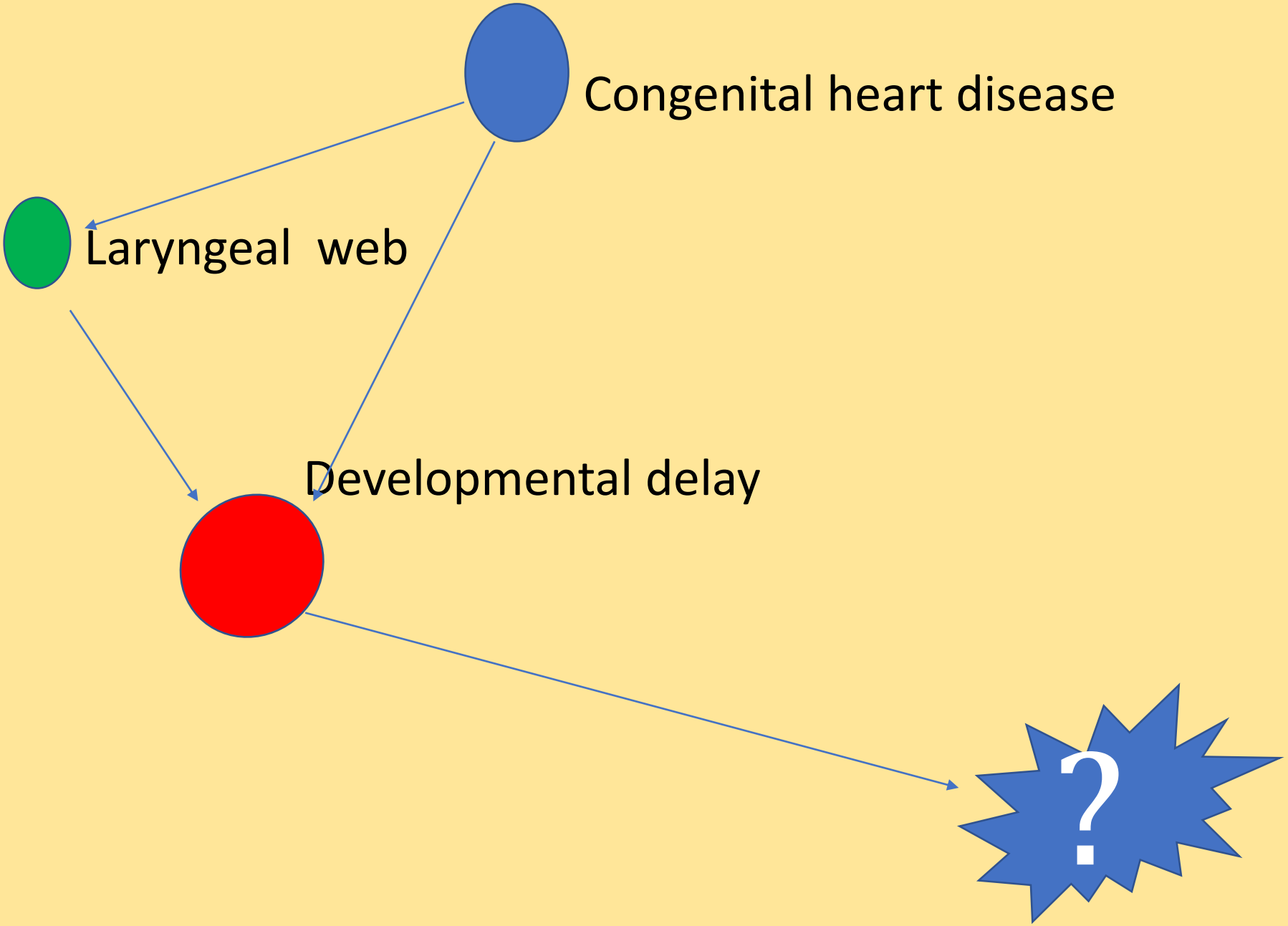
Alert/ Febrile(100.4F)

No dysmorphic facies

Vitals: stable

Systems: Normal

TRANSIENT SYNOVITIS OF RIGHT HIP


Congenital heart disease
Laryngeal web
Developmental delay
?

DI GEORGE SYNDROME????

Calcium sent…….**6.5 mg/dl(?) ,** Serum albumin normal,

Lab error?

Family keen on going home

Repeat sample,

- Alkaline phosphate, Vitamin D and PTH levels done
- Oral calcium supplements

AFTER 2 WEEKS……

Admitted with history of fever for 1 day and seizure- uprolling of eyes and tonic posturing of limbs.

Lab values: Serum Calcium: 6.4mg/dl

Lookback at previous values:

Test	Patient value first admission	Patients value second admission	Normal values
Serum Calcium	**6.6mg/dl**	**5.3mg/dl**	9-11mg/dl
Serum Magnesium	2.1mg/dl	1.7mg/dl	1.6 – 2.6 mg/dl
Phosphorus	**6.1mg/dl**	**5.5 mg/dl**	4.0- 7.0 mg/dl
Serum albumin	4.2gm/dl	3.7gm/dl	3.5-4.5gm/dl
Alkaline phosphatase	189	189U/L	54- 369IU/L
Vitamin D	**16.8ng/ml**	**12.5ng/ml**	<20 ng/ml Deficient
PTH	**14.2pg/ml**	**8.3 pg/ml**	10-65pg/ml
TSH	2.90uIU/ml	1.37uIU/ml	0.7-6.4uIU/ml

Treatment given:

IV Calcium gluconate

Endocrinologist consultation

1,25, hydroxy Vitamin D (Rocaltrol), Vitamin D3 and calcium supplements

Repeat calcium 9.0mg/dl

- FISH for 22q11 deletion : POSITIVE
- DIAGNOSIS: DIGEORGE SYNDROME

- WAS THERE A DELAY IN DIAGNOSIS??

- WHEN HAS THE DIAGNOSIS TO BE MADE:

  HEART DEFECTS???

  LARYNGEAL WEB??

  HYPOCALCEMIC SEIZURES??

CHILD 2:

6 year old girl

Presented with a history of fever and multiple episodes of vomiting,

This was followed by an episode of hyperventilation and carpo-pedal spasm

First child, Non- consanguineous parents,

Birth weight : 4kg

Routine newborn visit : Found to have a murmur

ECHO:VSD, closed at 2 years of age

Development : Normal

Blood gas: Respiratory alkalosis

Serum calcium : 8mg/dl, Other electrolytes normal

Hyperventilation and carpopedal spasm resolved

Diagnosis :Dengue fever, primary

Discharged on calcium supplements

Admission 2, one year later

Fever, vomiting,1 episode of brief **carpopedal spasm**

History of at least one episode of carpopedal spasm in the intervening one year, with fever

O/E: **Flat elongated facies**

Small palpebral fissures

Thin philtrum

Systems: Normal

DIAGNOSIS: SECONDARY DENGUE FEVER

Worsening thrombocytopenia, ICU

Intensivist asked…Could this be Di George Syndrome?

Test	Patients value	Normal values
Serum Calcium	**7.5mg/dl**	9-11mg/dl
Serum Magnesium	1.7mg/dl	1.6 – 2.6 mg/dl
Phosphorus	**5.2 mg/dl**	4.0- 7.0 mg/dl
Serum albumin	3.7gm/dl	3.5-4.5gm/dl
Alkaline phosphatase	141U/L	54- 369IU/L
Vitamin D	**13.9ng/ml**	<20 ng/ml Deficient
PTH	**9.2 pg/ml**	10-65pg/ml
TSH	1.20uIU/ml	0.7-6.4uIU/ml

WITH ENDOCRINOLOGIST: TREAT WITH VITAMIN D AND CALCIUM SUPPLEMENTS

REPEAT ALL VALUES

IF PTH STILL LOW THEN CONSIDER HYPOPARATHYROIDISM

? DI GEORGE

FISH: NEGATIVE FOR CHROMOSOME 22q11.2 DELETION

NOT DI GEORGE?.....

Di George Syndrome

One of a group of phenotypically similar disorders-

- **Velocardiofacial syndrome (VCFS)**
- **Conotruncal anomaly face syndrome (CTAF)**

That share a microdeletion of chromosome **22q11.2**

Thus they are now known as

22Q11.2 DELETION SYNDROME

Earlier also known by the acronym CATCH 22

(Cardiac**, A**bnormal facies**, T**hymic hypoplasia**, C**left palate **H**ypocalcemia).

History

- First described in 1829 and congenital absence of the thymus and parathyroid glands was reported by Dr Angelo DiGeorge in 1965
- In 1980's it was discovered that deletions in chromosome 22q11.2 were present in most patients with DGS, as well as in patients with other similar syndromes.

Epidemiology

- Estimates of incidence 1:4000 to 1 per 7000 live births

  (1990's – 2000 , FISH technology , may have missed small deletions)

- Study done by Botto LD, May k, Fernhoff et al in United States -Chromosome 22q11.2 deletions are relatively common in general population, making 22qDS the most prevalent microdeletion syndrome.
- 22qDS is probably underdiagnosed because the phenotypic findings may be mild.

Age at presentation :

Variable

Depends on severity and types of birth defects

Serious congenital heart defects, hypocalcemia-

Newborn

Submucous cleft, delayed speech, mild cardiac , minimal facial anomalies

present later

Pathogenesis:

- **90% sporadic inheritance, 10% from parent AD**
- **Microdeletion in long arm of chromosome 22**

In 85% is a deletion that has 3 million base pair units including 40 genes.

Including **TBX1 gene** (major role in the phenotypic features)

In 15% atypical smaller deletions

22q11.2 DELETION

Developmental field of the 3rd and 4th Pharyngeal pouches

Embryonic developmental disruption of portions of heart , head ,neck, thymus and parathyroids derived from these disrupted arches

- Hypocalcemia and variable T cell deficiency

Types:

Partial and complete 22q11.2DS- Based upon the level of immunologic function and degree of thymic hypoplasia.

- **T cell response to mitogens**

- **Partial**: Have variable and non-life threatening immunologic defects. Immune parameters may improve with time.
- **Complete**: Rare, Form of SCID in which there is no responce of T cells to mitogens and profound immunodeficiency.

Fatal if not recognized and treated with thymic or hematopoietic stem cell transplant

Characteristic facies

More prominent in white children

- 1. High and broad nasal bridge
- 2. Long face
- 3. Narrow palpebral fissures
- 4. Widened area below nasal bridge
- 5. Bulbous nose tip
- 6. Micrognathia
- 7. Assymetric crying face
- 8. Low set malformed ears
- 9. short philtrum
- 10. Small teeth

NONIMMUNOLOGIC CLINICAL FINDINGS	PERCENTAGE
PALATAL ANOMALIES	69-100
SPEECH DELAY	79-90
LEARNING DISABILITIES	45-90
CARDIAC ABNORMALITIES	74-83
DEVELOPMENTAL DELAY	75
OPHTHALMOLOGIC ABNORMALITIES	7-70
HYPOCALCEMIA	17-60
PSYCHIATRIC DISORDERS	9-60
SKELETAL ABNORMALITIES	17-45
RENAL ABNORMALITIES	31-37
SHORT STATURE	20
NEUROLOGIC	8
DENTAL	2.5

Palatal abnormalities: 69%

Hyper nasal voice indicate velopharyngeal incompetence

- Submucosal cleft, overt cleft, bifid uvula
- Significant feeding difficulties in 36%

Developmental delay , Learning difficulties 70-90%

Delayed language

Low performance in IQ testing and problems with non verbal learning, abstract reasoning and math

Cardiac findings : 74-80 %

Conotruncal anomalies: TOF, Truncus Arteriosus

Interrupted aortic arch, VSD

Behavioural and Neuropsychiatric:

Children: ADHD, anxiety an autistic spectrum disorder

Teenagers: Bipolar disorder and schizophrenia

in 10 – 30 % .

Endocrine:

Problems with parathyroid deficiency

Hypocalcemia:17-60%

50% may resolve by 1 year

Diagnosis

- **Array comparative genomic hybridization, aCGH**

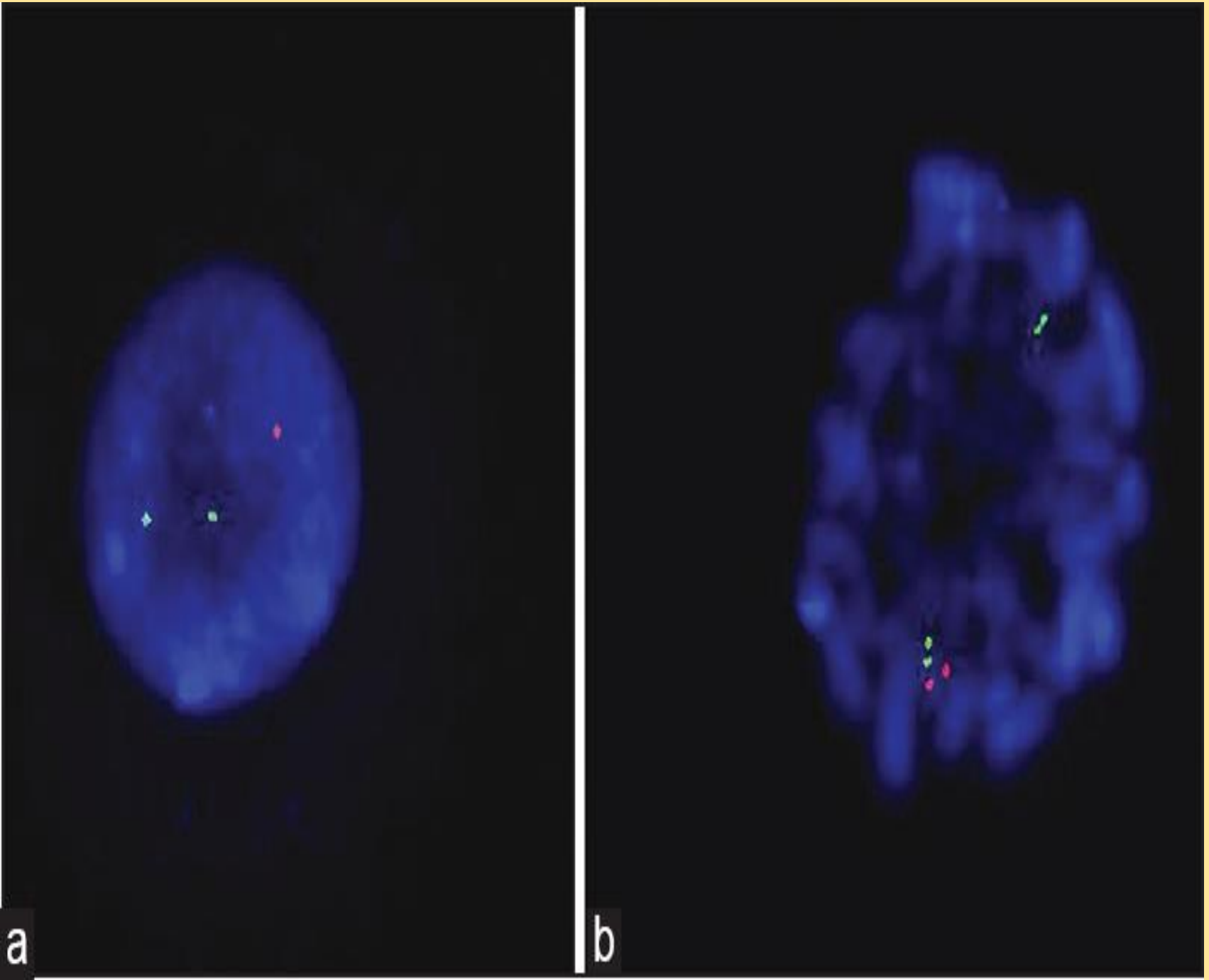
  Preferable and most appropriate test.

  It picks up large and small deletions on all chromosomes in addition to the 22q11.2

- **FISH- Readily available**

  Smaller deletions may not be detectable

- If aCGH is negative and syndrome suspected a geneticist can help with **sequencing the TBX1 gene**


a
b

Indications for deletion screening:

Newborns:

All newborns with conotruncal anomalies as 20-30% of them have been found to have 22q11.2 deletion

Interrupted aortic arch (50-60%)

Velopharyngeal insufficiency (64%)

Neonatal hypocalcemia(74%)

Overall if 2 or more of the following are present

Conotruncal heart anomalies

Palatal defects

Hypernasal speech

Nasopharyngeal reflux

Developmental ,Learning disabilities

Behavioural ,psychiatric propblems

Immunodeficiency

Hypocalcemia

Typical facial features

Should prompt a laboratory confirmation of diagnosis

- **Multidisciplinary team** with a primary phyisican in the lead to monitor growth and development
- **Calcium supplementation , Vitamin D**
- **Surgery**
- **Immunodeficiency:**

  Complete DGS: Thymic transfer, adoptive transfer of mature T- cells

  Partial: appropriate prophylaxis

Surveillance parameters:

- SERUM AND IONIZED CALCIUM:
  Infancy- every 3-6months
  Childhood- every 5 years
  adolescence and adulthood- every2 years
- TFT,CBC- Annually
- IMMUNE SYSTEM: Evaluation at birth
  9-12 months
  Reevaluation prior to any live vaccine
- OPHTALMOLOGICAL ASSESSMENT AT 1-5YEARS
- SPEECH ASSESSMENT
- AUDITORY ASSESSMENT
- ROUTINE PSYCHOLOGICAL ASSESSMENT

Prognosis

Varies widely with the nature and degree of involvement of different organs.

Many adults lead long and productive lives.

Most common cause of mortality is

a. **Congenital heart disease**
b. **Severe immune deficiency**

Large European Collaberative study,558 patients, **8 % died, More than half in the first month of life**

The life expectancy for infants with complete DGS who do not undergo transplantation is less than 1 year. In contrast, overall mortality rate for patients with partial DGS has been estimated to be less than 10 percent.

Genetic counselling

- VITAL IMPORTANCE TO SCREEN BOTH THE PARENTS FOR THE SAME(USING FISH OR MLPA) IN ORDER TO ASCERTAIN THE ORIGIN OF DELETION, SPORADIC OR INHERITED.
- Although 90 percent of deletions are believed be secondary to 22q11 deletion, parents of affected children should be offered genetic testing. If a parent is found to have the same mutation, then the risk of future children being affected is 50 percent irrespective of the sex of child(autosomal dominant inheritance

THANK YOU