An interesting case of developmental delay

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Particulars of patient

- 6½ month old infant
- 2nd child of consanguineous marriage
- Resident of Sulurpet (AP)
- DoB - 29/06/2011
- Delayed attainment of age appropriate milestones noticed since 5 months of life
History of presenting complaint

- Apparently well baby until 5 months of age
- Delayed attainment of developmental milestones
  - Not able to hold the head steadily and look around.
  - Cannot roll over completely
- Presently when lying supine he turns head to either side with partial head holding
Contd....

- He keeps hands open from 4 months
- Grasps object placed in hands from 5 months
- Now he brings both hands together
- Mouthing +
- Does not reach for objects
Contd....

- Responds to mothers voice
- Turns to TV sounds
- He started cooing from 4 months of age
- Smiles spontaneously / No social smile
- He blinks to torch light
- Does not follow objects.
- No exaggerated Startle
Baby moves all 4 limbs equally
No feeding difficulties
No h/o difficulty in changing diapers
No h/o slipping through hands while holding the baby
Mother has noticed bluish green skin lesions over trunk, back and limbs since birth - not increased or decreased in size.
Birth History

- Antenatal – Uneventful
- Natal – delivered at 9 months by caesarean section indication being previous LSCS, cried immediately, birth wt -3.7 kg
On Examination

- Child active & comfortable on mother's lap
- Head needs to be supported
- Moving all 4 limbs.
- Coarse facies +
Vitals and anthropometry

- TEMP - 98°F
- PR - 108/min, regular, all peripheral pulses felt equally
- RR - 58/min, Abdominal type
- BP - 70/50 mm Hg in Rt UL supine position
- Weight - 6.7 kgs, 3rd - 15th centile (WHO)
- Length - 68 cm, (exp-69) 98%
- OFC - 43 cm, 15th - 50th centile (WHO)
- CC - 39 cm
- Wt/Length - 3rd - 15th centile
Head To Foot Examination

- Head size appears Normal,
- Flat occiput
- AF -1.5cm x 1.5 cm ,
- Hair normal.
- Coarse facies +.
Head To Foot Examination

- No cataract
- Corneal clouding + on Rt side only
- Pupils equal and reacting to light.
Skin

- Multiple hyperpigmented macules over trunk, less than 0.5 cm in size.
- Bluish green macules + over back, shoulder and both feet
Extensive mongolian spots
CNS

- HMF – conscious, smiles spontaneously, no hand preferences

**Primitive reflexes**

- Suck, root, palmar, moro, STNR – absent
- ATNR - Present, plantar grasp - +nt
Corneal opacity on Rt
Not following objects, EOM are full
Fundus – cherry red spot +
Other CN

- No squint, nystagmus, no ptosis
- No drooling, deviation of angle of mouth
- No nasal regurgitation / no hoarse cry
- Turns head from side to side
- No fasciculation seen in tongue
Motor system examination

- BULK- no obvious wasting /atrophy

- TONE
  Inspection – no obvious floppiness and stiffness
  Palpation – normal tone.
<table>
<thead>
<tr>
<th></th>
<th>Shoulder</th>
<th>Elbow</th>
<th>Wrist</th>
<th>Hips</th>
<th>Knees</th>
<th>Ankle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R</strong></td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
</tr>
<tr>
<td><strong>L</strong></td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
<td>4/5</td>
</tr>
</tbody>
</table>

Neck- unable to hold head steadily, but turns to sides
Trunk – Rolls to either sides, does not sit with support
# Reflexes

<table>
<thead>
<tr>
<th></th>
<th>Biceps</th>
<th>Triceps</th>
<th>Supinator</th>
<th>Knee</th>
<th>Ankle</th>
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<tbody>
<tr>
<td>R</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>L</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Superficial reflexes

- **Abdominal**: R +, L +
- **Cremastric**: R +, L +

**Plantar reflexes**: 
- Babinsky +ve B/L
Abdomen

- Upper abdomen distended
- All quadrants move equally,
- Skin over abdomen – hyperpigmented macules+
- Hernial orifices Nrl
- Scrotal swelling +B/L
- Transillumination +
- Liver palpable 6 cm from right costal margin along midclavicular line
- Left lobe of liver palpable 3 cm below xyphysternum
- Smooth surface, firm, rounded margins, moves with respiration
- Spleen palpable 2 cm along its axis, firm with rounded margins
Other Systems

- CVS
  - S1 S2 Heard
  - No Murmur

- Resp
  - Breath sounds heard B/l Symmetrical
  - Conducted Sounds +
Provisional Diagnosis

Storage Disorder
Lab

- Xray was showing anterior beaking of vertebrae
- Xray pictures of wrist was also consistent with dysostosis multiplex
- Functional ECHO revealed normal study, No s/o cardiomyopathy
- Hematological & Biochemical parameters were WNL
**Lab Investigations- GM1 Gangliosidosis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Disorder</th>
<th>Results</th>
<th>Units</th>
<th>Status</th>
<th>Reference Range</th>
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</thead>
<tbody>
<tr>
<td>β-Galactosidase</td>
<td>GM1-Gangliosidosis</td>
<td>#2.2</td>
<td>nmoles/hr/mg</td>
<td>L</td>
<td>70 - 324</td>
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<tr>
<td>β-Hexosaminidase A</td>
<td>Taysach</td>
<td>185</td>
<td>nmoles/hr/mg</td>
<td>N</td>
<td>62 - 310</td>
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</tbody>
</table>

* Reference enzyme.  
# Rechecked with the homogenate.

**Method:** Artificial Fluorogenic substrates.

**Conclusion:** A markedly reduced activity (~ 96.9 %) of β-galactosidase and normal activity of β-hexosaminidase A is obtained in leukocytes.
Lab Investigations- GM1 Gangliosidosis

Name: BABY VISHAL
Lab. No: 12 7551292 Age: 7 months Gender: M
A/C Status: C Ref. By: -

<table>
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<th>Units</th>
<th>Ref. Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM1 Gangliosidosis, Quantitative, Blood</td>
<td>5</td>
<td>nmol/hr/mg</td>
<td>(&gt; 80)</td>
</tr>
<tr>
<td>GM1 Gangliosidosis</td>
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Deficient β-Galactosidase activity suggestive of GM1 gangliosidosis
GM1 gangliosidosis
Lysosomal storage disorders (LSDs) are a group of genetic diseases characterized by an inherited defect in the functional expression of any of the lysosomal enzyme.

**GM1 Gangliosidosis - Autosomal recessive LSD**

- Mutations in the *GLB1* gene
- *GLB1* gene codes for enzyme β-galactosidase
- Characterized by the generalized accumulation of GM1 ganglioside, oligosaccharides, and the mucopolysaccharide keratan sulfate (and their derivatives)
GM1 gangliosidosis

- 1 in 100,000 to 200,000 newborns.
- Type I is reported more frequently than the other forms of this condition.
- High prevalence of 8 per 100,000 births has been reported in the population of British Columbia.
- Most individuals with type III are of Japanese descent.
A wide spectrum of phenotypic expression is observed in children with LSDs.

Milestone regression, mental handicap, dysmorphic features, seizures, abnormal fundus findings and organomegaly are the clinical features leading to the suspicion for LSDs.
Three clinical subtypes of GM1 gangliosidosis are recognized, classified by age of onset.

**Infantile (type 1):**
- Combines the features of a neurolipidosis (i.e., neurodegeneration, macular cherry-red spots) + mucopolysaccharidosis (i.e., visceromegaly, dysostosis multiplex, coarsened facial features).
- Most frequently presents in early infancy and may be evident at birth.
GM1 gangliosidosis

**Juvenile (type 2):**
- Slightly later age of onset and clinical variability in the classic physical features.

**Adult (type 3):**
- Normal early neurologic development
- No physical stigmata
- Subsequent development of a slowly progressive dementia with parkinsonian features, extrapyramidal disease, and dystonia
Currently, no effective medical treatment is available

Bone marrow transplantation can be considered in individuals with infantile/juvenile GM1 gangliosidosis

No long-term benefit was reported

Symptomatic treatment for some neurologic sequelae is available but does not significantly alter the clinical course
Therapy

- Active research in the areas of enzyme replacement and gene therapy for GM1 gangliosidosis is ongoing but has not advanced to human trials.

**Chemical chaperone therapy for GM1-gangliosidosis**

- Synthetic chaperone compound $N$-octyl-4-epi-$\beta$-valienamine (NOEV) orally administered in a GM1-gangliosidosis model mice.

- NOEV entered the brain through the blood-brain barrier, enhanced $\beta$-galactosidase activity, reduced the substrate storage, and clinically improved neurological deterioration.
“………………We hope that chemical chaperone therapy will prove useful for some patients with GM1-gangliosidosis and potentially other lysosomal storage diseases with central nervous system involvement…….”
Association of Dermal Melanocytosis With Lysosomal Storage Disease

First recognized by Weissbluth & Etal in 1981

Case Report of 2 infants with extensive dermal melanocytosis in association with GM1 gangliosidosis type 1 and Hurler syndrome.

Pathogenetic mechanisms behind this association remain to be elucidated.

The pathogenesis of congenital DM is thought to reflect arrested transdermal migration of melanocytes from the neural crest to the developing epidermis.

“…..Unusual presentation of dermal melanocytosis in an infant may be a cutaneous sign of an underlying lysosomal storage disease…..”
Dermal Melanocytosis & Lysosomal Storage Disease

- Around 40 individual cases of DM associated with LySD reported world wide.
- Blue cutaneous patches in an extensive distribution were a unifying feature of all cases.
- In few cases the pigmentary changes were noted to progress over time.
- **No** report described spontaneous regression.
A 7-month old girl with GM1 gangliosidosis type 1 manifested with diffuse ecchymosis and Mongolian spots. The cutaneous lesions were present at birth before the appearance of the other features of the disease.

“……We postulate that dermal pigmentation may be recognized as an early sign of GM1 gangliosidosis….”
"…………of the prevalence of extensive mongolian spots in Oriental people, the association of GM1 gangliosidosis type 1 and mongolian spots in an infant from an Asian country may be a chance occurrence………………"
Prognosis

- Children with GM1 gangliosidosis type I usually do not survive past age 2
Aim of presentation

- Although individually rare, lysosomal storage disorders constitute a significant burden on society and an important health problem.
- Paucity of Indian studies makes reporting of even single cases worthwhile.
- Possible association of Dermal Melanocytosis with Lysosomal Storage Disease (although controversial), should be kept in mind, by clinicians for early detection.
Thank You

"Namaste'

I honor the place in you
in which the entire universe dwells
I honor the place in you
which is of love, of truth,
of light, and of peace.

When you are in that place in you
and I am in that place in me,
we are one.