Genetic CLINICS

Official Publication of Society for Indian Academy of Medical Genetics

Volume 9 | Issue 2 | April - June 2016

ISSN : 2454-8774

Table of Contents

Address for correspondence

Dr Shubha R Phadke

Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow-226 014 | EPABX : 0522-2668005-8 | Phone : 0522 249 4325, 4342 | E-mail : editor@iamg.in

In remembrance....

Professor Irene Manorama Thomas, world-renowned clinical geneticist, passionate teacher, legendary mentor, humanitarian and expert medical ethicist passed away in Bangalore on Sunday 21st February 2016 from complications following gastroenteritis. Dr. Thomas was a reputed anatomist and a pioneer of human genetics in India. Her career at St. John's Medical College, Bangalore from 1966 to 2001 was dedicated to teaching as well as to developing and promoting the field of clinical genetics. Her contribution to human cytogenetics in India remains unparalleled. In 1972, she set up the only clinical cytogenetics laboratory of its kind in South India and was instrumental in training several of the next generation geneticists. Her trainees and students who hold prestigious positions all over the world in the fields of genetics and medicine reflect her commitment to teaching and mentoring.

She supervised 11 Ph.D. Students and she was known for the stellar training and the international exposure she gave to all her students. Dr. Thomas' passion to train clinicians in medical genetics and genetic counselling was the hallmark of her contribution to bring awareness about clinical genetics in India. The training provided by her in clinical genetics resulted in several clinicians successfully running clinical genetics services in different parts of the country.

Dr. Thomas was a tireless advocate for integrity in scientific research and her contributions in the field of medical ethics are exemplary. In recognition of her achievements, she was a recipient of several awards for her research work, including the prestigious Dr. B.C Roy award in Medicine. She is survived by her husband, Dr John A. Thomas, her son David, daughter-in-law Yasmine, and grandchildren Yana and Yohan.

Compiled by: Dr. Sridevi Hegde
Consultant Geneticist & HOD
Dept. of Medical Genetics
Manipal Hospital, Bengaluru

Pathways to Cure

Editorial

The endpoint of research in human biology is cure of diseases and improvement in the quality and longevity of life. DNA, the basic molecule of life, has been the target of study and treatment over the last few decades. Techniques to correct the gene defect underlying Mendelian disorders are being pursued along with various forms of gene modifications for the treatment of cancers and autoimmune diseases. Success of gene therapy in immunodeficiency disorders is yet to be replicated for many other diseases, but trials are going on. The GenExpress in this issue mentions a study about successful gene therapy for Sanfilippo disease in mice model, wherein significant enzyme levels were reported in the cerebrospinal fluid. There was reversal of the behavioral phenotype in the treated mice along with improvement in the lifespan. Gene therapy is an important modality for lysosomal storage disorders with neurological involvement as currently available enzyme replacement therapies are unable to improve or prevent the neurological phenotype.

As many issues with gene therapy are yet to be sorted out, many other modalities of treatment are being explored. These include mRNA-based gene silencing of a disease modifier gene and use of ultrasonographic energy to take care of toxic aggregated material, as mentioned in the GenExpress in this issue. One of the interesting modalities, which appears relatively easy and is showing promise, is the use of molecules that work at the level of the mutant protein and molecules affecting the downstream pathways. Analogue of C Natriuretic Peptide (CNP) which is an antagonist of Fgfr3 in mouse models was recently used in children with achondroplasia, a disease caused by gain of function mutation in the *FGFR3* gene and improvement in growth was reported over a short period of time. Such types of novel drug therapies have been found to be effective in some other groups of disorders also. Inhibitor of mTOR, Sirolimus, has been found to be useful in the treatment of subependymal giant cell astrocytomas (SEGA) and renal angiomyolipomas (AML) related to Tuberous Sclerosis.

The functions of protein products of disease-causing genes are being understood. Better understanding of biochemical pathways has led to the development of molecules which can work at various levels of molecular pathways and can modify the course of disease. Noonan syndrome and other group of disorders with overlapping phenotypes have been discussed in this issue. The similarities and overlap of phenotypes of this group of disorders (known as RASopathies) is due to the proteins of the causative genes being involved in a common signaling pathway. The Ras/MAPK pathway has been well studied in cancer and is an attractive target for small-molecule inhibition to treat various malignancies. Trials to evaluate the effect of the MEK inhibitor MEK162 (Novartis) on adults with Noonan syndrome who have hypertrophic cardiomyopathy and the use of Simvastatin for improving cognitive function in Neurofibromatosis are underway. Phenotypic similarity is also observed in many groups of disorders due to commonalities in the pathogenesis at various level. The article on leukodystrophies in this issue gives an overview of genetic white matter disorders. Identification of the causative gene and understanding about the normal function and abnormal pathophysiology at the molecular level are important steps towards the development of drugs and that is increasingly happening these days. The publications on various strategies for treatment of genetic disorders have definitely raised our hopes for more definitive treatments for currently untreatable genetic disorders. Better understanding of the molecular pathology for the so-called non genetic disorders is also leading to development of newer drugs e.g. for the prevention of vascular complications in diabetes. The Human Genome Project has ushered the world into a new era of therapies.

Dr. Shubha R Phadke
1st April, 2016

Fetal myopericytoma: a rare tumour with good prognosis

Mamatha Gowda [1], Susheela Jaiswal [2] and Shubha Phadke [3]*

[1]Department of Obstetrics and Gynecology, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry

[2]Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh

[3]Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh

Email: shubharaophadke@gmail.com

Abstract

Reported here is a case of fetal myopericytoma, investigated by prenatal ultrasound and confirmed by autopsy and histopathological examination after termination of pregnancy. On antenatal ultrasonography, there was a large, multicystic neck mass with enhanced Doppler flow in the fetus at 20 weeks gestation. Parents terminated the pregnancy and an autopsy was conducted on the abortus. The tumor was located in the neck and had numerous, large calibre vessels within. Histopathological examination with immunohistochemistry revealed the tumor to be a benign myopericytoma. This is the earliest gestation at which fetal myopericytoma has been reported.

Introduction

Myopericytomas are benign pericytic tumours usually occurring in adults and involving the distal extremities. There are only few case reports of antenatally detected myopericytomas described at 32-33 weeks of gestation. We are reporting a case of fetal myopericytoma involving the neck detected at an early gestation of 20 weeks.

Case report

A twenty five year old primigravida presented for evaluation of a fetal neck mass detected on ultrasound at 20 weeks of gestation. There was a large multicystic mass of size 8 cm X 6 cm on the right side of the fetal neck. There were multiple hypo-echoic spaces within the mass which, on color Doppler, showed increased vascular signals and large feeding vessels arising from the aorta (Figure 1. A-B). Intracranial anatomy was normal and there were no other associated malformations. Amniocentesis was done and the fetal karyotype was reported to be normal. Differential diagnoses of arterio-venous malformations, haemangioma, vascular goiter and teratoma were considered. The extreme vascularity of the mass suggested increased risk of cardiac failure in the fetus. The family opted to terminate the pregnancy in view of the uncertain diagnosis and prognosis.

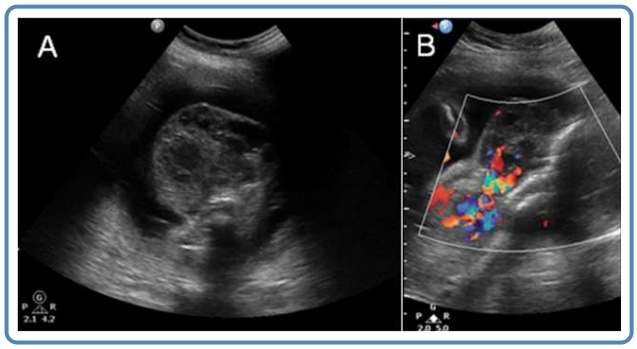


Figure 1 Ultrasound of the fetus showing, (A) the neck mass, (B) extreme vascularity on color doppler.

On postmortem examination of the abortus, there was a mass on the right side of neck, measuring 8 cm X 6.5 cm, extending from the ear lobule upto the clavicle (Figure 2). On dissection, numerous branching vessels were found within the mass. These vessels extended into the thorax and were connected by a major feeding vessel to the aorta. The tumor could be enucleated easily and there were no intracranial extensions or involvement of underlying bones. Histopathological examination,

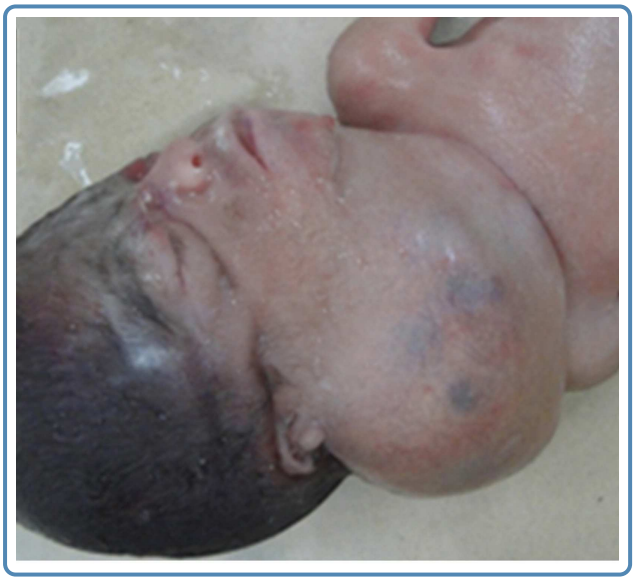


Figure 2 Autopsy of the fetus showing the neck mass.

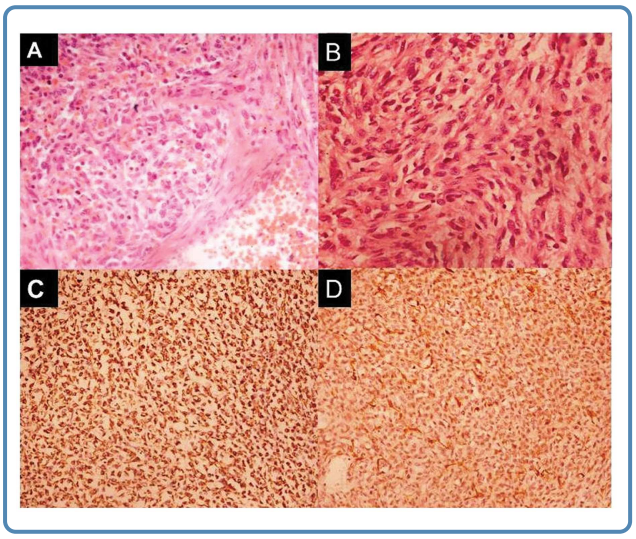


Figure 3 Hematoxylin and Eosin staining of the tumor tissue. (A) Tumor cells seen in sheets with intratumoral blood vessels. (B) Tumor cells displaying nuclear pleomorphism, coarse chromatin, conspicuous nucleoli and eosinophilic cytoplasm with spindling. (C) Positive immunohistochemistry (IHC) staining for vimentin. (D) Positive immunohistochemistry (IHC) staining for smooth muscle actin.

with the addition of immunohistochemistry, revealed the tumor to be a benign myopericytoma (Figure 3. A-D).

Discussion

This is a report of a 20 weeks fetus diagnosed to have a myopericytoma by prenatal ultrasound and confirmed by autopsy and histopathological examination. There are only few reports of prenatally detected myopericytomas involving the lip, nose, brain and fetal neck, all being diagnosed in the third trimester, after 32 weeks of gestation. In our case, the diagnosis was made at an earlier gestation of 20 weeks.

Stout and Murray (1942) were the first to describe hemangiopericytoma as a tumor composed of Zimmerman's pericytes showing the characteristic 'staghorn' branching vascular space. However, the histological features and the branching vascular pattern which were once considered to be its characteristic feature are nonspecific and are seen in many tumors such as benign fibrous histiocytoma, synovial sarcoma, leiomyosarcoma and others (Kempson et al., 2001).

The term myopericytoma was used in 1998 to describe a spectrum of tumours with clinicopathological features that overlap with hemangiopericytoma. WHO describes myopericytomas as pericytic lesions showing differentiation towards myoid/contractile perivascular cells with a characteristic tendency to grow in a circumferential perivascular fashion (Fletcher et al., 2002). Currently, this class of tumours encompasses infantile myofibromatosis-like lesions such as glomangiopericytomas of adults, infantile myofibromatosis and infantile haemangiopericytoma (Mc Menamin et al., 2002).

Myopericytoma usually presents in adults as painless, solitary, slowly growing, subcutaneous nodules involving the extremities, retroperitoneum and rarely the neck and head. Only 5-10% of hemangiopericytomas affect children and the infantile variety is very rare, usually occurring within the first year of life (Ferrari et al., 2001). Ultrasonographic findings are nonspecific and biopsy with immunohistochemical and ultra-structural studies are necessary for the diagnosis. Macroscopically, the tumors are uncapsulated, well circumscribed nodules. There are numerous vessels with characteristic multilayered concentric arrangement of oval-spindle shaped cells around (Fletcher et al.,

2002). Myopericytomas can be distinguished from other tumors with overlapping features by the fact that cells stain positively for alpha-smooth muscle actin (Dray et al., 2006).

There are few published cases of myopericytomas detected prenatally. The first case described by Hornoy et al. (2005), had an associated cerebral extensions of the neck mass on ultrasonography and magnetic resonance imaging at 33 weeks of gestation. In this prenatally detected case, there was a tumor near the temporal region and though there was no connection between the tumor and brain, the brain in the region showed abnormal gyration on fetal MRI. Another case was reported by Chung et al. (2010), where the fetus had a hemangiopericytoma of the forehead on ultrasonography at 32 weeks of gestation. This case was followed up postnatally for 18 months after complete excision at 7 days of birth. The baby had normal growth and development without any recurrence during the period of observation.

Malignant myopericytoma is very rare and shows high mitotic rate, high cellularity, pleomorphism and necrosis on histopathology (Mc Menamin et al., 2002). Malignant tumors may have an aggressive clinical behavior, with recurrence or metastasis, and complete local excision with continued observation is recommended as treatment (Dray et al., 2006).

To conclude, myopericytoma should be considered in the differential diagnosis of any vascular tumor detected antenatally in the fetus. It is especially so in earlier gestation, when a decision to either terminate or continue the pregnancy has to be made. It is important to rule out associated malformations by fetal MRI and utilize color Doppler to look for extension of tumor into the brain. Regular fetal echocardiography is useful for monitoring the fetus for heart failure. This benign tumor is reported to have good prognosis after postnatal surgical excision.

Key messages

Prenatally detected vascular tumors of the neck could be benign tumors. Further management plan needs to be carefully devised to optimize the outcome for the fetus.

References

1. Stout AP, Murray MR. Hemangiopericytoma: a vascular tumor featuring Zimmermann's pericytes. Ann Surg 1942; 116: 26–33.
2. Kempson RL, et al. Perivascular tumours. In: Atlas of tumour pathology. Tumours of the soft tissues. Fascicle 30, 3rd Series. Washington: AFIP 2001:371–383.
3. Fletcher CDM, et al, Eds. Pericytic (perivascular) tumours. In:World Health Organisation classification of tumours. Pathology and genetics. Tumours of soft tissue and bone. Lyon: IARC Press 2002:135–139.
4. Mc Menamin ME, et al. Malignant myopericytoma: expanding the spectrum of tumours with myopericytic differentiation. Histopathology 2002; 41: 450–460.
5. Ferrari A, et al. Hemangiopericytoma in pediatric ages: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. Cancer 2001; 92: 2692-2698.
6. Dray MS, et al. Myopericytoma: a unifying term for a spectrum of tumours that show overlapping features with myofibroma. A review of 14 cases. J Clin Pathol 2006; 59: 67–73.
7. Hornoy P, et al. Fetal hemangiopericytoma with an associated cerebral anomaly. Ultrasound Obstet Gynecol 2005; 26: 81–85.
8. Chung H Y B, et al. Fetal forehead hemangiopericytoma: prenatal diagnosis and postnatal outcome. Ultrasound Obstet Gynecol 2010; 36: 121–124.

GeNeViSTA

The Clinical Spectrum of RASopathies

Divya Agarwal, Ratna D Puri, Achint Kaur, Sunita Bijarnia-Mahay and IC Verma

Center of Medical Genetics, Sir Ganga Ram Hospital, New Delhi

Email: dr.divya2512@gmail.com

Introduction

The RASopathies are a specific group of genetic syndromes that occur as a result of germline mutations in genes encoding proteins of the Ras–mitogen-activated protein kinase (RAS–MAPK) pathway (Fig 1). These developmental disorders include Neurofibromatosis type 1 (NF1), the first RASopathy identified, followed by Noonan syndrome (NS), and a host of others including Noonan syndrome with multiple lentigines (NSML), capillary malformation–arteriovenous malformation syndrome (CM-AVM), Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFC) and Legius syndrome. The Ras-MAPK pathway is essential for signal transduction from the cell surface to the nucleus and plays a pivotal role in regulation of cellular proliferation, differentiation and cellular growth. The RAS multigene family includes KRAS, HRAS and NRAS and code for Ras proteins that are guanosine nucleotide bound and cycle between the active GTP-bound form and the inactive GDP-bound form. Activation of RAS occurs as an outcome of binding of the growth factor to the receptor tyrosine kinase (RTK) and SOS1 recruitment, that in turn increases the active GTP-bound Ras form. This further initiates activation of Raf (ARAF, BRAF, CRAF), the first MAPK pathway kinase, which in turn activates MEK1 / MEK2, which then regulate the downstream effector substrates ERK1and ERK2. These further activate downstream nuclear and cytosolic molecules that control cellular proliferation and differentiation (Fig 1) (Tidyman and Rauen, 2009). Understanding the pathophysiology is important to identify possible therapeutic targets for RASopathies, aimed at reduction of activity of RAS signaling (Korf B, et al., 2015; Bezniakow N, et al., 2014).

In the group of malformation syndromes that occur due to the Ras / MAPK pathway dysregulation, germline mutation in any of the genes exhibits numerous overlapping phenotypic features of facial dysmorphism, short stature, congenital heart defects (CHD), skeletal abnormalities, cutaneous abnormalities and variable developmental delay.

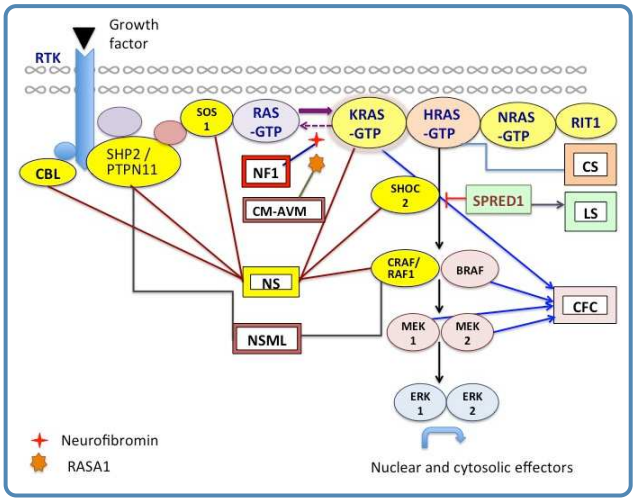


Figure 1 Ras-MAPK signal transduction pathway and molecular basis of RASopathies. NF-1: Neurofibromatosis type 1; NS: Noonan syndrome; CFC: Cardiofaciocutaneous syndrome; CS: Costello syndrome; LS: Legius syndrome; NSML: Noonan syndrome with multiple lentigines; CM-AVM: Capillary malformation-arteriovenous malformation.

These are one of the largest group of malformation syndromes with an estimated incidence of about 1 in 1000 persons. Activating mutations in *PTPN11* are present in 50% patients with Noonan syndrome, other causative genes being *SOS1, RAF1, KRAS, NRAS, SHOC2,* CBL and *MAP2K1 (MEK1)* which are implicated in a subset of patients. Genes associated with the other disorders of this pathway are illustrated in Figure 1. Recently, novel gene

variants, including *RIT1, RRAS, RASA2, A2ML1, SOS2* and *LZTR1*, have in addition been shown to be associated with RASopathies, further expanding the disease spectrum (Aoki Y et al., 2016). Table 1 lists the various genes responsible for causing Noonan and Noonan-like syndromes.

Table 1 Genes responsible for causing RASopathies.

Syndrome	RAS/MAPK pathway gene	Proportion of disease attributed to this gene
Neurofibromatosis 1	*NF1*	>95%
Noonan Syndrome (NS)	*PTPN11*	50%
	SOS1	10%-13%
	RAF1	3%-17%
	KRAS	<5%
	NRAS	4 individuals to date
	BRAF	<2%
	MAP2K1	<2%
	SHOC2	2%
	CBL	
Noonan syndrome with multiple lentigines	*PTPN11*	90%
	RAF1	<5%
	BRAF	2 individuals
	MAP2K1	1 individual
Capillary malformation-arteriovenous malformation	*RASA1*	>70%
Costello syndrome	*HRAS*	80%-90%
Cardio-facio-cutaneous syndrome	*BRAF*	75%
	MAP2K1	25%
	MAP2K2	
	KRAS	<2%-3%
Legius syndrome	*SPRED1*	98%
Novel genes in NS and NS like syndromes (No. of families reported)	*RIT1, RRAS, RASA2, A2ML1, SOS2, LZTR1* (Bezniakow N, et al., 2014; Korf et al., 2015; Aoki et al., 2016; Allanson & Roberts, 2011)	

We discuss here a few of the interesting cases that presented to the genetic clinic at our hospital from 2012 through December 2015, with characteristic features of Noonan and other RASopathies. Neurofibromatosis type 1 is not included in this series except one case of NF1 with developmental delay and craniofacial dysmorphism reminiscent of NS. A total of 20 patients including 13 patients with a provisional diagnosis of Noonan syndrome (NS), 5 patients with a diagnosis of Cardiofaciocutaneous syndrome (CFC), 1 patient with suspected NF - Noonan syndrome and 1 patient of Costello syndrome were seen during this time. The age of presentation varied from 3 months to 22 years and one fetus was evaluated after termination of the pregnancy at 18 weeks gestation. The clinical data of the patients is presented in the Table 2.

Cranio–facial dysmorphism

The most consistently found feature in all patients was the characteristic facial dysmorphism - low set and posteriorly rotated ears, broad nasal bridge, hypertelorism and downslanting palpebral fissures seen in 17/20 (85% of patients). Additionally ptosis was noted in 12/20 (60% of patients) (Fig 2A). In patients with clinical suspicion of cardiofaciocutaneous syndrome (5/20 patients), the face was broader and coarse looking with sparse, thick, curly wooly hair (Fig 2B). In our one patient of Costello syndrome (Table 2-IV) from Nigeria, the facies were much more coarse with thick, fleshy earlobes, full nasal tip and thick lips (Fig 2C; the mother's photo given for comparison). The facial features associated with NS and related disorders vary considerably with age, being most striking in the neonatal period and childhood. Since the presentation can be mild and the typical facies recede with age, the diagnosis may be overlooked. Hence, the facial dysmorphism should be carefully noted at the initial visit as "gestalt" assessment is the commonest diagnostic tool for disorders of the RAS-MAPK pathway.

Cardiac manifestations

Heart disease was present in 17 out of 20 patients (85%) similar to the estimated frequency between 50 - 80% (Allanson & Roberts, 2011). NS and related disorders are one of the most common syndromic cause of heart defects. Several cardiovascular phenotypes are found, with pulmonary valvular stenosis being the most common in our cohort followed by hypertrophic cardiomyopathy and atrial septal defects.

Table 2 Clinical characteristics and mutations of patients with suspected Noonan Syndrome (I.1-I.13), Cardiofaciocutaneous syndrome (II.1-II.5), Neurofibromatosis Noonan syndrome – NFNS (III), Costello syndrome-(IV).

Patient ID	Age at presentation /Sex	Antenatal	Development /Intellect	Stature	Heart disease	Facial features	Skeletal	Others/ Mutation
I.1	18 weeks fetus / M	Bilateral hypoplastic kidneys with oligohydramnios. Echocardiography-Pulmonary stenosis.	-	Crown rump length: 18 cms (18-19 weeks)	Pulmonary stenosis	Telecanthus, broad nose, low set ears, downslanting palpebral fissures	Normal radiographs	-
I.2	3 months / M	NT-5.6 mm, Femur - 5th centile for gestation, Antenatal Karyotype-46,–, Normal	Appropriate	59 cms (50th centile)	not present	Sparse eyebrows, downslanting eyes, triangular chin, low set ears, high arched palate, bulbous tip of nose	Right CTEV, limitation of elbow joint extension, right clinodactyly.	
I.3	5.5 months / M	Antenatal data not available.	Appropriate	55.6 cms (- 4 SD)	Hypertrophic cardiomyopathy	Downslanting eyes, Bulbous nasal tip	Short neck, shield like chest, wide spaced nipples	-
I.4	5.5 months / M	Antenatal period-uneventful	Global development delay	56 cms (-4SD)	Atrioventricular canal defects	No dysmorphic features	-	Juvenile myelomonocytic leukemia, feeding difficulty & vomiting, retrocollis failure to thrive, loose skin, scant hair. Heterozygous mutation (c.218C>T, p.Thr73Ile) in *PTPN11* gene

I.5	10 month / M	Antenatal data not available	Appropriate	63 cms (-3 SD)	ASD with severe valvular pulmonary stenosis	Downslanting eyes	-	Feeding difficulty & vomiting, bilateral undescended testes
I.6	1 year / M	Antenatal data not available	Appropriate	70 cms (-2 SD)	Severe valvular pulmonary stenosis with RVH	Facial asymmetry, left ptosis, hypertelorism, epicanthic folds	Bilateral 2nd-3rd toe syndactyly, left Simian crease	Micropenis
I.7	4 years / M	Antenatal data not available	Mild development delay	90 cms (-2 to -3 SD)	Atrial septal defect	Downslanting eyes, hypertelorism	-	Undescended testes, hypospadias
I.8	4 years / M	Antenatal data not available	Normal	91 cms (-3 to -2 SD) at diagnosis	Atrialseptal defect	Ptosis, broad nasal bridge	-	On Growth hormone therapy
I.9	4.5 years / M	Antenatal data not available	Normal	88 cms (-5 to -4 SD) at diagnosis	Supravalvular tethering of pulmonary valve	Mild ptosis, depressed nasal bridge	Winging of scapula, pectus excavatum, short neck, limitation of elbow extension	On Growth hormone therapy
I.10	7 years / M	Antenatal data not available	Development delay present	100.5 cms (-4 SD)	Soft systolic murmur, recurrent respiratory infections. Echo - Not done.	Downslant palpebral fissures, low set ears, small philtrum, teeth pigmentation	Short neck, small hands and feet	CT head- Hydrocephalus Heterozygous mutation (c.2536G>A, p.Glu346Lys) in exon 16 of *SOS1* gene
I.11	10 years 8 month / F	Antenatal data not available	Mild ID	111 cms (-5 SD)	Echocadiography - Normal	Ptosis	Short neck, pectus carinatum	

I.12	14 years / F	Antenatal data not available	Mild ID	135 cms (-3 SD)	Pulmonic stenosis	Epicanthal folds, hypertelorism, low nasal bridge, downward eye slant, low set ears	-	Lentigines
I.13	22 years / M	Antenatal data not available	Mild ID	158 cms	CHD- Unspecified	Broad nasal bridge, maxillary hypoplasia, small curved eyelashes, preauricular sinus	Bilateral pedal edema, broad laterally deviated toes	-
II.1	1 year / F	Unilateral hydronephrosis	Severe development delay	68 cms (-3 to -2 SD)	Pulmonary stenosis	Depressed nasal root, wide base of nose, bulbous tip	-	Feeding difficulty with GERD
II.2	3 years / F	Polyhydramnios	Mild global development delay	87 cms (3- 50th centile)	Left ventricle hypertrophy, left ventricle dysfunction, mild mitral regurgitation	Coarse facies, downslant palpebral fissures, low set ears, broad forehead, hypertelorism, strabismus	Short broad thumbs, fingers and toes, widely spaced nipples	Generalised dry skin, keratosis pilaris,sparse eyebrows, curly wooly hair
II.3	5 years / M	Antenatal data not available	Moderate ID	95 cms (-3 to -4SD)	Atrial septal defect	Coarse, broad face, downslanting palpebral fissures, bulbous tip of nose.	-	Curly wooly hair

II.4	8 years / M	Antenatal data not available	Moderate ID	115 cms (-2 to -3SD)	Hypertrophic cardiomyopathy	Coarse, broad face. downslanting palpebral fissures, bulbous tip of nose. ptosis	-	Curly hair
II.5	18 months / M	Polyhydramnios	Mild development delay	73 cms (-3 SD)	Atrial septal defect	Coarse, broad face. downslanting palpebral fissures, bulbous tip of nose.	-	Curly, scant hair
III	15 months / M	Antenatal data not available	Mild development delay	71 cms (-3 SD)	-	Downslanting palpebral fissures, bulbous tip of nose	-	Multiple café au lait spots, plexiform neurofibroma Heterozygous mutation (c.2033dupC) in exon 18 of *NF1* gene
IV	6 year / F	Antenatal data not available	Delayed psychomotor development	107 cms (5^{th} to 25^{th} centile)	Hypertrophic cardiomyopathy	Coarse facies, broad forehead, depressed nasal bridge, epicanthic folds, hypertelorism, thick, fleshy earlobes, full nasal tip, thick lips		Sparse, fine scalp hair, skin - small papilloma at the root of the nasal tip was noticed, hyperkeratosis of palms & soles

NT: nuchal translucency; CTEV: congenital Talipes equinovarus, ID: intellectual disability; M: male; F: female; RVH: right ventricular hypertrophy; GER: gastro-esophageal reflux.

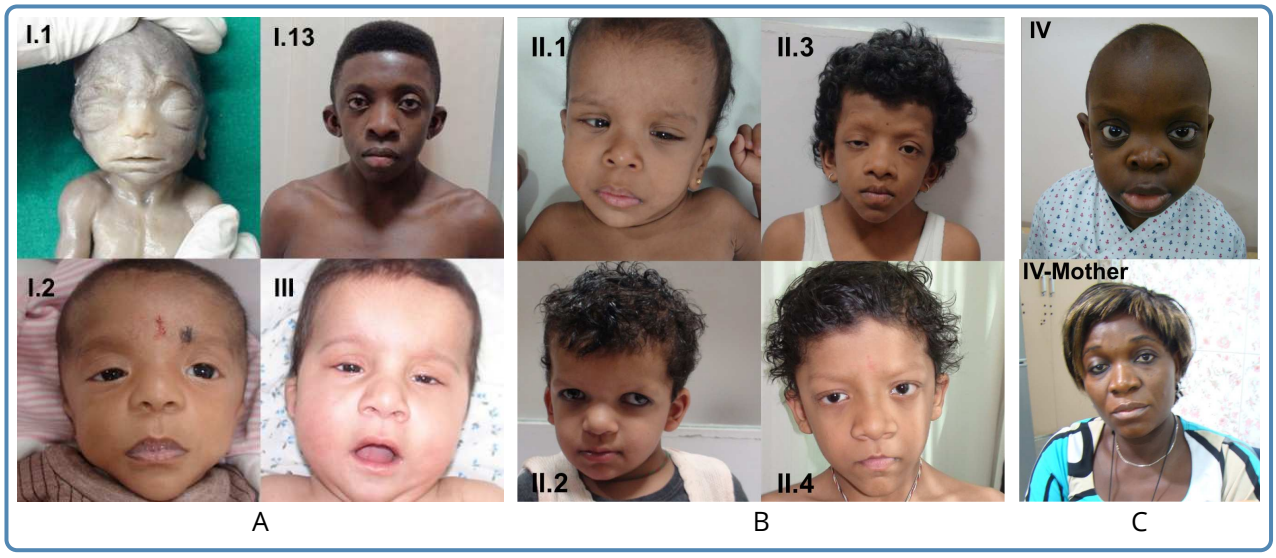


Figure 2 Facial features of patients with suspected Noonan syndrome (A), Cardio-facio-cutaneous syndrome (B) and Costello syndrome (C).

Growth

Neonates with NS usually have normal birth weight and body length. Infants, however have feeding difficulties that result in failure to thrive, most evident in the first year of life. Severe feeding difficulty and gastroesophageal reflux disease were present in three of our patients (Table 2- I.4, I.5, II.1), requiring prolonged gastrostomy in one of them.

In childhood, short stature is almost a universal finding and height usually follows the third centile with an attenuated pubertal spurt. A study reported that 30% of individuals with Noonan syndrome have a height in the normal adult range while 40 – 50% individuals have an adult height below the third centile (Noonan et al., 2003). This may be due to growth hormone deficiency because of neurosecretory dysfunction or growth hormone resistance. The US Food and Drug Administration in 2007 approved Growth Hormone (GH) replacement therapy with recombinant human growth hormone for Noonan Syndrome. Several long and short term studies on the use of GH in different parts of the world reveal significant improvement in the height velocity in children with NS (Tamburrino et al., 2015; Romano et al., 2009; Noordam et al., 2008; Osio et al., 2005; Ogawa et al., 2004).

In our study cohort, sparing an adult and a fetus, short stature was recorded in all the patients. Two patients have been receiving growth hormone therapy for a few years. One of the boys (Table 2- I.9) had height at -5 to - 4 SD at 4.5 years of age, delayed bone age, low IGF-1 levels and inadequate response to clonidine in growth hormone stimulation test. On receiving an average 0.15 units/ kg /day of GH subcutaneously, he showed significant increase in height velocity initially and gained 7.5 cm in the first year of therapy. At 14 years of age, his height is at -2SD from the mean (comparable to the mid parental height centile). For the second boy (Table 2- I.8) who received growth hormone treatment, GH was initiated at 0.15 units/kg/day from 4 years of age. The height increased from -3 SD to -2 SD within 3 years of initiation of therapy. However, it has not increased beyond -2 SD from the mean demonstrating a short-term increase in growth. There were no complications of hypertrophic cardiomyopathy or hematologic disturbances in these patients.

Occasionally NS is referred to as 'Pseudo-Turner or Male Turner syndrome', due to similar findings of short stature, webbed neck and lymphedema. Interestingly, we had one girl (Table 2- I.10) who was evaluated for short stature. The karyotype revealed 45,X [3] / 46, XX [47] confirming the diagnosis of mosaic Turner syndrome. However, she also had some characteristic NS-like craniofacial dysmorphism and systemic malformations - epicanthic folds, hypertelorism, low nasal bridge, downward eye slant, low set ears, pulmonary stenosis and lentigines. Molecular panel testing for

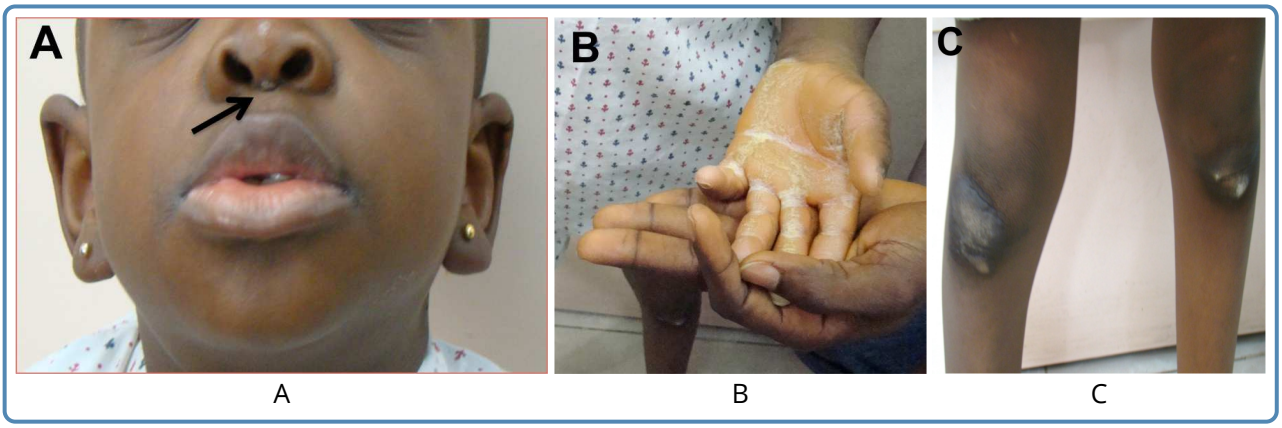


Figure 3 Patient IV- Costello syndrome. (A) Skin papilloma (B) Deep skin creases (C) Hyperkeratosis.

Noonan-related genes identified a heterozygous mutation (c.2536G>A) in the *SOS1* gene that has been implicated in Noonan syndrome.

Psychomotor development

In most affected individuals of NS, intelligence is within the normal range, with the intelligence quotient ranging from 70-120. Mild to severe learning disability is reported in 25% and 10% of the patients respectively. Furthermore, in literature it has been noted that the verbal performance is significantly lower than the non-verbal performance. In contrast, neurologic abnormalities have been reported to be universally present in CFC and range from mild to severe (Yoon et al., 2007). In our cohort of NS patients, development / intellect was appropriate for age in 54% (7/13) of patients. The children with a clinical diagnosis of CFC syndrome and Costello syndrome in the cohort had global development delay that was of mild to moderate severity.

Dermatological manifestations

Among the RASopathies, the dermatologic findings are the most common in cardiofaciocutaneous syndrome (CFC). These include xerosis, hyperkeratosis, ichthyosis, keratosis pilaris, ulerythema ophryogenes, eczema, pigmented moles, hemangiomas, and palmoplantar hyperkeratosis. The hair is typically sparse, curly, fine or thick, wooly or brittle; eyelashes and eyebrows may be absent or sparse. Nails may be dystrophic or fast growing. Apart from these similar features, Costello syndrome is characterised by papillomas of face and perianal region, as also found in our patient IV (Fig 3).

Patients with NF1 have café au lait spots, axillary freckling and neurofibromas in skin. NS may also have skin manifestations, particularly follicular keratosis over extensor surfaces, lentigines and café-au-lait spots. One child in the current cohort (Table 2-III) presented with clinical features characteristic of both neurofibromatosis type 1 and Noonan syndrome (NFNS syndrome- OMIM 601321). The NF1 features at presentation were > 6 café-au-lait spots. Follow up MRI identified cervical plexiform neurofibroma (Fig 4A, 4B). In addition the child had short stature, hypertelorism, ptosis, nystagmus, low-set ears, webbed neck and pectus deformity suggestive of NS. Mutation analysis revealed a heterozygous truncation mutation in *NF1*:c.2033dupC, thereby confirming the diagnosis of NFNS. The parents were normal on clinical examination. Recently, a similar report of a family with multiple café au lait spots and NS-like facial features in a child (fulfilling criteria of NF1) and mother (not fulfilling criteria for NF1) revealed mutation in MAP2K2 gene (Takenouchi et al., 2014). This gene has been originally implicated in CFC syndrome which further illustrates the phenotypic and genetic overlap in RASopathies.

Leukemias and other malignancies

Individuals with Noonan syndrome have upto three fold increased risk of malignancies which include juvenile myelomonocytic leukemia, acute lymphoblastic leukemia, acute myeloid leukemia

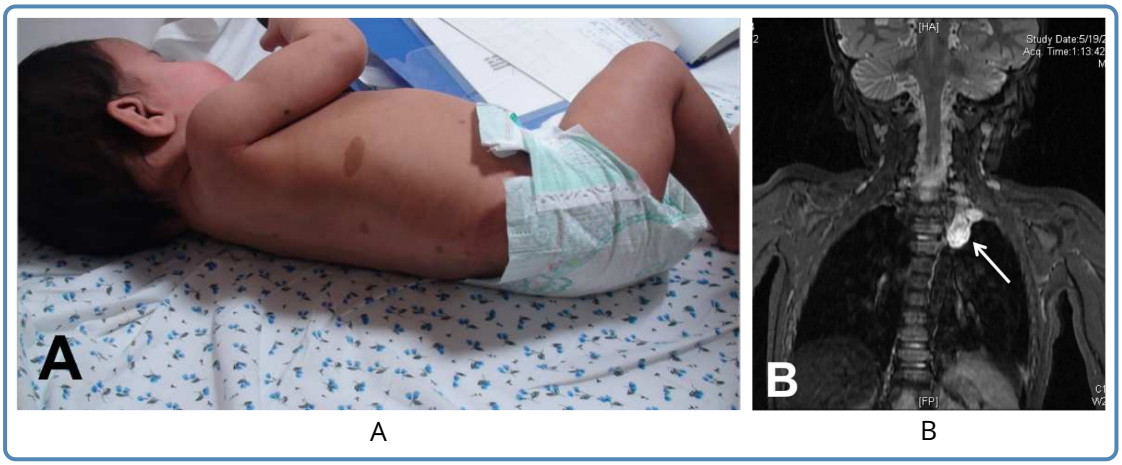


Figure 4 Patient III (A) Café au lait spots (B) Plexiform Neurofibroma.

and solid tumours such as rhabdomyosarcoma and neuroblastoma (Jongmans et al., 2011; Strullu et al., 2014).

In particular, individuals with germline mutations in the *PTPN11* gene have a predisposition to Juvenile myelomonocytic leukemia (JMML) (Strullu et al., 2014). In our cohort, patient I.4 was diagnosed with JMML at 3 months of age. He also had atrioventricular canal defect, feeding difficulties and severe failure to thrive. In view of these, he was clinically suspected and found to be carrying a heterozygous mutation in the *PTPN11* gene (c.218C>T, p.T73I), confirming the diagnosis of Noonan syndrome. This mutation has been previously identified in multiple Noonan patients with JMML, with a milder clinical course (Aoki et al., 2008).

Prenatal Diagnosis

For prenatal diagnosis, the ultrasonographic markers for NS are non specific. In the absence of family history NS is not routinely suspected and prenatal testing is not typically offered. In our cohort, the antenatal data of five patients was available and showed abnormalities. One patient (Table 2-I.2) had increased nuchal fold thickness (NFT) of 5.6 mm with femur length at 5th centile and polyhydramnios in the 2nd trimester scan. Fetal chromosomes were tested and were normal. The neonate came to medical attention at 3 months of age for dysmorphism and joint movement restriction.

One fetus (Table 2-I.1) which was terminated in view of increased NFT (5.68 mm), bilateral hypoplastic kidneys and severe pulmonary stenosis on antenatal ultrasound at 18 weeks gestation was clinically diagnosed with Noonan syndrome in view of the facial phenotype.

The other three patients (Table 2-II.1, II.2, II.5) who had antenatal polyhydramnios and unilateral hydronephrosis came to medical attention after birth for developmental delay, facial dysmorphism and congenital heart disease.

The prenatal features described for NS are increased nuchal translucency (NT), distended jugular lymphatic sacs (JLS), cystic hygroma, hydrops fetalis, pleural effusion, polyhydramnios, congenital heart disease and renal abnormalities (Myers et al., 2014).

Out of these, increased NT has the strongest association with Noonan syndrome. However, there is considerable debate as to when to offer prenatal molecular testing for Noonan syndrome, either following a first trimester increased NT or if there are associated anomalies in the 2nd trimester scan with normal fetal chromosomes.

In recent studies in fetuses with an increased NT and a normal karyotype, mutations have been reported in 9–18% of cases. Lee et al. (2009) identified *PTPN11* mutations in 2% of fetuses with increased NT and 16% of fetuses with increased NT and cystic hygroma. In another study, in fetuses with increased NT and normal karyotype, *PTPN11* and *KRAS* mutations were found in 15.8%. This group strongly advocated genetic counseling and testing for Noonan syndrome in case of increased NT and normal karyotype, even in the absence

of additional associated abnormalities (Houweling et al., 2010). On the other hand, Croonen et al. (2013), based on their mutation detection rate of 17.3% in fetuses with ultrasound findings of increased NT, distended jugular lymphatic sacs (JLS), hydrothorax, renal anomalies, polyhydramnios, cystic hygroma, cardiac anomalies, hydrops fetalis and ascites, recommended prenatal testing of *PTPN11*, *KRAS* and *RAF1* in pregnancies with an increased NT and at least one of the additional ultrasonologic features.

In conclusion, Noonan syndrome and the other RASopathies have multisystem morbidities. The clinical features are overlapping and there is extensive genetic heterogeneity. In case of antenatal or postnatal clinical suspicion, with availability of next generation panel testing, the genes in the Ras/MAPK pathway implicated with the phenotypes of RASopathies can be tested for confirmation of diagnosis. Furthermore, in view of multisystemic involvement, multidisciplinary management and follow up of diagnosed patients is essential.

References

1. Allanson JE, Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2011 Aug 4]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1124
2. Aoki Y, et al. The RAS/MAPK Syndromes: Novel Roles of the RAS Pathway in Human Genetic Disorders. Hum Mutat 2008; 29: 992-1006.
3. Aoki Y, et al. Recent advances in RASopathies. J Hum Genet 2016; 61: 33-9. doi: 10.1038/jhg.2015.114.
4. Bezniakow N, et al. The RASopathies as an example of pathway disturbances- Clinical Presentation and Molecular Pathogenesis of selected syndromes. Dev Period Med 2014; 18: 285-296.
5. Croonen EA, et al. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. Eur J Hum Genet 2013; 21: 936-942.
6. Houweling AC, et al. Prenatal detection of Noonan syndrome by mutation analysis of the PTPN11 and the KRAS genes. Prenat Diagn 2010; 30: 284–286.
7. Jongmans MC, et al. Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation. Eur J Hum Genet 2011; 19: 870-874.
8. Korf B, et al. The Third International Meeting on Genetic Disorders in the RAS/MAPK Pathway: Toward a Therapeutic Approach. Am J Med Genet A 2015; 167: 1741–1746.
9. Lee KA, et al. PTPN11 analysis for the prenatal diagnosis of Noonan syndrome in fetuses with abnormal ultrasound findings. Clin Genet 2009; 75:190–194.
10. Myers A, et al. Perinatal features of the RASopathies: Noonan syndrome, Cardiofaciocutaneous syndrome and Costello syndrome. Am J Med Genet Part A 2014; 164A: 2814–2821.
11. Noordam C, et al. Long-term GH treatment improves adult height in children with Noonan syndrome with and without mutations in protein tyrosine phosphatase, non-receptor-type 11. Eur J Endocrinol 2008; 159: 203–208.
12. Ogawa M, et al. Clinical evaluation of recombinant human growth hormone in Noonan syndrome. Endocr J 2004; 51: 61–68.
13. Osio D, et al. Improved final height with long-term growth hormone treatment in Noonan syndrome. Acta Paediatr 2005; 94: 1232–1237.
14. Romano AA, et al. Growth response, near-adult height, and patterns of growth and puberty in patients with Noonan syndrome treated with growth hormone. J Clin Endocrinol Metab 2009; 94: 2338–2344.
15. Strullu M, et al. Juvenile myelomonocytic leukaemia and Noonan syndrome. J Med Genet 2014; 51: 689-697.
16. Takenouchi T, et al. Multiple café au lait spots in familial patients with MAP2K2 mutation. Am J Med Genet A.2014; 164A: 392-396.
17. Tamburrino F, et al. Response to long-term growth hormone therapy in patients affected by RAsopathies and growth hormone deficiency: Patterns of growth, puberty and final height data. Am J Med Genet A 2015:167: 2786-294.
18. Tidyman WE, Rauen KA. The RASopathies: Developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev 2009; 19: 230–236.
19. Noonan JA, et al. Adult height in Noonan syndrome. Am J Med Genet A. 2003; 123A: 68–71.
20. Yoon G, et al. Neurological complications of cardio-facio-cutaneous syndrome. Dev Med Child Neurol 2007; 49: 894–899.

GeNeViSTA

An approach to genetic disorders affecting the white matter

Vijayalakshmi SR and Prajnya Ranganath

Department of Medical Genetics, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Email: prajnyaranganath@gmail.com

Introduction

The white matter lies beneath the gray matter and consists of millions of nerve fibre bundles (axons) that serve as functional circuits linking different regions of the brain. White matter forms the bulk of the deep parts of the brain and the superficial parts of the spinal cord. Aggregates of gray matter are spread within the cerebral white matter. The gray matter is primarily associated with cognition and processing, while the white matter serves to conduct the action potentials and coordinate communication between different brain regions. Genetic disorders affecting the white matter of the brain are heterogeneous with variable and overlapping phenotypes. There is an ongoing process for classification of these disorders based on the genetic, histopathology and the neuroimaging pattern observed in these disorders. Few of the recent consensus definitions are as follows:

- Leukodystrophy: (Greek: leukos (white), dys – (disturbance), trophê (nutrient)-defective nutrition) refers to a group of genetic disorders primarily affecting the white matter with or without peripheral nervous system involvement. They are characterised by glial cell or myelin sheath abnormalities with magnetic resonance imaging (MRI) showing a hyperintense T2 signal in the affected white matter and a variable T1 signal (Vanderver A et al., 2015).

- Leukoencephalopathy: though often used interchangeably with leukodystrophy, actually refers to genetic or acquired disorders which have white matter changes comparable to that found in leukodystrophies, but primarily have either neuronal, vascular or systemic involvement with myelin involvement occurring as a secondary event (Vanderver A et al., 2015).

- Genetic leukoencephalopathies: have been defined as heritable white matter abnormalities which do not meet the criteria of being a leukodystrophy. Hence, all leukodystrophies are genetic encepahlopathies but not all genetic leukoencephalopathies are leukodystrophies.

Myelin and myelination

The myelin sheath, a modified plasma membrane extension of the oligodendroglial cells, spirals around the axons and encases it throughout its length except at the nodes of Ranvier. Myelin sheaths act as insulation sheaths and serve to transmit action potentials by saltatory conduction which is fast and energy efficient. Myelin also provides trophic support and protection for axons. Disturbances in myelin therefore result in motor, sensory and cognitive impairment.

Myelin is made up of an outer layer of glycolipid (galactocerebroside and sulfatide) and cholesterol, an inner phospholipid layer (phosphoinositol serine, phosphoinositol 4,5,diphosphate and ethanolamine plasmalogen) and an intervening area of hydrocarbon chains (long chain fatty acids). In addition, there are structural proteins namely the myelin basic protein (MBP) and the proteolipid protein (PLP) which maintain myelin structure and stability, the myelin-associated glycoprotein (MAG) which is essential for initiation of myelination by mediating axonal-glial contact, and myelin zero protein (MZP), myelin oligodendrocyte glycoprotein (MOP), oligodendrocyte myelin glycoprotein and 2,3-cyclic nucleotide 3-phosphodiesterase (van der Knaap, 2001).

Myelination begins as early as the 12th week of intrauterine life and occurs significantly from mid-gestation to the second year of postnatal life. Myelination is a high energy requiring process. Initiation of myelin and its maintenance is regulated by the availability of glycolytic and lipid substrates. Abnormalities of myelination can be in the form of failure of myelin formation (hypomyelination), for-

mation of abnormal myelin (dysmyelination) and loss of formed myelin (demyelination).

Classification of myelin disorders

There are various classifications of myelin disorders (based on pathological, biochemical, genetic and combined clinical/ histopathological/ biochemical criteria). As per the classification proposed by van der Knaap for myelin disorders, integrating the MRI pattern and pathophysiology (van der Knaap, 2001), all white matter disorders have been included under the umbrella term of leukoencephalopathies and these have been categorized as:

- Well defined leukoencephalopathies
- Undefined leukoencephalopathies

Under this classification, well defined leukoencephalopathies have been further subdivided into categories as listed in Table 1 (Di Rocco et al., 2004).

As per the recent GLIA (Global Leukodystrophy Initiative) Consortium consensus statement, more than 30 distinct leukodystrophy conditions have been characterized, which are listed below in the alphabetical order in Table 2 (Vanderver A et al., 2015).

Table 1 Types of well defined leukoencephalopathies.

Type of well defined leukoencephalopathy	Underlying pathophysiology	Examples
Hypomyelinating disorders	Primary disturbance in the formation of myelin	• Pelizaeus- Merzbacher (PMD) and PMD-like diseases
	Secondary to neuron or astrocyte dysfunction (including abnormal interaction between oligodendrocytes and neurons)	• Cockayne syndrome • Tay syndrome • Salla disease • GM1 and GM2 gangliosidoses • Infantile neuronal ceroid lipofuscinosis • Hypomyelination with atrophy of the basal ganglia and cerebellum (HABC) syndrome
Dysmyelinating disorders (Delayed or disturbed myelination)	• Altered sequence of myelination • Irregular pattern of myelination • Additional component of hypomyelination observed	• 18q minus syndrome • Untreated aminoacidopathies • Organic acidurias
Demyelinating disorders (leukodystrophies)	• Abnormal myelin composition • Myelin instability and subsequent loss (demyelination)	• Metachromatic leukodystrophy (reduction of cerebroside and accumulation of sulphatides which is toxic to oligodendroctyes) • X-linked Adrenoleukodystrophy (ALD) (dysfunction of microglia-inflammatory response; incorporation of very long chain fatty acids in myelin leads to membrane instability) • Krabbe disease (accumulation of cerebroside and toxic metabolite psychosine leads to oligodendrocyte death) • Peroxisomal disorders such as Zellweger syndrome, neonatal ALD and Refsum disease. (decrease in myelin substrates)

Disorders related to myelin splitting (cystic degeneration of myelin)	With myelin loss	• Canavan disease (accumulation of N-acetyl aspartate and precursor N-acetylaspartlyglutamate leads to intramyelinic edema, vacuolization and oligodendrocyte failure) • Mitochondrial disorders • 1,2-hydroxyglutaric aciduria
	Without myelin loss	• Megalencephalic leukoencephalopathy with subcortical cysts
Disorders secondary to axonal damage		• Giant axonal neuropathy
Others		• Alexander disease (primary genetic disorder of astrocytes) • Childhood ataxia with central nervous system hypomyelination (CACH) • Sjogren-Larsson syndrome • Cerebrotendinous xanthomatosis • Leukodystrophy with polyol metabolism abnormality

Table 2 Different types of leukodystrophies with the causative genes and modes of inheritance.

Disorder	Gene(s)	Pattern of inheritance
Adrenoleukodystrophy X linked (X-ALD)	• *ABCD1*	XL
Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia (ALSP): • Hereditary diffuse leukoencephalopathy with spheroids (HDLS) • Pigmentary type of orthochromatic leukodystrophy with pigmented glia (POLD)	• *CSF1R*	AD
Aicardi– Goutières Syndrome (AGS)	• *ADAR1* • *RNASEH2A* • *RNASEH2B* • *RNASEH2C* • *SAMHD1* • *TREX1*	Usually AR but maybe AD
Alexander disease (AxD)	• *GFAB*	AD
Autosomal Dominant Leukodystrophy with Autonomic disease (ADLD)	• *LMNB1*	AD
Canavan disease	• *ASPA*	AR
Cerebrotendinous Xanthomatosis (CTX)	• *CYP27A1*	AR
Chloride Ion Channel 2 (ClC-2) related leukoencephalopathy with intramyelinic oedema (leukoencephalopathy with ataxia)	• *CLCN2*	AR

eIF2B-related disorders (Vanishing White Matter Disease (VWMD) or Childhood ataxia with central nervous system hypomyelination (CACH))	• *EIF2B1* • *EIF2B2* • *EIF2B3* • *EIF2B4* • *EIF2B5*	AR
Fucosidosis	• *FUCA1*	AR
Globoid cell Leukodystrophy (Krabbe)	• *GALC* • *PSAP*	AR
Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)	• *TUBB4A*	AD
Hypomyelination with brainstem and spinal cord involvement and leg spasticity (HBSL)	• *DARS*	AR
Hypomyelination with congenital cataract (HCC)	• *FAM126A*	AR
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)	• *DARS2*	AR
Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)	• *EARS2*	AR
Megalencephalic Leukoencephalopathy with subcortical cysts (MLC)	• *MLC1* • *HEPACAM*	AR
Metachromatic leukodystrophy (MLD) and its biochemical variants	• *ARSA* • *PSAP*	AR
Oculodentodigital dysplasia (ODDD)	• *GJA1*	Usually AD maybe AR
Pelizaeus Merzbacher disease (PMD)	• *PLP1*	XL
Pelizaeus Merzbacher like-disease (PMLD)	• *GJC2*	AR
Peroxisomal Biogenesis disorders (including Zelleweger, neonatal Adrenoleukodystrophy and Infantile Refsum)	• *PEX* genes	AR
Pol-III related disorders (4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism)	• *POLR3A* • *POLR3B*	AR
Polyglucosan Body Disease (PGBD)	• *GBE1*	AR
RNAse T2 deficient leukoencephalopathy	• *RNASET2*	AR
Sialic acid storage disorders (Salla disease, Infantile sialic acid storage disease and Intermediate form)	• *SLC17A5*	AR
Single enzyme deficiencies of peroxisomal fatty acid beta oxidation: • D-Bifunctional Protein Deficiency • Sterol Carrier Protein X (SCPx) deficiency • Peroxisomal acyl-CoA-Oxidase Deficiency	• *HSD17B4* • *SCP2* • *ACOX1*	AR
Sjögren–Larsson syndrome	• *ALDH3A2*	AR
SOX10-associated PCWH - peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease	• *SOX10*	AD
18q minus syndrome	• Contiguous gene deletion involving the *MBP* gene	Majority are de novo; deletion can be inherited

AD = autosomal dominant; AR = autosomal recessive; XL = X-linked

Leukoencephalopathies include inherited vasculopathies (eg. Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and *COLA1* & *COLA2*-related disorders), inborn errors of metabolism (e.g. organic acidemias and disorders of aminoacid metabolism), disorders affecting the neurons of the cerebral cortex or other gray matter structures (e.g. infantile variants of GM1 and GM2 gangliosidosis and neuronal ceroid lipofuscinosis), those with both white and gray matter involvement (e.g. mitochondriopathies such as Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and Myoclonic Epilepsy with Ragged-Red Fibers (MERRF) syndromes, POLG-related disorders and familial hemophagocytic lymphohistiocytosis) and acquired myelin disorders (eg. multiple sclerosis) which may be of infectious or post infectious etiology or due to toxic, hypoxic or non-genetic vascular insults.

Prevalence

There is limited data on the overall prevalence of leukodystrophies and the relative frequencies of different leukodystrophies. Metachromatic leukodystrophy is reported to occur in 1 in 40,000 to 170,000 individuals world-wide (von Figura et al., 2001). Ethnic preponderance has been reported in some leukodystrophies. Canavan disease is relatively common with a high carrier frequency in the Ashkenazi Jewish population. Two common mutations (E285A and Y231X) accounting for 98% of the disease-causing alleles of the *ASPA* gene (Sistermans et al., 2001). Megalencephalic leukodystrophy with subcortical cysts (MLC) is a common leukodystrophy described in the Agarwal community in India and in a study by Gorospe et al (2004) all 31 cases tested were found to result from a common mutation (320insC) in the MLC1 gene, suggesting a founder effect in this population (Gorospe et al. 2004).

Evaluation of leukodystrophies and genetic leukoencephalopathies

The clinical diagnosis of leukodystrophies and genetic leukoencephalopathies is often challenging due to considerable overlap in the clinical features. Though the advances in recognition of the neuroimaging patterns of these disorders has improved the diagnostic yield, more than half of these disorders still remain undiagnosed.

Clinical features

The clinical features are predominantly neurologic and almost invariably affect the motor system and are progressive in nature. Extra neurologic features provide vital clues to arrive at a specific diagnosis.

Age of onset

The onset of the symptoms is variable ranging from connatal (at birth) to adulthood (Table 3) and most of these disorders present with variable severity across all age groups.

Neurologic manifestations

- Motor impairment: Motor symptoms are the predominant presenting feature in majority of the white matter disorders, while cognitive decline (personality changes and dementia) and seizures are the initial manifestations in neuronal (gray matter) disorders. These caveats may not be applicable in all cases as many disorders with primary gray matter involvement may also affect the white matter due the underlying pathology, leading to a clinical dilemma.

A variable period of normal development followed by regression is the most common presentation. The pattern of motor regression may vary in each condition (Table 4). They may also present with delayed or stagnated development in some cases.

Hypomyelinating conditions usually present as developmental delay, while genetic leukoencephalopathies are characterised by a period of normal development followed by stagnation i.e. no further acquisition of skills. Older children and adults may report frequent falls, altered gait or difficulty in sporting activities.

Spasticity and hypereflexia are characteristic signs in majority of the white matter disorders. There may be an initial hypotonia which invariably progresses to spasticity. Severe hypotonia with head lag is a feature of Canavan disease. A hypotonic infant with facial dysmorphism, seizures, dolichocephaly and a wide open anterior fontanelle may suggest Zellweger syndrome. Spasticity with diminished deep tendon reflexes occurs when the peripheral nervous system is involved as in Metachromatic leukodystrophy(MLD), Krabbe and other hypomeylinating conditions such as with *PLP*-null mutations.

Table 3 Age of onset of common leukodystrophies.

Disorder	Infantile (first year)	Late infantile (1-5yrs)	Juvenile (5-12yrs)	Adolescent and adulthood
Metachromatic leukodystrophy (MLD)		√ (most common type of MLD)	√	√
Pelizaeus Merzbacher Disease	√	√ (classic form)		
Krabbe disease	√ (classic form)	√	√	√
Alexander disease	√ (most common variant)	√	√	√
Canavan disease	√			
X-linked adrenoleukodystrophy			√	√
Childhood ataxia with central nervous system hypomyelination (CACH)	√	√	√	√
Megalencephalic Leukoencephalopathy with subcortical cysts (MLC)	√	√	√	√
Aicardi–Goutières Syndrome (AGS)	√			
Giant axonal neuropathy type I		√		
Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)	√	√		
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)		√	√	√

Table 4 Pattern of motor regression.

Gradual progressive decline	• Majority of leukodystrophies • Megalencephalic leukoencephalopathy with subcortical cysts (MLC)
Rapid decline	• Infantile Krabbe
Episodic decline (triggers may be an event of minor head trauma or febrile illness)	• Childhood ataxia with central nervous system hypomyelination (CACH)/Vanishing white matter disease • Inborn errors of metabolism • Mitochondrial disorders • Pol III related disorders • X-linked adrenoleukodystrophy

• Ataxia: Ataxia, a feature of cerebellar involvement, may occur as an isolated finding, as a predominant finding e.g. Childhood ataxia with central nervous system hypomyelination (CACH) and 4H syndrome (hypomyelination, hypodontia and hypogonadotropic hypogonadism) or in association with predominant spasticity. Sensory ataxia may be present due to impaired proprioception in

peripheral sensory system involvement.

- Extrapyramidal symptoms: Extrapyramidal symptoms appear with involvement of the deep gray nuclei and are seen in 1,2 hydroxyglutaric aciduria. Choreoathetosis is a feature of the classic form of Pelizaeus-Merzbacher disease. Dystonia, when it occurs, is usually generalised and appears as repetitive movements, torsion or abnormal posturing, which may be exacerbated by voluntary movements, emotions and physical discomfort.

- Cognitive impairment: Cognitive decline inevitably appears in the course of the disease, although the nature and severity varies. It presents as intellectual disability in childhood, or as dementia and psychiatric features in adult onset leukodystrophies. Cognitive decline can be rapid in X-ALD and lysosomal storage leukodystrophies. Relative sparing of the mental abilities is seen in MLC and CACH. Irritability is a feature of Krabbe, Canavan and Aicardi–Goutières syndromes.

- Seizures: Seizures usually occur in the more advanced stage of the disease, but may be the presenting feature of Alexander disease or may occur early in the course in Canavan, Krabbe, Cerebrotendinous Xanthomatosis (CTX), Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL), Metachromatic leukodystrophy (MLD), Oculodentodigital dysplasia (ODDD), Megalencephalic leukoencephalopathy with subcortical cysts (MLC), peroxisomal disorders, sialic acid storage disorders and Sjogren Larsson syndrome. An acute onset with focal seizures may be seen in childhood onset X-ALD. Impact seizures (following minor head trauma) are seen in MLC.

- Autonomic dysfunction: Autonomic dysfunction causes bladder (retention, incontinence), bowel (constipation/ incontinence), cardiac (arrhythmias), vascular (postural hypotension) and thermoregulatory (decreased sweating) symptoms. It is a prominent feature of adult onset or adolescent phenotypes of Alexander disease, Autosomal dominant leukodystrophy with autonomic disease (ADLD) and MLD, and can affect younger patients late in the disease.

- Others: Progressive loss may appear in speech, ability to eat (swallowing, chewing), vision and hearing as the disease advances. Deafness can occur early in mitochondrial disorders and 18q deletion syndrome. Bulbar dysfunction (palatal myoclonus and dysphonia) is unique to Alexander disease. Macro or microcephaly may be a feature of the different leukodystrophy conditions, as listed below in Table 5.

Extraneurologic manifestations

Associated extraneurologic features provide additional clues to the diagnosis. They are summarised in the following table (Table 6).

Table 5 Diagnostic clues from head circumference.

Macrocephaly
• Alexander disease- head circumference exceeds 98th centile at 6 to 18 months; obstructive hydrocephalus may be present
• Canavan disease- occurs by the first year of life; normal head size is described in some variants
• Childhood ataxia with central nervous system hypomyelination (CACH) -megalencephaly
• Megalencephalic leukoencephalopathy with subcortical cysts - megalencephaly
• 1,2-hydroxy glutaric aciduria - relative macrocephaly which is usually an inconsistent feature
• GM2 gangliosidosis - infantile Tay-Sachs and Sandhoff
Microcephaly
• Krabbe syndrome
• Cockayne syndrome
• Tay (Trichothiodystrophy) syndrome

Table 6 Extraneurologic manifestations of leukodystrophies and genetic leukoencephalopathies.

Clinical feature		Disorder
Facies		
Dysmorphism		18q microdeletion Peroxisomal disorders Cohen syndrome Costello syndrome
Coarse facies		Sialic acid storage disease, Fucosidosis, Multiple sulfatase deficiency, Mucopolysaccharidosis
Progeroid appearance		Cockayne syndrome
Dental anomalies		
Dental anomalies		Oculodentodigital dysplasia (enamel hypoplasia)
		POL III related disorders (not universal and highly variable-oligodontia, hypodontia, delayed eruption, altered sequence of eruption, abnormal colour /shape)
		Cockayne syndrome (propensity for cavities (most common), abnormal shape, hypodontia, oligodontia and enamel hypoplasia)
		Peroxisomal disorders (enamel defects of secondary teeth)
Eyes		
Cataracts	At birth	Hypomyelination with congenital cataract (HCC), Childhood ataxia with central nervous system hypomyelination (CACH) (only connatal cases), peroxisomal disorders
	Childhood onset	Cerebrotendinous Xanthomatosis
Cherry red spot		Sialidosis GM1 gangliosidosis GM2 gangliosidosis (helps differentiate from other disorders with infantile onset macrocephaly) Metachromatic leukodystrophy (some cases)
Glaucoma		Aicardi–Goutières Syndrome, Oculodentodigital dysplasia
Optic atrophy		Metachromatic leukodystrophy Canavan, Childhood ataxia with central nervous system hypomyelination (CACH), Cerebrotendinous xanthomatosis, peroxisomal disorders (+/-), Pol III related (+/-) Hypomyelinating and mitochondrial disorders
Retinitis pigmentosa (night blindness)		Refsum disease (adolescent and adults) Peroxisomal disorders
Vascular retinal defects		Cerebroretinal microangiopathy with calcifications and cysts (Coats plus syndrome)
Glistening white dots in the retina (perifoveal)		Sjogren Larsson syndrome (pathognomonic in a patient with ichthyosis)
Nystagmus	Early onset/ congenital	PMD & PMLD (prominent feature) SOX10 related disease
	Later age	Oculodentodigital dysplasia, Pol III related 4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism),18q del, Alexander, Canavan

Skin manifestations		
Angiokeratoma corporis diffusum		Fucosidosis
Icthyosis	Congenital	Sjogren Larsson syndrome
	Childhood	Multiple sulfatase deficiency Sialic acid storage disorder
	Adulthood	Refsum disease
Hyperpigmentation		X-ALD/AMN [Figure 1]
Xanthomas		Cerebrotendinous xanthomatosis
Photosensitivity		Cockayne, Tay syndrome
Chilblains		Aicardi– Goutières Syndrome
Endocrinologic manifestations		
Adrenal insufficiency		X-ALD, peroxisome biogenesis disorders
Hypothyroidism		4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism), Aicardi– Goutières Syndrome
Hypogonadotropic hypogonadism		4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism)
Ovarian dysgenesis (Premature ovarian failure)		Ovarioleukodystrophy (CACH), *AARS2* mutation-related
Hepatobiliary manifestations		
Hepatosplenomegaly		Lysosomal storage disorders's, (multiple sulfatase deficiency, galactosialidosis, sialic acid disorders)
Hepatic dysfunction		Peroxisomal disorders (isolated hepatomegaly +/- hepatic dysfunction) Aicardi– Goutières Syndrome (congenital period, rarely in infancy) Mitochondriopathies
Gall bladder dysfunction		MLD (causes gall bladder papillomatosis) Cerbrotendinous xanthomatosis (can present as neonatal jaundice)
Skeletal system		
Chondrodysplasia punctata		Peroxisomal disorders
Dysostosis multiplex		Multiple sulfatase deficiency, sialidosis
Short stature		Cockayne syndrome, 4H leukodystrophy
Hearing deficit		
Hearing impairment (Commonly central origin-sensorineural)		Peroxisomal biogenesis disorders (early onset) SOX 10 associated LD (early onset) RNAseT2 deficiency Refsum disease (adult onset)

Diagnostic workup

- Neuroimaging: MRI pattern recognition is an important step in the further workup towards a specific diagnosis of white matter disorders. Myelin assessment by MRI with associated features can provide clues to a differential diagnosis. In general, myelinated white matter is hyperintense to the cortex on T1-weighted images and hypointense to the cortex on T2-weighted images. This pattern is

reversed in demeylination with the white matter demonstrating T1 hypointensity and T2 hyperintensity relative to the cortex. While T1 weighted images are most useful for assessing myelination until the first year of life, T2-weighted images are most useful in later stages of myelination. A high signal on T2-weighted images is abnormal for cerebral white matter after 1.5 years. Furthermore, knowledge of the sequential pattern of myelination is essential for distingushing abnormal and normal patterns of myelination.

The minimum sequences recommended are (Parikh et al., 2015):

- Sagittal T1
- Axial T1
- T2 weighted
- Fluid attenuated inversion recovery (FLAIR) (Cystic lesions are best detected using FLAIR studies)

Figure 1 Generalised skin hyperpigmentation in a patient with juvenile onset X -linked adrenoleukodystrophy (confirmed by plasma VLCFA analysis).

Table 7 Hypomyelination on MRI.

With cerebellar involvement (inconstant)	**Normal corpus callosum** • Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) • Oculodentodigital dysplasia **Thin corpus callosum** • 4H syndrome - hypomyelination, hypodontia and hypogonadotropic hypogonadism) • Salla disease • Fucosidosis • Cockayne • PMD
With basal ganglia involvement	• Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) (atrophy especially putamen) • Oculodentodigital dysplasia • Fucosidosis (globus pallidus) • Mucolipidosis type IV
With absence of cerebral atrophy (or atrophy in late stages) with normal basal ganglia	• 18q del (cerebellar hypoplasia) • Hypomyelination with congenital cataract (HCC) • HEMS (hypomyelination of early myelinating structure) • PMD • PMLD (hypomyelination of brainstem especially pons) • Salla disease • SOX 10 associated disorders
With global atrophy	• Infantile sialic acid storage disorders • Aicardi– Goutières Syndrome (calcifications present)

Other specific sequences include:

- Contrast administration- for disorders with an inflammatory component eg. cerebral X-ALD
- Susceptibility weighted- for disorders with calcifications eg. Aicardi– Goutières Syndrome, Cockayne syndrome (basal ganglia calcifications), Krabbe (calcifications of thalami, basal ganglia and putamen)
- MR spectroscopy (MRS)- lactate peak is seen in mitochondrial disorders and Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), while a markedly increased N-acetyl aspartate (NAA) peak is typical of Canavan disease.
- Diffusion weighted- for AARS2-related leukoencephalopathy

Serial imaging with an interval of atleast 6-12 months is pertinent to distinguish between permanent hypomyelination and delayed myelination especially in children less than 2 years of age. CT scan is useful for detecting calcifications.

A stepwise approach to recognising the MRI pattern helps in differentiating various white matter disorders (Schiffmann & van der Knaap, 2009). This involves first recognising whether it is hypomyelination or delayed myelination or demyelination.

- Hypomyelination: Hypomyelination on MRI is characterised by mild T2 hyperintensity in combination with T1 hyperintensity (=normal signal), T1-isointensity or mild T1-hypointensity relative to gray matter structures. Table 7 lists the conditions with hypomyelination and additional findings which provide a possible clue to diagnosis.

- Demyelination: Demyelination on MRI is characterised by prominent T2 hyperintensity with prominent T1 hyporintensity relative to gray matter structures. These can be further analysed as to whether they are confluent or isolated and multifocal and further on the area of predominance of the lesion. Confluent and bilateral symmetric lesions are characteristic of genetic white matter disorders while isolated and multifocal are suggestive of acquired causes such as infections and vasculopathies and is also seen in structural chromosomal disorders. Table 8 lists the conditions with confluent lesions and their area of predominance.

- Delayed myelination: Improvement of myelination on serial MRI is suggestive of delayed myelination and can occur in SOX 10 related, MCT8 related and other neuronal disorders.

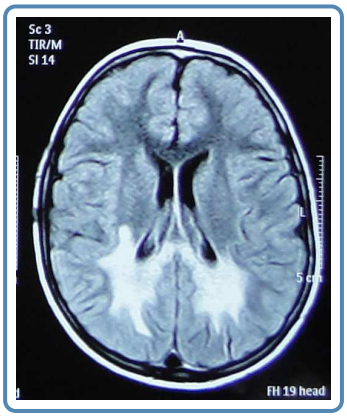


Figure 2 Brain MRI (axial FLAIR image) showing bilateral deep white matter involvement with posterior predominance and sparing of the subcortical U fibers in X-linked adrenoleukodystrophy. (Courtesy: Dr Shubha R Phadke, SGPGIMS, Lucknow)

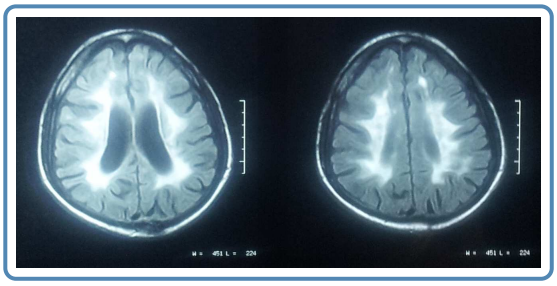


Figure 3 MRI brain (axial FLAIR image) showing periventricular hyperintensities in the frontal and parieto occipital region in metachromatic leukodystrophy.

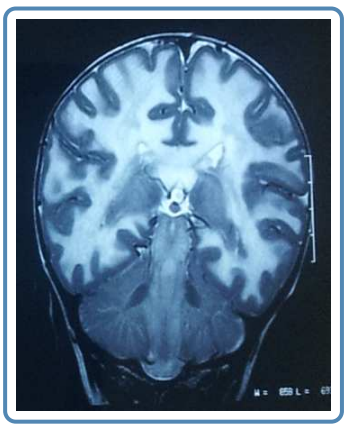


Figure 4 MRI brain (coronal FLAIR image) showing diffuse extensive white matter involvement in Canavan disease.

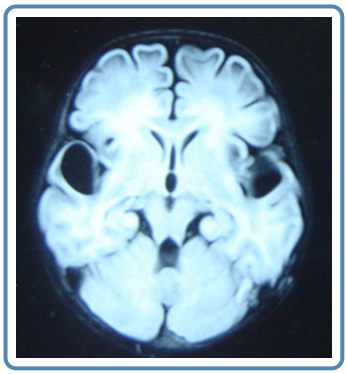


Figure 5 MRI brain (axial FLAIR image) showing diffuse white matter involvement with temporal subcortical cysts in a case of megalencephalic leukoencephalopathy with subcortical cysts (van der Knaap disease).

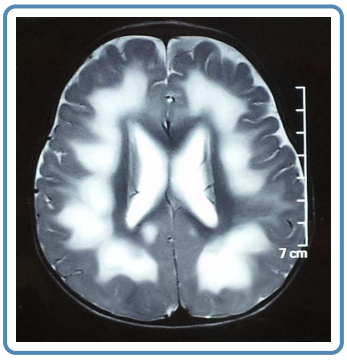


Figure 6 MRI brain (axial T2 image) showing periventricular deep white matter as well as subcortical white matter involvement in a case of Leigh disease.

Table 8 Disorders with MRI features of demyelination and confluent lesions and their area of predominance.

Confluent lesions	
Predominant localization	**Disorder**
Frontal	• Alexander disease • Metachromatic leukodystrophy • Aicardi– Goutières Syndrome • X-ALD (frontal variant) • Hereditary diffuse leukoencephalopathy with spheroids (HDLS)
Pareito-occipital	• X-ALD (involvement of splenium of corpus callosum and sparing of the occipital arcuate fibers) [Figure 2] • Krabbe • Adult Polyglucosan Body Disease (PGBD) • Early onset peroxisomal disorders • Neonatal hypoglycemia
Periventricular	• MLD (sparing of the arcuate fibers) [Figure 3] • Krabbe (sparing of the arcuate fibers) • Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) (sparing of the arcuate fibers) • Sjogren Larsson syndrome • Adult Polyglucosan Body Disease (PGBD) • Oculodentodigital dysplasia • Inborn errors of metabolism • Periventricular leukomalacia • HIV related encephalopathy
Subcortical	• Canavan [Figure 4] • L2 glutaric aciduria • Propionic acidemia • Urea cycle defects • Ribose 5 phosphate isomerase deficiency

	• Kearns Sayre syndrome • Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)
Diffuse cerebral	• Childhood ataxia with central nervous system hypomyelination (CACH) / vanishing white matter disease (cystic degeneration of white matter) • Megalencephalic leukoencephalopathy with subcortical cysts (subcortical sycts in the anterior-temporal regions with sparing of central white matter) [Figure 5] • Inborn errors of metabolism • Early onset peroxisomal disorders • Laminin alpha 2 deficiency • Mitochondrial defects [Figure 6] • End stage of progressive white matter disorders
Posterior fossa	Cerebellum + middle cerebellar peduncles + Brainstem predominance • Peroxisomal disorders • Alexander disease • Autosomal Dominant Leukodystrophy with Autonomic disease (ADLD) • Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) • Mitochondriopathies
	Cerebellum and cerebellar peduncles predominance • Histiocytosis • Early onset Mple syrup urine disease • Cerebrotendinous xanthomatosis • FMR1 premutation • FA2Hrelated disorders • Heroin and cocaine toxicity
	Brainstem predominance • Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL) • Adult Polyglucosan Body Disease (PGBD) • Wilson disease • Leigh syndrome • Dentatorubral-pallidoluysian atrophy (DRPLA)
Temporal	• Menkes disease • Herpes simplex encephalitis • Aicardi– Goutières Syndrome (AGS) • Congenital Cytomegalovirus infection • RNASET2 deficiency

Metabolic testing

Serial biochemical testing can be done to look for the disease etiology. The type of testing, either biochemical testing or direct single gene testing, may be dictated by the clinical and neuroimaging findings. If a specific etiology cannot be conclusively established by clinical evaluation and imaging features then an approach of ruling out the rapidly diagnosable and those with treatment options may be undertaken. Table 9 lists the biochemical screening tests and the specific target disorders. It is also important to rule out nutritional deficiencies which can cause white matter changes such as vitamin B12 deficiency which can be treated. Some laboratory tests useful in diagnosing genetic white matter disorders are listed below in Table 9.

Table 9 Some laboratory tests useful in diagnosing genetic white matter disorders.

Screening test		Disorder
Enzyme assays		Krabbe (galactosyl cerebrosidase) MLD (arylsulphatse A) Multiple sulfatase deficiency (arylsulphatase A,B,C,D) GM1 gangliosidosis (beta galactosidase) GM2 gangliosidosis (hexosaminidase A & B) Sialidosis (neuraminidase) Galactosialidosis (neuraminidase + beta galactosidase)
Urinary Analysis	Sulfatides	MLD
	Glysoaminoglycans	Multiple sulfatase deficiency
	Organic acids	L2 glutaric aciduria (↑ concentration of L-2-hydroxyglutaric acid and lysine) Canavan disease (↑ N-acetylaspartic acid) Mitochondrial disorders (Krebs cycle intermediates)
	Aminoacids	Aminoacidopathies
Plasma Very long chain fatty acids		ALD (C26:0, ↑ ratio of C24:0 to C22:0, ↑ ratio of C26:0 to C22:0) Peroxisomal biogenesis disorders Peroxisomal beta oxidation defects
Plasma cholestanol		CTX
Mitochondrial disorders Blood lactate, pyruvate, aminoacids		

Other tests

Additional specific testing can be done at the discretion of the physician and as required, to detect abnormalities which may either provide additional diagnostic clues or may help in the overall patient management such as ophthalmologic evaluation (including slit lamp examination and fundoscopy), hearing evaluation, endocrinologic workup and neurophysiologic studies such as BAER, EMG/NCV,VEP, SSEP) to characterise the involvement of cranial and peripheral nerves (AMN, MLD, Krabbe), optic tracts and spinal tracts.

Molecular genetic testing

Molecular diagnostic confirmation can be done by sequence analysis of the relevant gene, based on the recognition of a definitive pattern in MRI or based on the metabolic testing results. However, for many of the leukoencephalopathies, especially the rarer types, there is often a significant overlap in the clinical and neuroimaging features and reliable metabolic testing may not be available; therefore, broad spectrum testing in the form of next generation sequencing-based multigene panel testing for leukodystrophy and genetic leukoencephalopathy genes or whole exome sequencing can be applied to come to a conclusive diagnosis.

Management

Treatment options in general at present are largely symptomatic and supportive, while curative therapies are limited and inadequate. Supportive therapy is aimed at improving the quality of life and involves various strategies, common as well as tailored to individual needs. These include management of spasticity (medications, physiotherapy, orthotics), seizure control and prevention (anticonvulsants), surgical release of contractures and scoliosis correction, gastrostomy for severe dysphagia, proper wheelchair seating, special education, assistive communication devices, and nutritional support.

Genetic counseling is an important component of management of these conditions and the affected families can be offered appropriate counseling about the recurrence risks and about prenatal diagnostic testing options to prevent re-

currence.

Specific therapies are available for certain disorders. Early hematopoietic stem cell transplantation (HSCT), though not curative, attenuates the clinical course and prolongs survival of infantile Krabbe disease and X-ALD. Dietary therapy with oral chenodeoxycholic acid (750 mg/day) corrects the biochemical abnormalities and reverses symptoms in Cerebrotendinous xanthomatosis. Hormone therapy can be life saving by preventing Addisonian crisis in susceptible individuals with X-ALD. Early institution (prior to occurrence of MRI abnormalities) of oral Lorenzo's oil (erucic acid and oleic acid combination) lowers plasma levels of very long chain fatty acids (VLCFA) in patients with X-ALD. Early recognition can be beneficial in those conditions with definite treatment options, and on the whole, preventive, symptomatic and supportive care with multidisciplinary involvement, are of prime importance in the management of patients with genetic white matter disorders.

References

1. Di Rocco M, et al. Genetic disorders affecting white matter in the pediatric age. Am J Med Genet B Neuropsychiatr Genet. 2004; 129B: 85-93.
2. Gorospe JR, et al. Indian Agarwal megalencephalic leukodystrophy with cysts is caused by a common *MLC1* mutation. Neurology 2004; 62: 878-82.
3. Parikh S, et al, A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. Mol Genet Metab 2015; 114: 501-515.
4. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. Neurology 2009; 72:750-759.
5. Sistermans EA, et al. Mutation detection in the aspartoacylase gene in 17 patients with Canavan disease: four new mutations in the non-Jewish population. Europ J Hum Genet 2000; 8: 557-560.
6. van der Knaap MS. Magnetic resonance in childhood white matter disorders. Dev Med Child Neurol 2001; 43:705-712.
7. Vanderver A, et al. Case definition and classification of leukodystrophies and leukoencephalopathies. Mol Genet Metab 2015; 114: 494-550.
8. von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2001: 3695-3724.

GeNeXpreSS

Therapy for genetic disorders: How far have we come?

Dhanya Lakshmi

Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh

Email: dhanyalakshmi@gmail.com

How to make short a bit longer?

(Klag & Horton, 2016)

Achondroplasia is the most common chondrodysplasia in humans. Gain of function mutation in the *FGFR3* causes achondroplasia. *FGFR3* is a receptor tyrosine kinase, which negatively regulates growth plate activity, leading to short stature. C Natriuretic Peptide (CNP) was identified as an antagonist of fgfr3 in mouse models. CNP has a low plasma half life and hence a synthetic analogue, BMN111 was developed. BMN111 (Vosoritide) is the only candidate therapy to enter clinical trial. Recently the data of treatment of 26 children with a dosage of 15micro g/kg/ day for 6 months was released. Ten children showed 50% increase in annual growth velocity compared to their pretreatment rate. Only mild adverse effects like head ache, back pain and cough were noted. Future research is aimed at developing strategies to deliver the drug to the affected growth plate, so that adverse effects due to systemic administration can be minimized.

Modifying beta thalassemia by changing alpha genes (Mettananda et al., 2015)

Alpha globin genes have been identified as a target for modifying the disease phenotype in beta thalassemia. Alpha chain precipitation leads to most of the cellular pathogenic mechanisms of beta thalassemia. Alpha genes may be silenced by RNA interference. Voon et al. have shown a 50% reduction in alpha gene expression in murine primary erythrocytes, by using siRNA targeting alpha globin mRNA. This was associated with a significant improvement in phenotype. Xie et al. used lentiviral vectors with shRNA targeting alpha globin gene, producing transgenic mice with 25-30% less alpha globin. There is evidence that the upstream enhancer element MCS-R2 plays a critical role in alpha gene expression. Using genome editing tools like zinc finger nucleases and CRISPER cas 9, disruption of this single element has a potential to become an effective therapeutic strategy in beta thalassemia.

Gene therapy in Sanfilippo disease

(Ribera et al., 2014; OÇonnor & Boulis, 2015)

Sanfilippo disease (Type III MPS) is caused by mutations in the gene for alpha N acetyl glucosaminidase (NAGLU), causing accumulation of heparan sulfate in lysosomes, especially in the central nervous system. Ribera et al. injected AAV9 vectors encoding for NAGLU into the cerebrospinal fluid (CSF) of MPS Type III mice and demonstrated restoration of normal enzyme activity in the brain. Treated animals showed reversal of behavioral phenotype and extended the life span. Normal level of enzyme activity was noted in the CSF of canine models with pre-existing antibodies, after being treated with AAV9, demonstrating that CNS efficacy is not compromised in patients seropositive for AAV antibodies.

Ultrasound restores memory in Alzheimer disease (Leinenga & Gotz, 2015)

Amyloid beta peptide is responsible for the pathogenesis of Alzheimer disease. Gerhard Leinenga and Jürgen Götz, from Australia, used repeated ultrasound scanning on mice models with Alzheimer disease and showed that there was a significant decrease in the plaque burden compared to non treated mice. This was proposed as a novel non pharmacologic agent to improve the memory in Alzheimer disease.

References

1. Klag K, Horton W. Advances in treatment of achondroplasia and osteoarthritis. Hum Mol Genet 2015; ddv419. [Epub ahead of print]
2. Leinenga G, Gotz J. Scanning ultrasound removes amyloid and restores memory in an Alzheimer's disease mouse model. Sci Transl Med 2015; 7: 278ra33-278ra33.
3. Mettananda S, et al. Alpha Globin as a molecular target in the treatment of beta thalassemia. Blood 2015; 125:3694-3701.
4. O'Connor D, Boulis N. Gene therapy for neurodegenerative diseases. Trends Mol Med 2015; 21: 504-512.
5. Ribera A, et al. Biochemical, histological and functional correction of mucopolysaccharidosis Type IIIB by intra-cerebrospinal fluid gene therapy. Hum Mol Genet 2014; 24: 2078-2095.

National Task Force Multicentric Collaborative Study of the Clinical Biochemical and Molecular Characterization of Lysosomal Storage Disorders in India

The Department of Health Research and Indian Council of Medical Research have constituted a National Task Force to perform a multicentric collaborative study at different research institutes across the country. The goal is to establish a smooth network of referral and counselling facilities for affected families. Accurate data management is planned to understand the overall impact of lysosomal disorders on patients, families and the communities. Nine different centres conduct mutation screening for about 30 different lysosomal storage disorders. Interested physicians can contact the principal investigators directly for mutation analysis. Further information can be found at,

http://www.icmrmetbionetindia.org/task-force-disoredrs.php

Lysosomal Storage Disease	Genes Tested	Principal Investigator (PI) and Co-PI	Centre
MPSI Hurler Syndrome	IDUA	Dr Madhulika Kabra madhulikakabra@hotmail.com Dr Neerja Gupta neerja17aiims@gmail.com	**AIIMS** All India Institute of Medical Sciences, New Delhi
Sanfilippo syndrome Type A/MPSIII A	SGSH		
Sanfilippo syndrome Type B/MPSIII B	NAGLU		
Sanfilippo syndrome Type C/MPSIII C	HGSNAT		
Sanfilippo syndrome Type D/MPSIII D	GNS		
Fucosidosis	FUCA1		
Gaucher Disease	GBA	Dr Jayesh Sheth jshethad1@gmail.com	**FRIGE** Foundation For Research in Genetics and Endocrinology, Ahmedabad
Juvenile Onset NCL	PPT1 TPP1		
Tay-Sachs/GM2 gangliosidosis	GM2A HEXA		

Niemann-Pick Disease Type A	SMPD1	Dr Ashwin Dalal ashwindalal@gmail.com Dr Prajnya Ranganath prajnyaranganath@gmail.com	**CDFD** Centre for DNA Fingerprinting and Diagnostics, Hyderabad
Niemann-Pick Disease Type C 1	NPC1		
Niemann-Pick Disease Type C 2	NPC2		
Mucolipidosis I/Sialidosis	NEU1		
Mucolipidosis II (I Cell Disease) & Mucolipidosis III A/B (Pseudo-Hurler polydystrophy)	GNPTAB /GNPTG		
Mucolipidosis type IV	MCOLN1		
Farber disease	ASAH		
MPS VI Maroteaux-Lamy	ARSB		
MPS VII Sly Syndrome	GUSB		
Sandhoff disease/GM2 gangliosidosis-Infantile	HEXB	Dr Parag Tamhankar paragtmd@gmail.com Dr Susan Thomas thomass@nirrh.res.in	**NIRRH** National Institute for Research in Reproductive Health, Mumbai
Krabbe disease	GALC		
Activator Deficiency/GM2 Gangliosidosis	GM2A		
Alpha-mannosidosis	MAN2B1		
Beta Mannosidosis	MANBA		
Morquio Type A/MPS IVA	GALNS	Dr Girisha KM girishkatta@gmail.com	**KMC** Kasturba Medical College, Manipal
GM1 gangliosidosis	GLB1		
Metachromatic Leukodystrophy	ARSA	Dr Seema Kapoor drseemakapoor@gmail.com	**MAMC** Maulana Azad Medical College, New Delhi
Sphingolipid activator protein deficiencies	PSAP		
Infantile Free Sialic Acid Storage Disease /ISSD	SLC17A5		
Gaucher Disease	GBA	Dr Sankar VH sankarvh@gmail.com	**SATH** SAT Hospital, Trivandrum
Galactosialidosis	PPGB		
Fabry disease	GLA	Dr Shubha Phadke shubharaophadke@gmail.com	**SGPGIMS** Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow
MPS II Hunter syndrome	IDS		
Schindler disease	α-NAGA		
Pycnodysostosis	CTSK		
Wolman disease	LIPA		
Pompe Disease/Glycogen storage disease type II	GAA	Dr Ratna Dua Puri ratnadpuri@yahoo.com	**SGRH** Sri Ganga Ram Hospital, New Delhi
Multiple sulfatase deficiency	SUMF1		
Aspartylglucosaminuria	AGA		

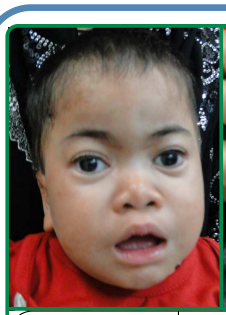
PhotoQuiz - 32

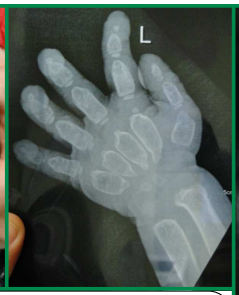
Contributed by: Dr. Shubha R Phadke

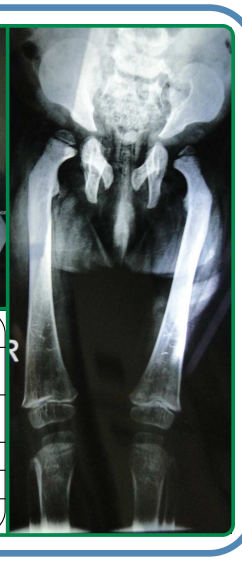
Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow
Email: shubharaophadke@gmail.com

This 3 year old male child presented with global developmental delay, growth failure and coarse facies. Radiographs of the pelvis, bilateral hip joints, femurs and knee joints and left hand are shown. Results of the metabolic testing done are also shown. Identify the condition.

Please send your responses to editor@iamg.in
Or go to http://iamg.in/genetic_clinics/photoquiz_answers.php
to submit your answer.







Nature of specimen	Blood (Plasma)			
Method	Fluorimetric assay using 4-Methyl Umbelliferone, and Spectrophotometric assay using Para nitro catchecol sulphate			
Enzyme Assay	ArylsulphataseA (nmol/hr/ml)	Total Hexosaminidase (nmol/hr/ml)	Hexosaminidase A (nmol/hr/ml)	Hexosaminidase B (nmol/hr/ml)
TEST	650.26	59335	16732	42603
CONTROL	15.5	1325	882	443
NORMAL VALUES	7 - 50	800 - 1600	464 - 1088	336 - 512

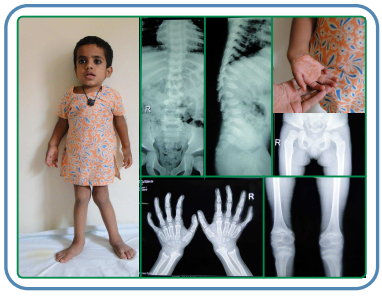
Answer to PhotoQuiz 31

Mucopolysaccharidosis Type IV (OMIM # 253000 & 253010)

Mucopolysaccharidosis (MPS) type IV, also known as Morquio syndrome, is an autosomal recessive lysosomal storage disorder characterized by short stature, dysostosis multiplex, significant skeletal deformities, mild coarsening of facies and variable degree of corneal clouding and hepatospleno-megaly. Affected individuals have normal intelligence. MPS IVA is caused by homozygous or compound heterozygous mutations in the *GALNS* gene on chromosome 16q24, which result in deficient activity of the lysosomal enzyme galactosamine-6-sulfate sulfatase. MPS IVB is caused by homozygous or compound heterozygous mutations in the *GLB1* gene on chromosome 3p22, which result in deficient activity of the beta-galactosidase enzyme.

Correct Responses Were Given By:

1. Adhisivam B, Pondicherry
2. Risha Nahar Lulla, Hyderabad
3. Poonam Singh Gambhir, Lucknow
4. Mohandas Nair, Kozhikode
5. Diksha Shirodkar, Goa
6. Gireesh S, Kozhikode
7. Ravi Goyal, Kota, Rajasthan
8. Namrata Das, Bhubaneshwar



Gaucher Disease

A Treatable Lysosomal Storage Disorder

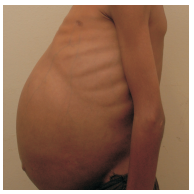
YOU can make the difference!

- Chronic progressive disease with multi-systematic pathology
- Inherited enzyme insufficiency
- May cause disability, negatively impact quality of life and shorten life span
- Causing hepatosplenomegaly, anemia, thrombocytopenia and bone involvement
- Increases the risk of hematological malignancies, in particular multiple myeloma (up to 50x)
- Majority of children with Gaucher disease will see a pediatrician in their pursuit of a diagnosis!

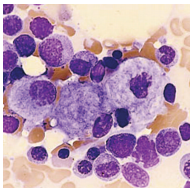
- A simple Dried Blood Spot (DBS) test can be used to definitely establish the diagnosis

Early recognition of Gaucher disease is important because safe and effective treatment is available with Cerezyme (imiglucerase for injection).

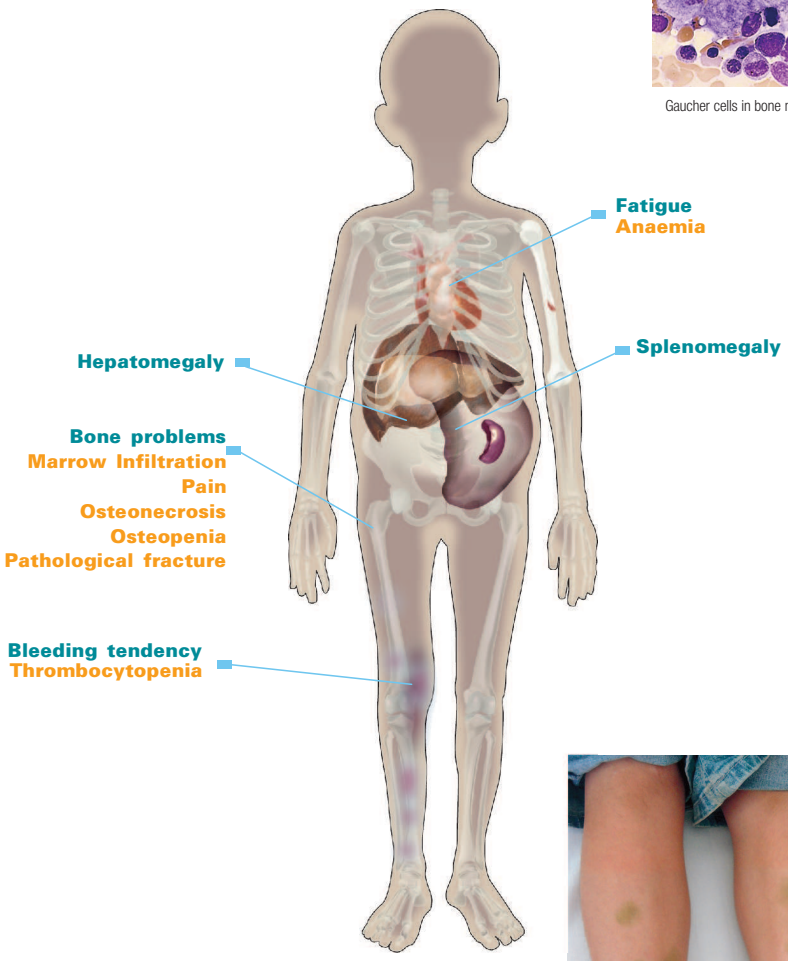
Cerezyme™
imiglucerase



Enlarged Liver and Spleen



Gaucher cells in bone marrow



Hematoma[6]

COMPLIMENTARY DRIED BLOOD SPOT TESTING KIT & SERVICE FROM GENZYME FOR DIAGNOSIS OF GAUCHER DISEASE

To place a request for your complimentary kit or to know more about the "Free of Cost" testing service, Gaucher Disease and Cerezyme, you can sms **LSD** to **9225592255**, or email us at: **lsdinfoindia@genzyme.com**. You can also contact the Genzyme India office at **09560552265**.

References: 1.Weinreb N et al. Clin Genet 2007 June; 71(6): 576-588. 2.Grabowski GA Lancet 2008 Oct. 372: 1263-1271. 3.Weinreb N et al. Am J Hematol. 2008 Dec. 83 (12): 896-900. 4.De Fost M et al. Blood Cells Mol Dis. 2006 Jan-Feb; 36 (1), 53 – 58. 5.Keutzer J Clin Therap 2009, 31, Supplement 3, Page S176. 6.Courtesy of Dr. E. Mengel

genzyme
A SANOFI COMPANY

1st Floor, Technopolis, Golf Course Road, Sector - 54, Gurgaon - 122 001, Haryana, India
+91 124 452 8300 +91 124 452 8400 www.genzyme.in

CZINA140709(b)