MEDICINE-PEDIA
NEET-SS

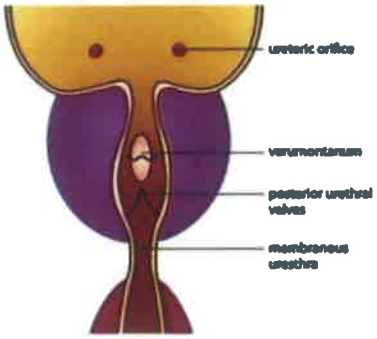
CONTENT

POSTERIOR URETHRAL VALVES

Posterior urethral valves (PUV) 00:00:11

PUV are valve like structures below and extending distally from the verumontanum (at the prostatic urethra) and is usually at the junction of anterior and posterior urethra.

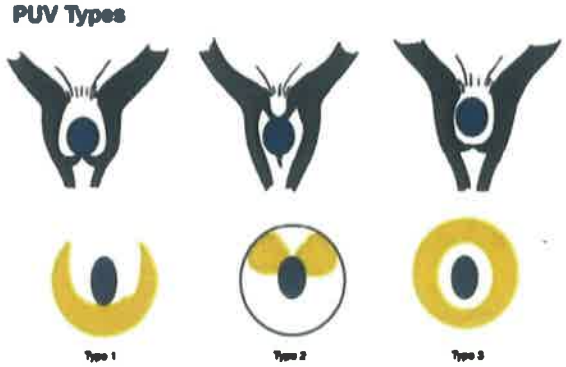
PUV are the most common cause of severe of severe obstructive uropathy in children.
The condition is only seen in males.



The condition is classified into three types :

- Type I is the most common type. Valve extends below the verumontanum causing obstruction.
- Type 2 : the valve is above the verumontanum and is usually unnoticed as there is no obstruction or symptoms.
- Type 3 : Ring shaped valve below the verumontanum. Symptoms are mild.

Type 2 and 3 are found rarely.



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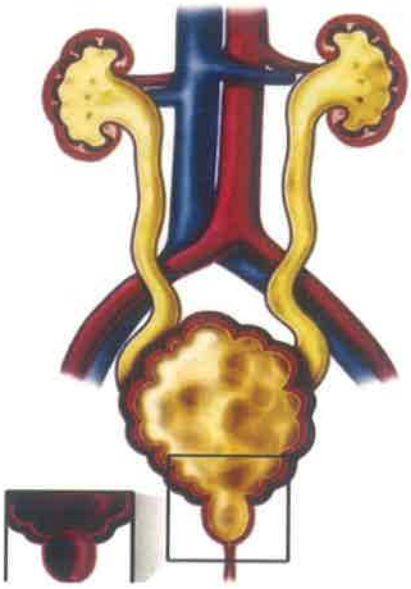
Consequences of PUV

00:05:03

- Obstruction leading to dilatation of posterior urethra.
- Bladder neck hypertrophy.
- Trabeculation or sacculation of the bladder due to hypertrophy.
- Secondary reflux leading to reflux nephropathy in long standing cases.
- Predisposes to development of recurrent urinary tract infections.

PUV consequences



Antenatally, PUV must be suspected in a fetus if :

- Bilateral hydronephrosis.
- Hydroureter.
- Thick-walled bladder are observed on scan.

There is severe oligohydramnios as well.
If antenatal severe type of obstruction is detected, the prognosis of the fetus is poor.

Clinical features :
Features of obstruction like straining, dribbling of urine and poor stream of urine.
Palpable bladder on physical examination.
Recurrent urinary tract infection.

Diagnosis :
It is diagnosed by micturating cystourethrogram (mcu).

- Up to 80% of children with PUV have associated vesicoureteral reflux.

Active space

- 30% of VUR are bilateral.

The affected children must be evaluated for renal function and upper urinary tract.
DMSA scan is performed to assess the anatomy of the kidney. USG may also be done.
MCU showing dilated urethra and bladder.

Treatment :
The immediate step involves relieving the obstruction.

Neonatal period :
Obstruction is relieved by inserting a polyethene feeding tube (size 5 or 8). Foley's catheter must not be used as it can cause bladder spasm.

Serum creatinine levels are assessed after relieving the obstruction.

If the creatinine levels are normal, definitive procedures using cystoscopy can be done : Fulguration (transurethral ablation of valves) can be performed.

If the creatinine levels are raised, it should warrant suspicion of conditions like :

- Ureteral obstruction.
- Renal dysplasia and other renal anomalies.

Prognosis is relatively poor.

Temporary procedure to divert the urine like vesicostomy is

preferred in such cases. Vesicostomy improves the outcome as it relieves the bladder pressure and provides adequate time for it to develop.

In a sick child with high creatinine level and sepsis due to infection of kidney, IV antibiotics are started. Electrolyte imbalance is corrected. Nephrostomy is performed to save the kidneys.

Prognosis in PUV 00:05:03

Prognosis is poor if conditions like hydroureters or hydronephrosis is detected in prenatal USG during 18 –24 weeks.
Prognosis is good if the antenatal scans were unremarkable.

The prognosis is good if the creatinine levels are 0.8 – 1mg/dl (checked after relieving the obstruction).
It is an unfavorable prognosis if the levels are raised beyond 1mg/dl.
Scarring or any other anomalies in the kidneys detected in a renal USG is associated with unfavorable prognosis.

Follow up:

- Antimicrobial prophylaxis after treatment of PUV (for few months to few years, these children are prone to UTI).
- Annual assessment by performing a renal USG, blood pressure monitoring, growth monitoring and urine analysis.
- Bladder dysfunction must be checked for as it is common in PUV.
- The child may develop progressive renal damage.

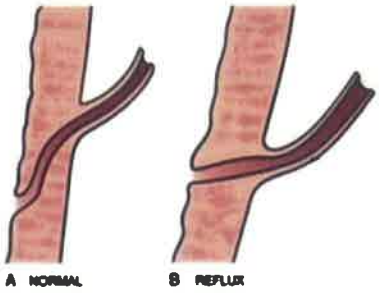
VESICOURETERIC REFLEX

Vesicoureteric reflux(VUR) is the retrograde flow of from the bladder into the ureter.
If the VUR is severe it can enter into the Kidney too.

Primary vesicoureteric reflux:

- Mechanism : Short and a lack of obliquity of the submucosal and intravesical segments of ureter.
- More common in females (80% of cases).
- Age at diagnosis is usually 2-3 years.

Secondary vesicoureteric reflux :
Less common compared to primary vesicoureteric reflux.



It is due to abnormalities in bladder.

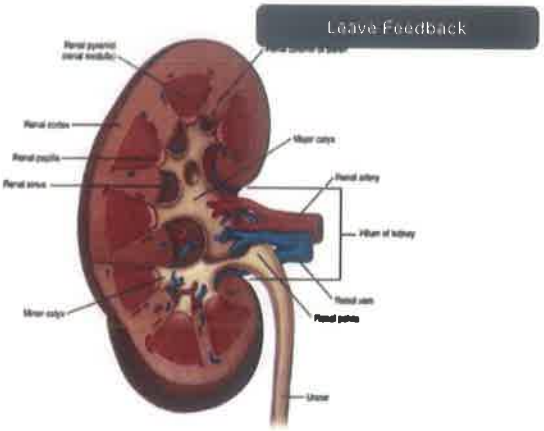
- Neuropathic bladder.
  Seen in Meningomyelocele, sacral agenesis.
- Hypertrophy of neck of bladder.
- Inflammation inside the bladder.
  Due to stones, infection.

Consequences of VUR 00:04:08

Retrograde flow of urine -> Intrarenal reflux -> Urinary tract infection (pyelonephritis) and scarring in Kidney -> Chronic Kidney disease (CKD).

VUR is usually suspected when children present with

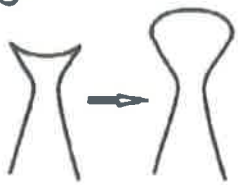
recurrent UTI.

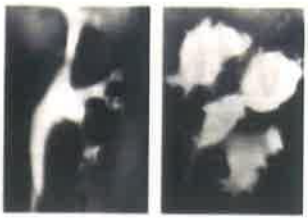


Reflux nephropathy :
The consequences of VUR in the kidney is termed as reflux nephropathy. It includes scarring and CKD.

In VUR, initially the papillae are damaged and then the renal parenchyma.
Papillae at poles are commonly affected. This is because the orifices of papillae at these areas are wide open.
Typical scarring due to VUR : Wedge shaped scarring.
Other changes include clubbing of the calyx.

In scar formation (due to papillary damage), the scar tends to retract and pulls the calyx, resulting in a clubbed appearance of the calyx.





40% of children with recurrent UTI have vesicoureteric reflux.
Out of these children, 20-40% develop chronic kidney disease.
Primary vesicoureteric reflex is most commonly inherited in an autosomal dominant pattern.
This is why if the siblings of an affected child has suspected UTI, he/she should be evaluated for VUR.

Diagnosis of VUR

00:11:55

Investigation of choice : micturating cystourethrogram/ voiding cystourethrogram.

Radionuclide cystography : Has less radiation exposure compared to micturating cystourethrogram. more often used for follow up.

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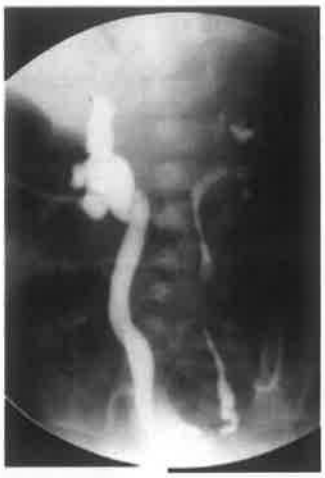
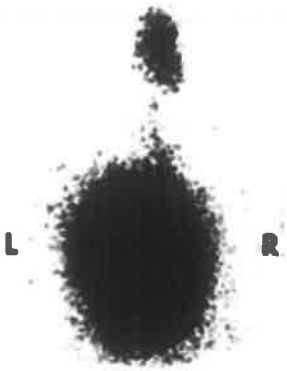
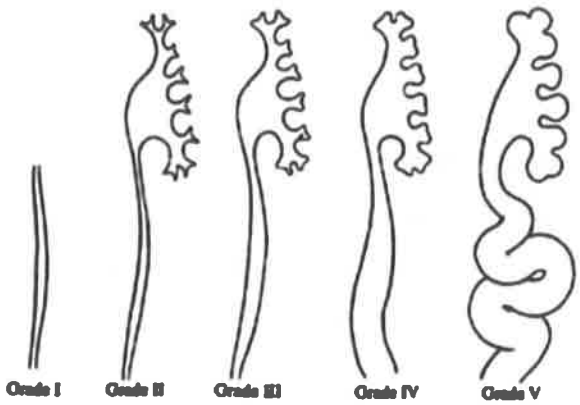




Grading :



Mild to moderate VUR: Grade1 – Grade 3.

Severe VUR: Grade 4 and Grade 5.

- Grade 1 : Partial reflux into ureter.
- Grade 2 : Entire length of ureter shows reflux.
- Grade 3 : Complete reflux + Increase in the size of ureter.
- Grade 4 : Grade 3 + tortuosity of ureter.
- Grade 5 : Grade 4 + pelvis of kidney is affected (clubbing of calyces). High chance of renal scarring.

High pressure vs low pressure VUR :

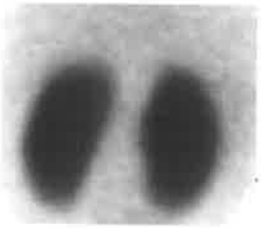
- Low pressure vesicoureteric reflux occurs during filling of bladder. It is unlikely to resolve spontaneously.
- High pressure vesicoureteric reflux occurs during

Active space

contraction of bladder. There is a high chance of spontaneous resolution.
However, there is increased risk of renal damage.

Evaluation of upper urinary tract :
After diagnosis, imaging of upper urinary tract is important.

- DMSA scan : Changes in kidney can be seen with DMSA scan. This scan evaluates the kidney for scarring changes.
  If scarring has occured, then it becomes irreversible



Evaluation for bladder dysfunction with urodynamic studies is also to be done. A child associated with bladder dysfunction has longer duration of symptoms and difficult to control symptoms of VUR.

Natural history of VUR :

- Improves with age.
- mean age of resolution of VUR is 5-6 years.
  This occurs because of bladder growth and VUR resolves.

If a child has

- High grade VUR (grade 4 or 5), or
- If the child has associated bowel bladder dysfunction or
- If the child has low pressure vesicoureteric reflex,

then the chance of spontaneous resolution is low.

Treatment

00:22:56

Treatment goal is to prevent the occurrence of urinary tract infection and renal scarring.
Prevention of occurence of UTI is by antibiotic prophylaxis :

- Decreases the periurethral colonization.
- Cotrimoxazole or nitrofurantoin OD is used.
  In children < 3 months, cephalexin is used.
- Grade 1 and grade 2 : Antibiotic prophylaxis is given till 1 year. After 1 year, it is very unlikely for the VUR to cause

UTI. For breakthrough UTI (UTI developing after stopping antibiotics), restart antibiotic prophylaxis.

- Grade 3 to 5 : Antibiotic prophylaxis is given till age of 5 years. For breakthrough urinary tract infections, surgical correction is required.

Other than antibiotic prophylaxis, behavioral modifications are needed to prevent UTI :

- Liberal fluid intake.
- Normal bowel and bladder habits.

Surgical treatment :

- Delayed till 1-2 years.
  This is done for spontaneous resolution to occur and the surgery can lead to complication in very young individuals.
- Ureteric re-implantation (open repair is preferred and has better results).
  Length : Width ratio, of ureter inside the bladder should be maintained between 4:1 to 5:1.
  This leads to very high cure rates (97-98%).
- Endoscopic repair of VUR :

Bulking agent inserted at the urethral opening into the bladder, compresses the ureter and causes constriction of the orifice of the ureter.

Bulking agent used is dextranomer/hyaluronic acid copolymer (DEFLUX).
Teflon can also be used. Cure rate is 60-70%.
This is not a curative surgery, because the bulking agent can slip away at any time.

Surgery of choice is : Ureteric reimplantation.
The long term outcome of the child is determined by the extend of scarring.

Active space

CONGENITAL NEPHROTIC SYNDROME

Congenital nephrotic syndrome 00:00:12

Onset of nephrotic syndrome within the first 3 months of life. There is generalized edema (anasarca), hypoalbuminemia, significant albuminuria along with hyperlipidemia.

Infantile nephrotic syndrome : Onset of nephrotic syndrome withing 3 months – 1 year.

Childhood nephrotic syndrome : Onset after 1 year of age.

Congenital nephrotic syndrome is classified into:

Primary :

Classic Finnish type (most common type). Mutation in NPHS1 gene in the long arm of chromosome 19 and codes for nephrin protein.

Some syndromic conditions are associated with diffuse mesangial sclerosis which may present with congenital nephrotic syndrome include:

- Denys-Drash syndrome : Mutation in the WT1 gene in the short arm of chromosome 11. Associated with ambiguous genitalia along with congenital nephrotic syndrome. There is increased risk of Wilms's tumor.
- Galloway-Mowat syndrome : There is developmental delay, microcephaly, and hiatal hernia.
- Pierson syndrome : Mutation in LAMB2 gene which codes for laminin. The protein is present in the ocular epithelium and can present with microcoria.

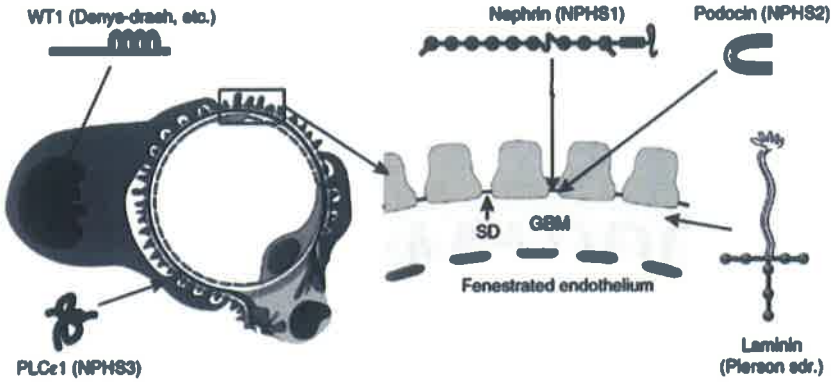
Secondary :

Associated with other primary conditions like :

- Intrauterine or congenital infections (TORCH infections). Syphilis and toxoplasmosis are most common.

Podocin is coded by NPHS2 gene present in the long arm of chromosome 1.

Genetics



Classical Finnish type of congenital nephrotic syndrome 00:08:06

It is the most common form and has autosomal recessive pattern of inheritance. The onset is within first 3 months of life.

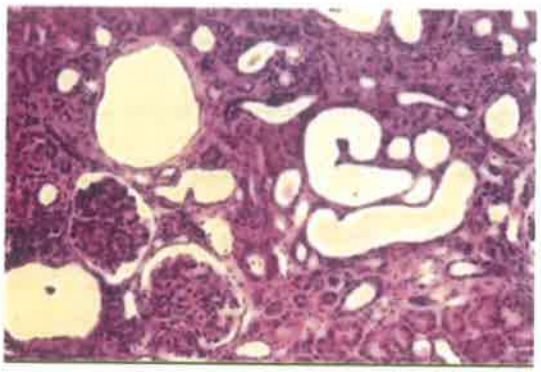
The condition is associated with the presence of large placenta and prematurity. The affected children are prone for infections and can present with failure to thrive.

There is increased risk of vascular thrombosis.

Biopsy may show cortical microcysts which are basically dilated proximal tubules. Glomerular changes like mesangial proliferation or expansion may be seen as well.

Associations of Finnish type CNS :

- Polyhydramnios (also associated with neonatal Bartter's syndrome).
- Elevated AFP (15 – 18 weeks of gestation). It is seen associated with neural tube defects as well.



Cortical microcysts

Management :

Most important aspect is symptomatic management. Edema is controlled by diuretics or albumin infusions. High protein diet (3 – 4 g/kg/day) and supplements of vitamin D, calcium, and magnesium.

Hypothyroidism must be looked out for and managed accordingly.

TORCH infections must be actively checked for as it can be treated.

Congenital nephrotic syndrome is almost always resistant to steroids and cytotoxic drugs.

ACE inhibitors or ARBs help control the proteinuria. NSAIDs like indomethacin also assist in the management of proteinuria.

Nephrectomy is indicated in the resistant cases. Outcome is usually poor in CHS.

Active space

SICKLE CELL NEPHROPATHY

Sickle cell disease 00:00:12

It occurs due to point mutation in the beta globin chain of hemoglobin. The mutation is in the chromosome 11p14.4.

The condition is common in malaria endemic countries.

Pathophysiology of renal disease in sickle cell disease :

- Hemolysis.
- Vaso-occlusion: Hemoglobin-S can undergo polymerization and lead to vaso-occlusion. There is resultant renal medullary ischemia as there is relative hypoxia in the medulla which predisposes polymerization of hemoglobin.
- Drug use (NSAIDs).

A significant anemia due to the hemolysis, there is increased cardiac output thus raising the blood flow to the kidney. There is increased GFR or hyperfiltration.

Perfusion paradox : Difference in perfusion within the kidneys. Increased blood flow leads to macrovascular hyperperfusion which raises the GFR. There is simultaneous microvascular hypoperfusion due to vaso-occlusion in vessels supplying the renal medulla.

Effects of chronic hemolysis :

- Endothelial activation -> decreased NO -> Vaso-occlusion -> Hypoxia -> Fibrosis inside the kidney.
- Tubulointerstitial damage like fibrosis or tubular dysfunction.

Leave Feedback

There are 4 patterns of glomerular pathology :

1. Sickle glomerulopathy : FSGS (most common type) -> leading to CKD.
2. membranoproliferative glomerulopathy.
3. Glomerulopathy without overt sclerosis.
4. Thrombotic microangiopathy.

Clinical features :

Albuminuria : Incidence increases with age. <20% of children affected with sickle cell nephropathy has albuminuria. The incidence increases with age.

Hematuria : Microscopic hematuria is a common finding. Gross hematuria indicates a significant underlying renal pathology like renal papillary necrosis and warrants urgent evaluation.

Renal papillary necrosis :

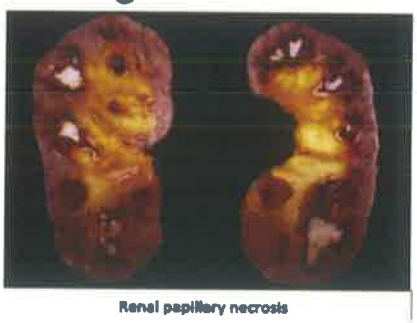
It occurs due to medullary ischemia.

NSAIDs abuse is a major risk factor.

The affected patients present with acute symptoms like colicky pain in the flanks, hematuria, and passage of clot like material (sloughed papillae).

The investigation of choice is contrast enhanced CT.

The characteristic findings include lobster claw sign and ball on a T sign.



Renal papillary necrosis

Lobster claw appearance.

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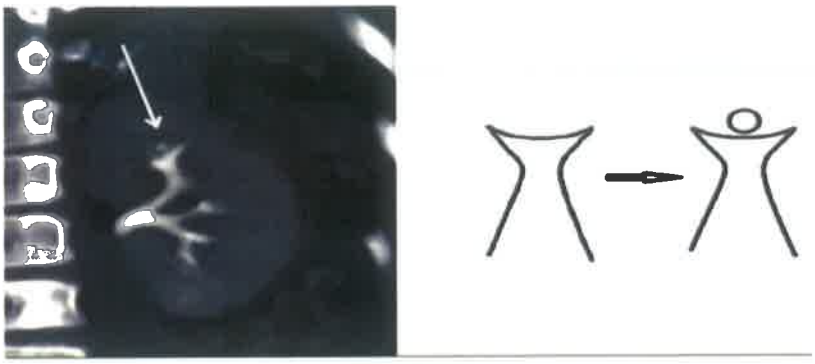


Ball on T sign.

Tubular dysfunction may be seen in sickle cell nephropathy. Chronic hemolysis -> hypoxia -> Tubular dysfunction -> Impaired concentrating ability -> Polyuria.

It can manifest as nocturnal anuria in children.

There is impairment of potassium secretion when the distal tubules are affected. It can lead to hyperkalemia.

Chronic kidney disease in sickle cell disease :

It occurs due to the fibrosis and is primarily seen in adults. The risk factors include nephrotic syndrome (FSGS type) and anemia of long duration.

Such patients have an increased susceptibility to carcinoma like renal medullary carcinoma. It is associated with the worst outcome as it is resistant to usual chemotherapeutic agents.

Early detection of sickle cell nephropathy can improve the outcome. It can be done by :

- Estimating the GFR: Schwartz formula is not currently used to estimate GFR. New biomarkers like cystatin C (secreted by all nuclear cells of the body and it does not have tubular secretion) is preferred.
- Screening for albuminuria : Started at 4 years of age.

Active space

New biomarkers :

1. Cystatin C.
2. Urinary KIM-1.
3. Urinary N acetyl beta D glucosaminidase.

Treatment 00:22:49

The management of sickle cell nephropathy include:

- Adequate hydration.
- Antifibrinolytic agents. Can increase the risk of thrombosis if used for a long period of time.
- ACE inhibitors in proteinuria with hypertension has a disease modifying role.
- Hydroxyurea : It increases the production of hemoglobin F and decreases the sickling and vaso-occlusive episodes.
- Renal replacement.
- EPO in long standing anemia.

Sickle cell trait :

There is increased incidence of hematuria and renal papillary necrosis.

It is also associated with increased risk for developing medullary carcinoma.

CONGENITAL MUSCLE DYSTROPHIES

Case scenario 00:01:04

37 week infant born by LSCS because of fetal tachycardia, Had significant hypotonia and poor respiratory effort. Patient was intubated and then switch to continuous positive airway pressure by nasal prongs the next day. He was fed by nasogastric tube from birth because of poor feeding. Family history was unremarkable.
O/E - hypotonic with tachypnea.
His head circumference - normal.
B/L ptosis, limited extraocular movements.
Inverted V- shaped upper lip, High arched palate & reduced facial movements.
No cataracts or Tongue fasciculations were noted.
His cry and gag were weak.
motor examination revealed paucity of spontaneous movement due to generalised weakness.
DTR +/+ in both knees.
Possible diagnosis : Congenital myopathy.

Classical features :

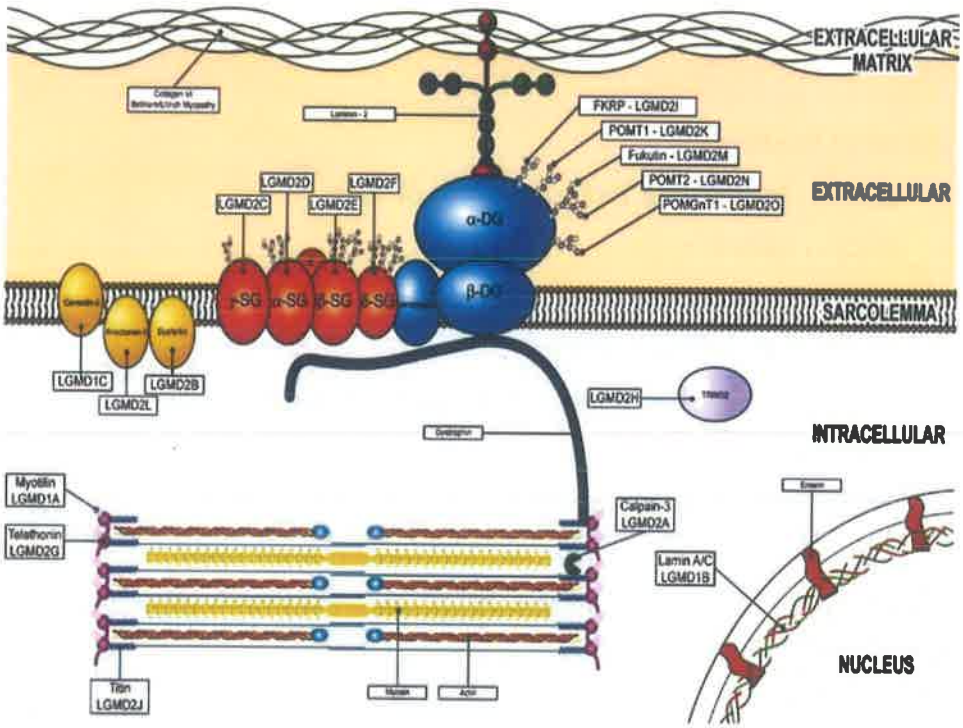
- usually present at birth /at < 1yr of age .
- Floppy infant -

1. congenital myopathy : non progressive ; affects contractile proteins more.
   Ptosis + ophthalmoplegia + bifacial involvement seen.
   Creatine Kinase/CK - not elevated.
2. congenital muscle dystrophy : progressive & affects structural proteins more (sarcolemmal membrane).
   Extramuscular involvement (CNS) common ; CK - elevated.

Congenital muscle diseases

Collagen is attached to → Laminin → attached to Dystroglycan complex → defect → congenital muscle dystrophy.
Dystrophin is attached to contractile protein → Defect → Congenital myopathy.
collagen disorders - Bethlem/Ulrich myopathy.
Laminin disorders - merosinopathy/Lamininopathy/ merosin congenital dystrophies (MCD).
MCD is divided into :
A - merosin.
B - Integrin (Collagen is attached to merosin by Integrin).
C - FKRP (dystroglycan is attached to merosin by FKRP) ; high CK.
Glycosylation of dystroglycan by POMT1, POMT2, POMGnT1, Fukutin (required for neuronal migration)→ Defect → Dystroglycanopathies.
Lamin A/C → nuclear membrane formation → Defect seen in CMD.

Bethlem - MC (outermost).
and MC disease - Laminin disorders.



Active space

3rd MC - Dystroglycan disorders.
Fukayama (Japanese disease) due to mutation on fukutin.

Collagen disorders 00:11:31

muscle dystrophies associated with collagen 6 :
Ulrich (severe)/Bethlem (milder) myopathy.
Intermediate form myopathy.

Classical Features :

- Hyperlaxity of distal joint.
- Contraction of proximal joint.
- Hyperkerartosis & Keloid formation on skin.

Respiratory distress (also seen in metabolic disease & pompe disease).
Cardiac is never involved.

Merosinopathy 00:13:50

Usually milder disease.
Generalised weakness and floppy child.
Contractures (mainly in hip/feet & jaw - difficulty in feeding).
Cognition - normal.
30% can have epilepsy.
MRI may show some white matter abnormalities.
Limited ambulation.
merosin are also present in skin (Biopsy showing absence of merosins is diagnostic), Periferal nervous system - late onset periferal neuropathy..

Dystroglycanopathy 00:16:27

Fukyama : Fukutin mutation defect.
Normal at birth.
By 3 months, contractures of ankles and knees seen.
Generalised weakness and floppy.

Leave Feedback

Limited ambulation (dependant on another).
Can survive till adulthood.
Extramuscular involvement :
Severe brain involvement.
mental retardation - positive.
Language & speech abnormality.
Pachy, agyria, hetrotrophias.

Walker warberg disease :
Severe.
Muscle, Eye & brain are affected.
FKRP, Fukutin, POMT 1 & 2 defect.
Eye : micro-ophthalmia, corneal opacities, Coloboma (iris), Cataract, glaucoma, retinal dysplasias & optic atrophy.
Brain : Hydrocephalus, aquiduct stenosis, posterior cranial fossa malformation.

Muscle Eyebrain disease :
Defect of POMGnT1.
Myopia or Pre-retinal membrane.
Mild brain involvement.

LAMA2-related (merosin deficient) congenital muscular dystrophy	*LAMA2* Integrin FKRP	Autosomal recessive	Most patients never achieve independent ambulation; peripheral neuropathy occurs in later childhood, normal intelligence despite abnormality in white matter on brain MRI; 30% experience seizures; milder phenotypes possible with partial deficiency
Collagen VI–related muscular dystrophy	***COL6A1, COL6A2, COL6A3***	**Autosomal** dominant, autosomal recessive	Milder Bethlem myopathy and severe Ullrich congenital muscular dystrophy phenotypes, but most patients intermediate; distinguishing features are marked distal hyperlaxity with proximal contractures; skin changes including keloid formation, hyperkeratosis pilaris, and soft palms and soles; creatine kinase level may be normal to mildly elevated
α-Dystroglycanopathies	*FKTN, POMT1, POMT2, FKRP, POMGNT1, ISPD, POMGNT2, B3GNT1, GMPPB, LARGE, DPM1, DPM2, ALG13, B3GALNT2, RXYLT1*	Autosomal recessive	Defect in glycosylation of α-dystroglycan; broad spectrum of clinical phenotypes from very severe Walker-Warburg syndrome and muscle-eye-brain disease to milder limb-girdle muscular dystrophy phenotypes; central nervous system involvement can be profound in severe cases and includes cobblestone lissencephaly, severe mental retardation, and seizures; Fukuyama subtype due to *FKTN* mutation is common in Japan due to ancestral mutation; *FKRP* most common in other populations
Laminopathy	***LMNA***	Autosomal recessive	Neonatal onset of severe weakness for neck/postural muscles (dropped head syndrome) with early loss of ambulation; other phenotypes include Emery-Dreifuss muscular dystrophy, familial partial lipodystrophy, limb-girdle muscular dystrophy, dilated cardiomyopathy, Charcot-Marie-Tooth disease, and Hutchinson-Gilford progeria syndrome

Active space

White matter changes are focal & cortical changes - milder.

Lamin A/C

00:29:13

Drop head syndrome : neonatal onset + neck extensor weakness.

Rigid spine scoliosis with contractures of knee and elbow.

EDMD phenotype.

Cardiac arrhythmias are common.

CK - normal (moderate).

Selenoprotein N1 gene.

Active space

CONGENITAL MYOPATHIES

Congenital myopathies 00:00:42

Non progressive.
Present at birth.
Present as floppy infant.
Classical features :
Ophthalmoplegia + ptosis + facial weakness.
Contractures/ congenital hip dysplasias.

Severe form - respiratory & bulbar involvement.
CK - Normal to mildly elevated.
No CNS involvement.

Onset :

- Prenatal onset - presents with decreased fetal movements and polyhydraminos.
- <1yr onset - Classical form (mc).
- Late onset.

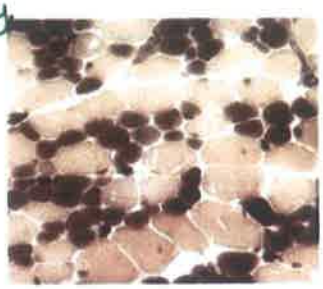
Types of congenital myopathies 00:03:54

Based on biopsy findings.

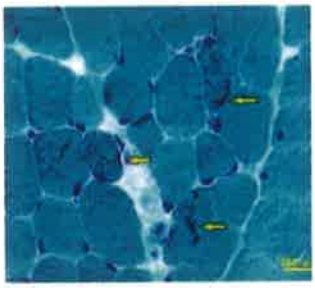
- Core myopathy - central core takes less stain due to absence of mitochondria.
  NADH, SDH - Negative (stains used).
  multi mini core - multiple patches (not central).
- Nemaline myopathy - nemaline rods present in perifery of cytoplasm.
  Dysmorphism present :
  Jaw abnormalities - jaw gnathism, Retrognathism etc.
  High arched palate.
  Dolicocephaly.
- Centro-nuclear myopathy - Large nucleus in centre

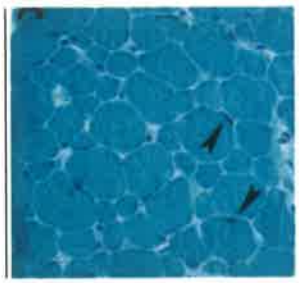
surrounded by large Halo area (looking like a rod/tube).
Also known as myotubular myopathy.

- Congenital fibre type disproportion
  - Type I (atrophied) & a (hypertrophied) fibres seen.
  The disproportion in size : 35-40%.
  Rule out histological features of other types.

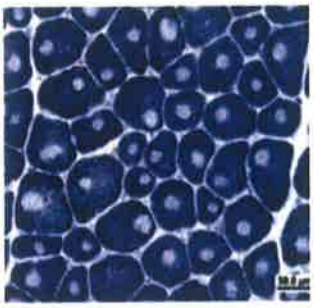


Congenital fibre type disproportion

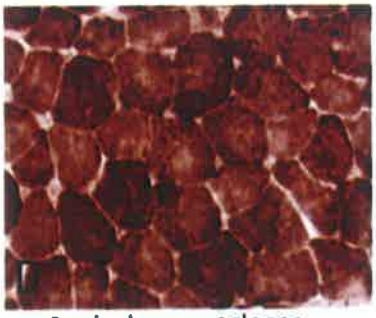




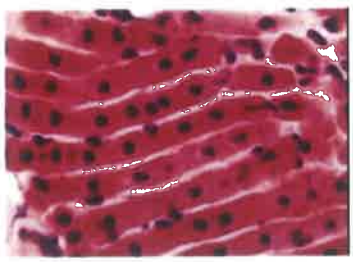
Nemaline bodiess (High & Low resolution)

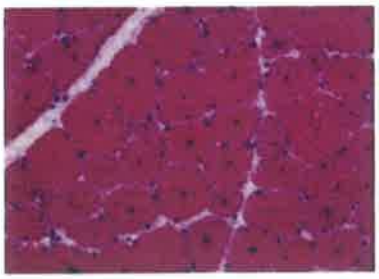


Central core - RYR mutation



Central core : selenon





myotubular myopathy

Nemaline	AR- NEB, Troponin,cofilin AD- actinin, alpha tropomyosin AD/AR - actin, beta tropomyosin.
Core myopathy	AD/AR - RYR1, TTN AR- Selenon AD- MYH7
Centronuclear	X linked - MTM1 AD/AR - DNM2 ,BIN1 AR- SPEG

Active space

Mutations 00:10:50

- Core myopathy - RYR 1 : malignant hyperthermia.
  Myosin H7 , TTN mutation associated with cardiac involvement.
  Multimini core -Selenon mutation.
- Nemaline - Nebulin gene (mc) mutation.
  Also associated with Actin, Actinin, Alpha & beta tropomyocin gene mutation.
- myotubular - MTM1 gene mutation (X-linked).
  Also associated with DNM2.
- Congenital fibre type disproportion - Associated with many genes.

Cases 00:17:28

37 week infant born by LSCS because of fetal tachycardia,
Had significant hypotonia and poor respiratory effort.
Patient was intubated and then switch to continuous positive airway pressure by nasal prongs the next day. He was fed by nasogastric tube from birth because of poor feeding.
Family history was unremarkable.
O/E - hypotonic with tachypnea.
His head circumference - normal.
B/L ptosis, limited extraocular movements.
Inverted V- shaped upper lip, High arched palate & reduced facial movements.
No cataracts or Tongue fasciculations were noted.
His cry and gag were weak.
motor examination revealed paucity of spontaneous movement due to generalised weakness.
DTR H+ in both knees.
Possible diagnosis : congenital myopathy

muscle biopsy of right vastus lateralis :
Type I fiber predominance with preserved fascicular architecture.
myofibers had a single internal nucleus with surrounding

Leave Feedback

pale- staining core (cental core myopathy).
MTM1

Case :
4 yr old girl was referred for abnormal gait, which was first noted by her parents at 3yrs of age.
She was clumsy, had difficulty getting up from ground, going up & down the stairs at home (proximal hip weakness).
Pregnancy & delivery were unremarkable.
she had CDH that was treated with casting (congenital dystrophy).
Had torticollis at 3 months of age, treated with physical therapy.
She had normal development for language & cognitive function.
No family History.
weakness is progressive (CMD).
O/E : marked hyperlaxity of hands, wrists & ankles with contractures in shoulder & hip.
Had rough skin on arms & lower legs.
Proximal muscle weakness - Gowers maneuver & trendelenburg gait.
Reflexes were normal
CK - 320 U/L.
Probable diagnosis : Collagen disorder.
sequencing test : COL6A1 , COL6A2 & COL6A3.
Mutation of COL6A1 - positive.
childhood onset (Ulrich).

Active space

HERDITARY NEUROPATHIES

Introduction 00:03:12

- Heriditary motor Sensory Neuropathy : Charcot marie Tooth disease.
- Heriditary Sensory Autonomic Neuropathies.
- Heriditary Neuropathy Pressure Palsy
- Gaint Axonal Neuropathies
- Hereditary neuralgic amyotrophy

When to suspect hereditary neuropathy 00:05:00

1. Chronicity.
2. Lack of positive symptoms.
3. Deformities like pes cavus, scoliosis, and hammer toes.
4. Family history : History of anyone in family with similar symptoms.

CMT classification 00:09:34

Based on numerical and genetics :

- CMT 1 : AD
- CMT 2 : AD
- CMT 3 : Later named as "Dejerine sottas disease"(DSS). It is AD > AR
- CMT 4 : AR
- CMT X : X-linked.

Classification based on pathology :

- Only CMT-2 is axonal and rest all are demyelinating. CMT2a is more common and classical deformities are not predominant in it.

Classification based on NCS :

Based on conduction velocity of median nerve of forearm segment.

- < 38 : Demyelinating.
- < 10 : DSS
- > 38 : X-linked or axonal.
- > 45 : Normal – axonal
- 38 – 45 : Intermediate.

CMT :

- It was first named as Peroneal muscle Atrophy due to inverted champagne bottle appearance of leg.
- DSS : It was called as Hypertrophic interstial neuritis.

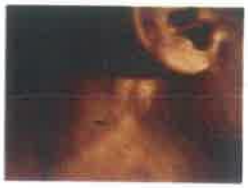
CMT 1

00:17:45

- It is most common and autosomal dominant.
- Presents with Pes cavus, hammer toes and scoliosis.
- Classical feature of thickened nerves is present.
- Onset : 1st decade.
- Uniform demyelination is present.
- It does not have conduction block or temporal dispersion.
- On biopsy : Onion bulb appearance without inflammation is seen.

CMT 1 : It is an AD and demyelinating disease. Genes associated are :

- CMT1A : PMP22 duplication
- CMT1B : MPZ
- CMT1C : LITAF
- CMT1D : EGR2



NCS :

Normal : > 45 – CMT.

Intermediate 35–45 : CMT X.

Slow 15–35 : CMT 1

Very slow : < 15 – DSS, CMT IX.

CMT 1b, HNPP : Can be asymmetrical slowing.

Note – PMP 22 :

- Deletion is associated with HNPP.
- Duplication is associated with CMT1A.
- Point mutation is associated with CMT1E and DSS (EGR2 and MPZ point mutations are also seen in this).

CMT 2

00:21:42

- Onset is 2nd decade.
- Deformity and nerve thickening are not seen.

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2A : MFN_a mutation and Optic atrophy.

2B : Basal foot ulcer.

2C : Vocal cord involvement, diaphragm and intercostal muscles are affected.

2D : Distal upper limb wasting.

2E : It is an exception. Conduction velocity is < 38. (In CMT-2 Conduction velocity is > 38).

2F : Frailty – old age. It can present in 35–76 years.

2G : Rare. Can be seen in Spanish families.

2H : Old age.

2J : Associated with adies pupil and SNHL.

CMT 3

00:28:23

- Present like CMT1 with deformity, demyelinating and nerve thickening.
- Infancy or early childhood : Severe motor developmental delay.
- By adolescence presents with difficulty to walk and may require wheel chair.
- They may have proximal muscle weakness symptoms also.
- NCV < 10, temporal dispersion, pseudo conduction block.
- CSF protein increased.
- PMP22 , EGR2, MPZ : Point mutuation.

CMT 4

00:30:05

- Genes involved are GDAP1 – CMT4A, MTMR – CMT 4B
- Very severe < 3 year onset. It has rapid progression. Unable to walk by adolescent.
- Bulbar diaphragmatic and vocal cord involvement.

- Clinical and EDX similar to DSS.
- CSF : normal protein.

CMT X :

- Second most common.
- GJB1 – CONEXIN 32.
- No male to male transmission,
- Severe in male, NCS is intermittent 30-40
- Similar to CMT 1, proximal bulbar, diaphragm, vocal cord.
- MRI : White mater abnormality + high altitude ataxia and gait disturbance.
- Abnormal BERA.

Approach to CMT

00:40:00

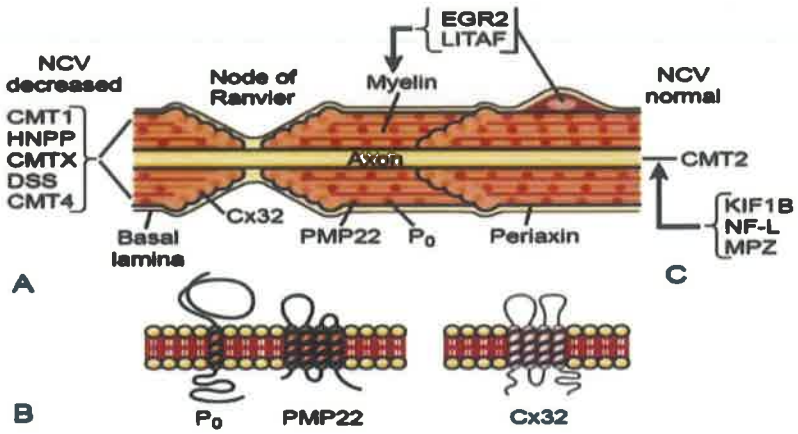
- Severe variants are CMT X and DSS.
- < 3 years onset : CMT X
- 3 years with severe disease is : DSS
- 1st decade : All other than CMT a
- and decade : CMT a.

NCV < 38 → PMP22 duplication → If negative PMP22 sequencing.

NCV < 38, No male to male transmission → PMP 22 duplication negative → CMTX

sever childhood with NCV < 15 → PMP, MPZ, EGR2 sequencing.

NCV normal/> 38 → MFN 2 mutation



- CMT with optic atrophy : CMT 2a
- CMT with adies pupil : CMT 2 J
- CMT with vocal cord : CMT 2 C, CMTX.
- CMT with prominent sensory and foot ulcer : CMT 2B.
- PMP22 mutation : CMT1 A , DSS.
- MPZ mutation : CMT 1 B, 2 J, DSS
- Vincristine and chemo therapy sensitivity A CMT 1A
- CMT with MRI abnormality and episodic ataxia A GJB1, CMTX

HSAN 00:45:41

I : AD, It has mild autonomic symptoms – Decreased pain.

II : AR, mild autonomic symptoms – pan sensory loss.

III : AR, predominant autonomic symptoms.

IV : AR

V : AR

HASAN I :

- 2nd – 4th decade Onset.

- AD : Serine palmatoyltransferase long chain 1 (SPTLC1).
- Autonomic : (mild) hypohydrosis.
- Sensory : Decreased pain, callus, ulcer, acrodystrophy.
- NCS : SNAP/CMAP – decreased.
- Biopsy : small fibre loss.

HSAN II :

- AR : WNK 1 /HSN2.
- Onset : Infancy.
- Autonomic : Mild involvement.
- Sensory : Pansensory loss.
- NCS : SNAP absent, normal CMAP.
- Biopsy : Loss of myelinated fibres, decreased unmyelinated.

HSAN III :

- Familial dysautonomia /Riley day syndrome.
- Autonomic : Labile autonomic system, autonomic crisis on emotional stimulation.
- Hypersensitivity to parasympathetic drugs.
- Sensory : Pain insensitivity
- Absent fungiform papillae on tongue.
- Oropharyngeal dysfunction, alacrimia.
- Onset : At birth with poor sucking, uncoordinated swallowing.

HSAN IV :

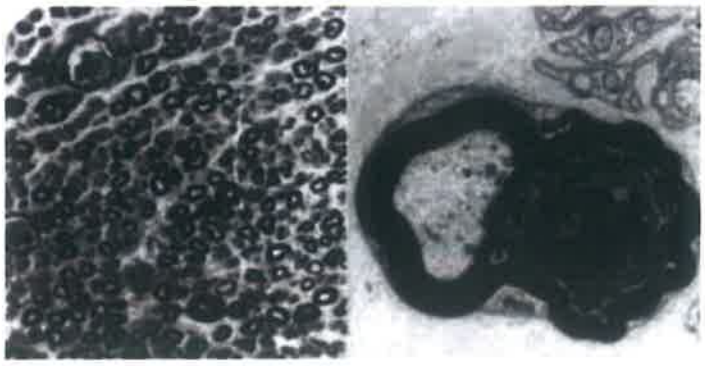
- Unhydrosis.
- Congenital insensitivity to pain.
- Mild mental retardation.
- NCS : Normal SNAP.

HSAN V : Similar to HSAN IV but no mental retardation, absent small fibre in biopsy.

Disease	Inheritance	Locus	Gene	Clinical features
HSAN I (HSN I)	AD	9q22	SPTLC1*	Small > large MF sensory loss, distal weakness, onset in second to fourth decade
HSAN II	AR		WNK1/HSN2	Paresensory loss in infancy
HSAN III (FD)	AR	9q31	IKBKAP*	Sensory loss, autonomic dysregulation, absent tears, hypoplasia of fungiform tongue papillae
HSAN IV	AR	1q21	NTRK1/NGF receptor	Insensitivity to pain, anhidrosis at birth, mental retardation, nl SNAPs
HSAN V	AR		NGFB NTRK1/NGF	Insensitivity to pain at birth, nl SNAPs, no mental disability, absent small MF

HNPP :

- AD.
- PMP22 deletion.
- Painless brachial plexus.
- Tomacula (swollen axons) on biopsy.
- Conduction block can be present.



GAN :

- AR
- Gigaxonin (GAN gene).

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- Curly hair and distal leg weakness.
- Cerebellar cortical white matter abnormality.

Hereditary neuralgic amyotrophy :

- Recurrent painful brachial plexus involvement.
- Dysmorphic features like hypertelorisum and epicanthial eye fold are seen.

MCQs

Q. CMT1A is associated with?

A. PMP22 deletion

B. PMP22 duplication

C. PMP22 point mutation

D. GJB1

Q. MPZ point mutation is associated with?

A. DSS

B. CMT 1A

C. CMT 1E

D. CMT 1B

Q. EGR2 mutation associated with ?

A. CMT 1 D

B. DSS B

C. DSS C

D. HNPP

Active space

TABLE 107.6 Molecular Genetic Classification of Charcot-Marie-Tooth Disease and Related Disorders (2012)

Disorder	Locus	Gene	Mechanism	Testing available
CMT1				
CMT1A	17p11.2	PMP22	Duplication > pm	Yes
CMT1B	1q22-q23	MPZ	Pm	Yes
CMT1C	16p13.1	LITAF	Pm	Yes
CMT1D	10q21	EGR2	Pm	Yes
CMT1E	17p11.2	PMP22	Pm	
CMT1F	8p21	NEFL		
CMTX				
CMTX1	Xq13.1	GJB1 (Cx32)	Pm	Yes
CMTX2	Xq24	?	?	–
CMT2				
CMT2A	1p36.2	MFN2	Pm	Yes
CMT2A	1p35	KIF1B	Pm	–
CMT2B	3q13-q22	RAB7	Pm	Yes
CMT2C	12q24	?	?	–
CMT2D	7p15	GARS	Pm	Yes
CMT2E	8p21	NEFL	Pm	Yes
CMT2F	7q11-21	HSPB1	Pm	Yes
CMT2G	12q12-q13.3	?	?	–
CMT2H	8q13/q21.3	GDAP1?	?	–
CMT2L	12q24	HSPB8	Pm	–
HMPP				
	17p11.2	PMP22	Deletion > pm	Yes
DSS				
DSS-A (CMT3)	17p11.2	PMP22	Pm	Yes
DSS-B (CMT3)	1q22-q23	MPZ	Pm	Yes
DSS-C	10q21-q22	EGR2	Pm	Yes
AR CMT (CMT4)				
CMT4A	8q21	GDAP1	Pm	Yes
CMT4B	11q22	MTMR2	Pm	–
CMT4C	5q23-q33	SH3TC2	Pm	Yes
CMT4D	8q24	NDRG1	Pm	Yes
CMT4E	10q21-q22	EGR2	Pm	Yes
CMT4F	19q13	Periaxin	Pm	Yes
CMT4G	10q23	?	?	–
CMT4H	12q11.1-q13.11	FGD4	Pm	–
CMT4J	6q21	FIG4/FIG4	Pm	Yes

Q. Amoung the following AR inheritance is ?

A. HNPP

B. GAN

C. HMSN I

D. CMT I

AR – CMT 4 , HSAN II,III,IV,V and GAN.

Polyneuropathies associated with genetic disorders that have systemic neurologic manifestations :

- Spinocerebellar Ataxias.
- Friedreich's ataxia.
- Hereditary Spastic Paraplegia.
- Tangier Disease.
- Abetalipoproteinemia.
- Refsum Disease.
- Lysosomal Storage Diseases : Fabry disease, Krabbe disease, MLD.