Hunter Syndrome: A Rare Case Report

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Abstract
Hunter syndrome, also known as mucopolysaccharidosis type II (MPS II), is a rare hereditary lysosomal storage disorder caused by mutations in the IDS gene. This leads to a lack of the lysosomal enzyme iduronate-2. Sulfatase (I2S), causing glucose accumulation and causing progressive lysosomal storage of GAGs in various organs. Diagnosis involves molecular traits, biochemical measurements, and clinical aspects. As patients age, it is crucial to ensure proper transition from paediatric to adult healthcare.Neuronopathic MPS II has involvement of the central nervous system, while non-neuropathic MPS II does not affect the central nervous system.Dermatan sulfate accumulation predominantly takes place in the non-neuronopathic type, sparing the central nervous system.
Keywords: Hunter Syndrome, Mucopolysaccharidosis Type II, Glycosaminoglycans (GAGs)

Introduction

Hunter syndrome, also referred to as mucopolysaccharidosis type II (MPS II), is a rare recessively inherited lysosomal storage disorder that is X linked.The lysosomal enzyme iduronate-2-sulfatase (I2S), which catalyses the hydrolysis of 2-sulfate groups on dermatan sulfate and heparan sulfate, lacks in the disorder.The IDS gene mutations responsible for this deficit allow glycosaminoglycans (GAGs) to accumulate extracellularly and lysosomally. Since the disorder is X-linked recessive, men are nearly always affected. Although there have been reports of impacted female patients, carriers of the mutant IDS gene are asymptomatic.[1]In virtually all cell types, tissues, and organs, increasing abnormal lysosomal storage of GAGs is the hallmark of the clinical phenotype of MPS II.GAG deposition in the oropharynx and tracheobronchial areas causes macroglossia, supraglottic constriction, and tracheomalacia, which are severe airway obstructions.[2]Airway blockage and sleep apnoea are caused by this obstructive anatomy and physiology.Cardiomyopathy, heart valve dysplasia, and hepatosplenomegaly are caused by GAG deposition in the heart, liver, and spleen.Joint and bone involvement leads to significant abnormalities of the skeleton and restricted joint movement.A protrusion of the tongue that might impair swallowing and speech clarity, as well as unique facial features and relatively large weight and length parameters at birth, comprise the clinical picture. Deficit in hearing is also prevalent.[3]

Case Report

A 3 years female patient reported to the department of oral medicine and Radiology, St Joseph Dental College complains of blackish discoloration of teeth at the upper and lower front teeth region of jaw in the past 1 year.Patient gives h/o blackish discoloration teeth in the last one year. No h/o pain and sensitivity of teeth, topical application of medicament, h/o stiffness of both upper and lower limbs, h/o increased gingiva on the tooth surface in the past 1 year.No h/o consanguine marriage or her parents.General Physical examination:Gait- Waddling gait is evident,built: Endomorphic (Short and thick body proportion), Clubbing is evident.

Figure 1: Showing Gait of the Patient

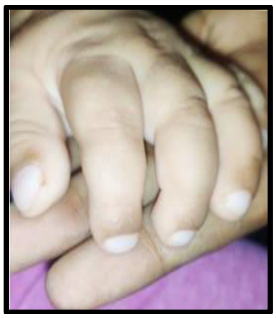


Figure 2: Showing Clubbing

Extra Oral Examination

Shape of head: Dolichocephaly (Long and narrow head), Posture: Kyphosis (Posterior rounding of thoracic spine, short neck, Stright profile, Gross facial asymmetry is evident on the right side of the face, Sparse hair is evident, Depressed sternum and frontal bossing is evident.

Figure 3:Showing Poster of the Patient

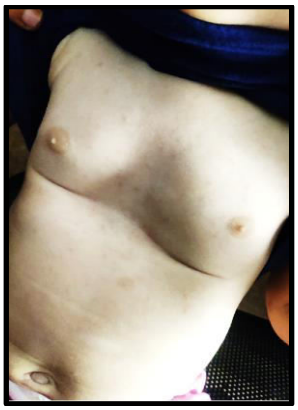


Figure 4: Showing Depressed Strenum

Soft Tissue Examination

Erythematous and soft in consistency and fibrotic gingiva, High frenal attachment is evident on upper labial mucosa.

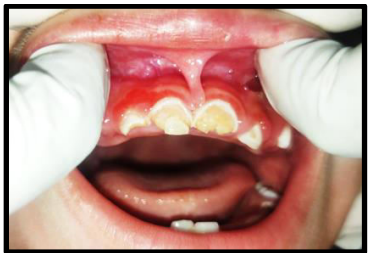


Figure 5: Showing Erythematous Gingiva & High Frenal Attachment

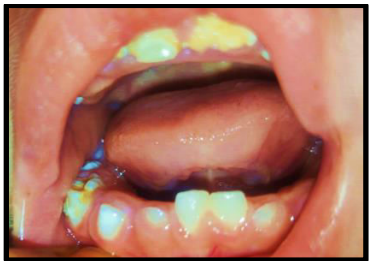


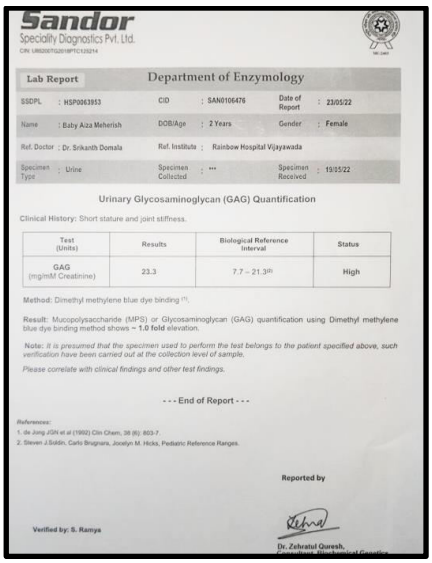
Figure 6: Showing Hypoplastic Teeth

Hard Tissue Examination

Hypoplastic Enamel is evident and deep dental caries irt 74,75. Clinical Diagnosis was given as congenital gingival Hyperplasia involving upper and lower arches, Syndrome Manifestations. Differential Diagnosis is given as Hurler syndrome, Scheie syndrome, Hunter and Sanfilippo syndrome, MaroteauxLamy syndrome, Morquio syndrome. Some of relative clinical features of Lysosomal storage disease like Skeletal findings include dwarfism, with rather characteristic radiologic changes of hands and the lumbar vertebral column, stiff articulation and Coarse facies.Patients with hurler syndrome usually die by they are aged 5-10years. The life expectancy of patients with Scheie syndrome may be normal, they can live until the fifth or six decades of life, and they can have healthy offspring. As for patients with Hunter syndrome and Sanfilippo syndrome, death usually occurs by the time of puberty.In classic form of Morquio syndrome long term survival is rare, with death occurring in persons aged 20-40 years.

Investigations Advised

1.Urinary Glycosaminoglycans (GAGs) Quantification
2.Enzyme analyses of Aryl Sulphate A and Alpha Iduronidase: for diagnosis of Metachromatic Leukodystrophy (MLD) and Hurler (MPS I) diseases respectively
3.Clinical Phenotype
4.X-Ray Pelvis (A-P) View



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Lab Report — Department of Enzymology

SSDPL	: HSP0063953	CID	: SAN0106476	Date of Report	: 23/05/22
Name	: Baby Aiza Meherish	DOB/Age	: 2 Years	Gender	: Female
Ref. Doctor	: Dr. Srikanth Domala	Ref. Institute	: Rainbow Hospital Vijayawada		
Specimen Type	: Urine	Specimen Collected	: ---	Specimen Received	: 19/05/22

Urinary Glycosaminoglycan (GAG) Quantification

Clinical History: Short stature and joint stiffness.

Test (Units)	Results	Biological Reference Interval	Status
GAG (mg/mM Creatinine)	23.3	7.7 - 21.3[R]	High

Method: Dimethyl methylene blue dye binding [1].

Result: Mucopolysaccharide (MPS) or Glycosaminoglycan (GAG) quantification using Dimethyl methylene blue dye binding method shows ~ 1.0 fold elevation.

Note: *It is presumed that the specimen used to perform the test belongs to the patient specified above, such verification have been carried out at the collection level of sample.*

Please correlate with clinical findings and other test findings.

--- End of Report ---

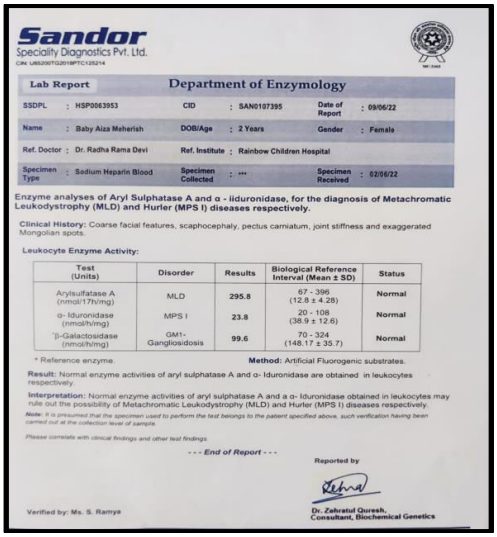
References:
1. de Jong JGN et al (1992) Clin Chem, 38 (6): 803-7.
2. Steven J.Soldin, Carlo Brugnara, Jocelyn M. Hicks, Pediatric Reference Ranges.

Reported by

Verified by: S. Ramya

Dr. Zehratul Quresh,

Figure7: Showing results of Urinary Glycosaminoglycan quantification



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Lab Report — **Department of Enzymology**

SSDPL	: HSP0063953	CID	: SAN0107395	Date of Report	: 09/06/22
Name	: Baby Aiza Meherish	DOB/Age	: 2 Years	Gender	: Female
Ref. Doctor	: Dr. Radha Rama Devi	Ref. Institute	: Rainbow Children Hospital		
Specimen Type	: Sodium Heparin Blood	Specimen Collected	: ***	Specimen Received	: 02/06/22

Enzyme analyses of Aryl Sulphatase A and α - Iiduronidase, for the diagnosis of Metachromatic Leukodystrophy (MLD) and Hurler (MPS I) diseases respectively.

Clinical History: Coarse facial features, scaphocephaly, pectus carniatum, joint stiffness and exaggerated Mongolian spots.

Leukocyte Enzyme Activity:

Test (Units)	Disorder	Results	Biological Reference Interval (Mean ± SD)	Status
Arylsulfatase A (nmol/17h/mg)	MLD	295.8	67 - 396 (12.8 ± 4.28)	Normal
α- Iduronidase (nmol/h/mg)	MPS I	23.8	20 - 108 (38.9 ± 12.6)	Normal
β-Galactosidase (nmol/h/mg)	GM1-Gangliosidosis	99.6	70 - 324 (148.17 ± 35.7)	Normal

* Reference enzyme. **Method:** Artificial Fluorogenic substrates.

Result: Normal enzyme activities of aryl sulphatase A and α- Iduronidase are obtained in leukocytes respectively.

Interpretation: Normal enzyme activities of aryl sulphatase A and α- Iduronidase obtained in leukocytes may rule out the possibility of Metachromatic Leukodystrophy (MLD) and Hurler (MPS I) diseases respectively.

Note: It is presumed that the specimen used to perform the test belongs to the patient specified above, such verification having been carried out at the collection level of sample.

Please correlate with clinical findings and other test findings.

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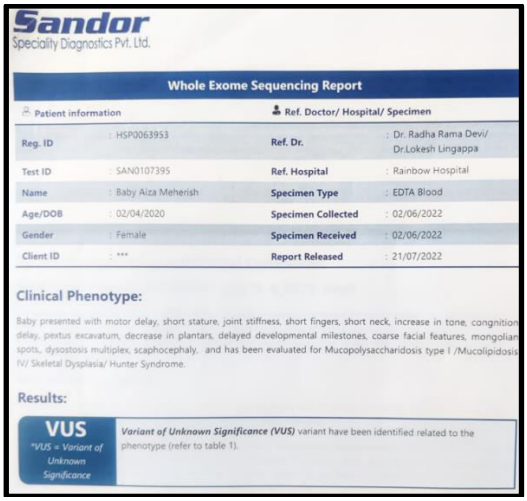
Verified by: Ms. S. Ramya

Dr. Zahratul Quresh,
Consultant, Biochemical Genetics

Figure 8: Showing Results of Leukocyte Enzyme Activity



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Whole Exome Sequencing Report

Patient information		Ref. Doctor/ Hospital/ Specimen	
Reg. ID	: HSP0063953	Ref. Dr.	: Dr. Radha Rama Devi/ Dr.Lokesh Lingappa
Test ID	: SAN0107395	Ref. Hospital	: Rainbow Hospital
Name	: Baby Aiza Meherish	Specimen Type	: EDTA Blood
Age/DOB	: 02/04/2020	Specimen Collected	: 02/06/2022
Gender	: Female	Specimen Received	: 02/06/2022
Client ID	: ***	Report Released	: 21/07/2022

Clinical Phenotype:

Baby presented with motor delay, short stature, joint stiffness, short fingers, short neck, increase in tone, congnition delay, pextus excavatum, decrease in plantars, delayed developmental milestones, coarse facial features, mongolian spots,, dysostosis multiplex, scaphocephaly, and has been evaluated for Mucopolysaccharidosis type I /Mucolipidosis IV/ Skeletal Dysplasia/ Hunter Syndrome.

Results:

VUS **VUS = Variant of Unknown Significance*

Variant of Unknown Significance (VUS) variant have been identified related to the phenotype (refer to table 1).

Figure 9: Showing Results of Whole Exome Sequencing Report

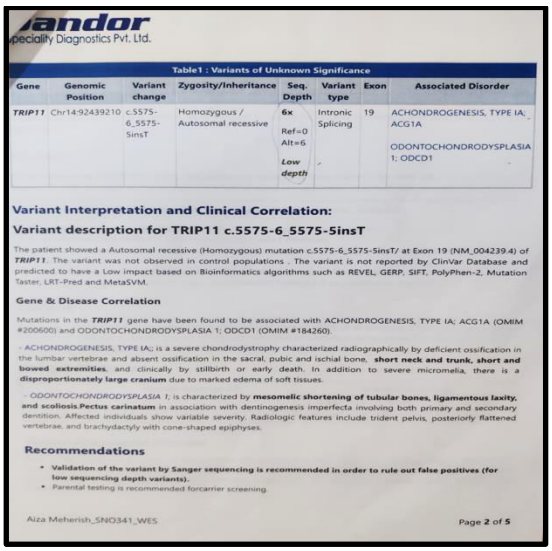

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Table1 : Variants of Unknown Significance

Gene	Genomic Position	Variant change	Zygosity/Inheritance	Seq. Depth	Variant type	Exon	Associated Disorder
TRIP11	Chr14:92439210	c.5575-6_5575-5insT	Homozygous / Autosomal recessive	6x Ref=0 Alt=6 *Low depth*	Intronic Splicing	19	ACHONDROGENESIS, TYPE IA; ACG1A ODONTOCHONDRODYSPLASIA 1; ODCD1

Variant Interpretation and Clinical Correlation:

Variant description for TRIP11 c.5575-6_5575-5insT

The patient showed a Autosomal recessive (Homozygous) mutation c.5575-6_5575-5insT/ at Exon 19 (NM_004239.4) of ***TRIP11***. The variant was not observed in control populations . The variant is not reported by ClinVar Database and predicted to have a Low impact based on Bioinformatics algorithms such as REVEL, GERP, SIFT, PolyPhen-2, Mutation Taster, LRT-Pred and MetaSVM.

Gene & Disease Correlation

Mutations in the ***TRIP11*** gene have been found to be associated with ACHONDROGENESIS, TYPE IA; ACG1A (OMIM #200600) and ODONTOCHONDRODYSPLASIA 1; ODCD1 (OMIM #184260).

- ACHONDROGENESIS, TYPE IA; is a severe chondrodystrophy characterized radiographically by deficient ossification in the lumbar vertebrae and absent ossification in the sacral, pubic and ischial bone, **short neck and trunk, short and bowed extremities**, and clinically by stillbirth or early death. In addition to severe micromelia, there is a **disproportionately large cranium** due to marked edema of soft tissues.

- *ODONTOCHONDRODYSPLASIA 1*; is characterized by **mesomelic shortening of tubular bones, ligamentous laxity, and scoliosis.Pectus carinatum** in association with dentinogenesis imperfecta involving both primary and secondary dentition. Affected individuals show variable severity. Radiologic features include trident pelvis, posteriorly flattened vertebrae, and brachydactyly with cone-shaped epiphyses.

Recommendations

- **Validation of the variant by Sanger sequencing is recommended in order to rule out false positives (for low sequencing depth variants).**
- Parental testing is recommended forcarrier screening.

Aiza Meherish_SNO341_WES

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Figure 10: Showing Results of Clinical Phenotype

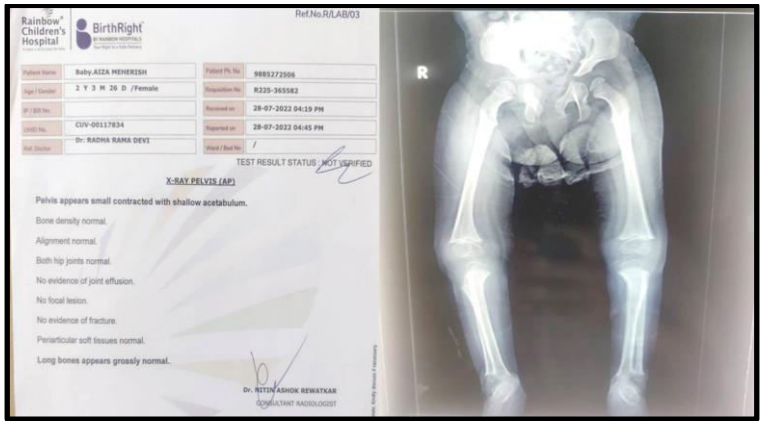

Figure 11: Showing Pelvic and Long Bone X-Ray

Discussion

An X-linked recessive mucopolysaccharide condition known as Hunter's syndrome or mucopolysaccharidosis (MPS) type II is brought on by a malfunction in the metabolism of glycosaminoglycans (GAGs), which is the consequence of an iduronatesulfatase enzyme deficiency.[4]Dermatan and heparansulfates accumulate as a result in different tissues. Charles A. Hunter, a physician, is honoured to have been the first to define the illness in 1917. Patients with this diverse condition usually seem normal at birth and start showing symptoms between the ages of 18 months and 4 years. Based on the duration of survival and the existence or absence of central nervous system (CNS) involvement, there are two types of Hunter's syndrome.The most severe kind, type A, has a substantially earlier start and a life expectancy of 14–15 years. Type B is a considerably milder variant with a 30- to 50-year life expectancy and physical characteristics that resemble but are less severe than those of Type A.[4]At birth, children with Hurler syndrome seem almost normal, but as glycosaminoglycans accumulate, increasing cell and tissue dysfunction develops, eventually leading to cognitive decline, hepatosplenomegaly, clouding of the cornea, and finally heart failure.[5]Infants with clear Hurler cells in the myocardium exhibit dwarfism, carpal tunnel syndrome, limited mobility, and facial deformities like enlarged heads, flattened nasal bridges, hypertelorism, and thickened patulous lips with a flattened philtrum.They have severe macroglossia, which eventually results in an anterior open bite and, when paired with a short neck, causes major difficulties from anaesthesia and sleep apnea. In the mandibular rami, there are dental irregularities such as widely spaced dentition, small conical teeth, and an excess of teeth.[5]Similarly, we have found some the clinical findings in our case report like Waddling Gait, Endomorphic Bulit, Clubbing is evident on upper limbs on general physical examination.On Extra oral examination we have found some of the features like Dolichocephaly head, Kyphosis, Frontal bossing, short neck, Saddle nose, depressed sternum.On Soft tissue examination we have found erythematous gingiva and soft in consistency and fibrotic, also we have found high frenal attachment on upper lip and hypoplastic enamel is evident.Based on these clinical and Urinary Glycosaminoglycans (GAGs) Quantification, Enzyme analyses of Aryl Sulphate A and Alpha Iduronidase: for diagnosis of Metachromatic Leukodystrophy (MLD) and Hurler (MPS I) diseases respectively, Clinical Phenotype, X-Ray Pelvis (A-P) View. We have diagnosed as

1. Congenital gingival Hyperplasia involving upper and lower arches.
2. Hunter Syndrome.
3. Achondrogenesis Type 1 A
4. Odontochondrodysplasia

Conclusion

In this case report we have found that some of the clinical features like frontal bossing, depressed sternum, spares hair, clubbing of upper limbs kyphosis, stiffness of joints, waddling gait. Hunter syndrome, or MPS II, is a severe progressive multisystemic condition that often affects a person in their second or third decade of life and has the ability to affect most bodily systems. All medical specializations should be accessible from large medical centres where administration is ideally centralized.Multidisciplinary care is necessary, and patients must be treated holistically, particularly if they have significant neurological involvement.

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