CASE HISTORY

A 7-month-old infant boy presented with chief complaints of fever and cough since 20 days and rapid breathing for 15 days.

BACKGROUND HISTORY

The child presented with high-grade fever for 20 days had a nonproductive cough with no diurnal or postural variation. He had a history of rapid breathing and chest indrawing for the last 15 days. The child also had three episodes of sudden uprolling of eyeballs in the first week of illness, with bluish discoloration of lips and hands lasting for 5 to 10 seconds during which child had altered sensorium. There was no history of any forehead sweating, suck-rest-suck cycle, or cyanosis before this episode, or any history of loose stools, rashes or abdominal distension. He was admitted for 11 days in two different hospitals and received intravenous antibiotics, and one unit of packed red blood cell (RBC) transfusion (prehospital Hb was not known). He showed improvement and was discharged. He remained at home for two days, but again developed fever and respiratory distress, and was referred to PGI for further management. The antenatal and birth history was uneventful. He was a term baby, cried at birth, with a birth weight of 3 kg. In the developmental history, the child could not sit with support, roll over (prone to supine), would vocalize when called for and had a developmental age of 4 to 5 months. His hearing and vision were normal and was immunized for age. In the family history, he was a product of the nonconsanguineous marriage. The child’s elder brother who is 3 years old has a history of birth asphyxia. He has a global developmental delay and can walk with support, can babble, recognize family members, but cannot feed independently. Apart from this, there is no history of any chronic illness in other family members.

EXAMINATION

He was conscious, cooperative, febrile, had a respiratory rate of 28 per minutes, pulse 110 per minute, BP 100/68 mm Hg, O₂ saturation 99% room air and mild pallor. No icterus, clubbing, pedal edema was noted and JVP was normal. Anthropometric measurements included weight-7kg (–1.3 z), height-66 cm (–1.1 z), OFC: 46 cm (2.4 z). The external features included bulging and pulsatile anterior fontanelle, coarse facies, dilated veins over the forehead, protruding eyes, squint of the left eye, chubby look, widening of the wrist (no Harrison sulcus or rachitic rosary), and protruding abdomen. Extremities, genitalia, and spine were normal.

Respiratory System

Chest movements were symmetrical with prolonged expiration, bilateral wheeze in all lung areas, basal crepitation. CVS-hyperdynamic precordium, parasternal heave
present, no palpable P2, S1 heard, the presence of short systolic murmur in the left parasternal area, S2 heard.  

Per abdomen: Soft, non-tender, liver palpable 3 cms below RCM, soft, span of 7 cms, smooth surface, rounded margins, left lobe not palpable. The spleen tip was palpable, and the bowel sounds were present.

CNS

E4V5M6, pupils bilateral reacting to light, bulging and pulsatile anterior fontanelle, cranial nerves-fixing and following light, squint present in the left eye, rest cranial nerves appear normal. Motor-bulk normal, the tone was hypotonic in all four limbs. Reflexes were sluggish/elicitable, power >3/5, plantar flexor, sensory response to pain and touch. No cerebellar or extrapyramidal signs were present.

Investigations (Tables 1 to 3)

Blood culture—sterile (25/12/16),  
Urine routine—normal,  
Urine culture—sterile (28/12/16),

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<th>Table 1: Complete blood count</th>
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<tr>
<td>Date</td>
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<tr>
<td>Hemoglobin (gm/dL)</td>
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<tr>
<td>Platelets (/mm$^3$)</td>
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<td>TLC(/mm$^3$)</td>
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<td>P/L/M/E</td>
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<td>MCH(pg) (27–32)</td>
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<td>RDW (cv%) (1)</td>
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<td>Na</td>
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<td>Total serum bilirubin</td>
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<td>CRP</td>
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<td>Procalcitonin</td>
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<th>Table 3: Blood gas analysis</th>
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<td>pH</td>
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<td>Procalcitonin</td>
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Urine fungal smear—yeast (28/12/16),  
Cerebrospinal fluid (CSF) study (29/12/16)– No cells, sugar–98, protein–45; culture-sterile,  
Endotracheal aspirate (ETA)–Gram stain and culture-sterile, gene Xpert–No mycobacterium tuberculosis (28/12/16),  
C3 and C4 levels–(28/12/16)-82 mg/dL and 20 mg/dL,  
Antinuclear Antibody Panel (ANA) IF–Negative (31/12/16),  
NBT (26/12/16)–Not consistent with the chronic granulomatous disease,  
IgG/IgA/IgM (mg/dL)–574/31/110–within normal limits,  
Human immunodeficiency virus (HIV) test (27/12/16)–Non-reactive,  
Creatine Kinase (CK-Nac) and LDH values–4561.4 and 3631u/l,  
Blood ketone–0.3 mmol/mL,  
Chest X-rays (CXR) dated 13.12.16, 18.12.16 and 28.12.16–Cardiomegaly with bilateral consolidation,  
X-ray right wrist (28.12.16): Dense metaphyseal band at distal end of radius and ulna,  
Ultrasonography (USG) cranium (26/12/16)–Supratentorial ventricular system is dilated extracranial spaces over b/l frontal region appears prominent,  
Ultrasonography abdomen (26/12/16)–Grossly normal study of the abdomen,  
Ultrasonography Doppler b/l renal arteries (28/12/16)–grossly normal study  
Two-dimensional echocardiography (2D ECHO)–moderate to large 12 mm ostium secundum ASD. No significant pulmonary arterial hypertension (PAH). Good left ventricular (LV) and RV function.
Course and Management

This child had subtle dysmorphism, macrocephaly, features of rickets, hyperdynamic precordium, systolic murmur, hepatomegaly, squint, and bulging and pulsatile anterior fontanelle. Initially, the child was given nasal prongs oxygen which was hiked to nasal prong continuous positive airway pressure on which saturation was maintained. X-rays showed collapse and consolidation with fluffy opacities in all lung fields. The child was started on broad-spectrum IV antibiotics initially. USG head and abdomen had revealed dilated venticles (VHR 39), mild hydrocephalus. Later National Council for Cooperative Training (NCCT) head confirmed mild supratentorial ventriculomegaly with BESS. Fundus evaluation was not suggestive of any papilloedema. Echocardiography showed Osmium Secundum–atrial septal defect (ASD) 12 mm and child was started on furosemide. Child was started on ACE inhibitors for hypertension. The child continued to have fever spikes, and blood gases showed progressive CO₂ retention for which child was put on manual ventilation. Antibiotics were upgraded to vancomycin and imipenem (elevated procalcitonin). Amphotericin was added for candiduria. Fever spikes had subsided after the change in antibiotics. Renal Doppler and urine analysis for cause of hypertension were normal. Child later had hypotensive records so anti-hypertensive medications were gradually stopped. Urine for reducing substances and TMS were normal. Then child had deranged renal function tests, oliguria, and puffiness. Echo was suggestive of dilated IVC with normal ejection fraction. Nephrology unit consultation was taken and supportive management was continued. Urine output started showing improvement and puffiness subsided. Serial X-rays were suggestive of bilateral diffuse infiltrates. On day 11 of hospital stay, the child developed hypoglycemic episodes necessitating intravenous glucose replacement up to 12. Critical sample for evaluation of hypoglycemia were taken and send for investigation (insulin, cortisol). Child was given hydrocortisone. Inborn error of metabolism (IEM) was also considered in view of hypoglycemia with normalketone bodies. Child also developed hemodynamic instability with poor peripheral pulses, hypotension, hypoxemia and prolonged CFT which was refractory to fluids and inotropes. The child developed bradycardia 9 hours after hemodynamic worsening, CPR was done as per the protocol, however, could not be revived. Parents were counseled for an autopsy, which was performed after their informed consent.

Case Analysis

So we have 7-month-old boy presenting with mild delay and complaints of fever, cough and respiratory distress for 20 days with three episodes of seizures in the first week of illness and severe anemia requiring blood transfusions. On examination, he was found to have coarse facial features, protruding eyes, macrocephaly, features of rickets, hypertension, systolic murmur, hepatosplenomegaly, squint, bulging and pulsatile anterior fontanelle, bilateral wheeze and basal crypts and during the hospital stay, he developed nonketotic hypoglycemia, hyperCKemia, and metabolic alkalosis. There was multisystemic involvement in this child.

- The first possibility is lysosomal storage disorders in which all these features can be seen, however, only feature against is the structural heart disease. It may be an isolated occurrence. In lysosomal storage disorders, mucolipidosis type 2 and mucoviscidosis Type 2 and 7 can be kept as differentials. These two entities have macrocephaly, organomegaly, mild delay and usually masquerade as rickets. Initially, these diagnoses are missed and confused with rickets.
- Other lysosomal storage disorders are also possible, but there are odd points especially macrocephaly. For GM1 gangliosidosis there is an only mild delay which is against this possibility. For Gaucher and Niemann–Pick disease, macrocephaly is an odd point, and massive hepatosplenomegaly is expected.
- Even fatty acid oxidation defect and glutaric acidemia Type 2 in which imaging findings are the same as described by ultrasound in this case.
- Disseminated tuberculosis cannot be ruled out, though many odd points are there.
- Another possibility could be severe combined immunodeficiency (SCID), Costello syndrome and cystic fibrosis. The final cascade of events is quite clear which is a respiratory failure which leads to refractory hypoxemia and finally multiple organ dysfunction syndrome (MODS) and death.

Final Clinical Diagnosis


Cause of death: ARDS, MODS

CLINICAL DISCUSSION

Prof D. Behera: Dr Lokesh please, your primary diagnosis is now one of the storage diseases. May I have the comments from the admitting unit. Yes, Dr Pankaj.

Dr Pankaj: Good morning, Dr Lokesh has reflected the approach which the unit had followed during the life of the child in the evaluation of the primary diagnosis. Of course, as he said it was the severe
persistent pneumonia that was the presentation and what took away the child was ARDS with multiorgan dysfunction. What we are discussing primarily here is the underlying possibility for which we have done this autopsy, and in life wherein, we have a child with subtle dysmorphism, macrocephaly, coarse facies and developmental delay with the involvement of the cardiac system and supratentorial ventriculomegaly. So it seems to be a syndromic association, and the genetic unit has proposed the possibility of CHOPS syndrome. And also there was associated hepatosplenomegaly, there was squint, there was a requirement of transfusions, and in the bones, there was metaphysical dysplasia along with osteopenia. So the possibilities of storage disorders like mucopolysaccharidosis or infiltration with Niemann-Pick or Gaucher, we cannot go away from that. During the course of hospital hypertension and repeated episodes of hypoglycemia were documented therefore possibility of inborn error of metabolism was considered. I am not very clear about the TMS report, but clinically and according to the algorithm what we follow I feel that fatty acid oxidation defect should be the topmost possibility. MRI brain could not be done because of the condition of the child. Otherwise, we have thought about it. So what I am expecting here that the pathologist is going to show us is some infiltration into various organ systems of some storage cells or may be fat cells. The unit is thankful to the parents for allowing us for this autopsy.

Dr Arushi: Thank you Lokesh for the presentation. In addition to what all has been discussed, I think this is the case where we can keep an underlying inborn error of metabolism because of multisystemic involvement. In addition to the possibility glutaric aciduria type 2, I would also like to keep CP2 deficiency which also presents as fatty acid oxidation defect. We can have all these with almost similar biochemical parameters and just a very simple cause which can also explain the other findings it would have been better if antemortem hypothyroidism would have been excluded because it can partly explain some of the findings.

Dr Lokesh: It was done, it was normal.

Professor D. Behera: Yes, Dr Saurabh.

Dr Saurabh: The issue of the metabolic alkalosis has not been adequately addressed, it could be because of the frusemide which was started for the ASD, but it was not clear when that was started. There was no date of echocardiogram however if it is not attributable to that, then cystic fibrosis I think becomes a possibility. Cystic fibrosis does present with severe metabolic alkalosis. Unfortunately, none of the chloride values have also come up in your table. So baby with recurrent respiratory infection, hepatosplenomegaly, rickets, and metabolic alkalosis, I think cystic fibrosis is the possibility.

Dr Vignesh: My point is also regarding cystic fibrosis, a child with persistent pneumonia, hyperinflation on chest X-ray, metabolic and respiratory problems like metabolic alkalosis and respiratory acidosis, cystic fibrosis should be a clinical possibility.

Dr Inusha: Actually in a child with macrocephaly and hepatosplenomegaly and also some of the other problems like cardiac, one should keep the possibility of syndromes like Costello syndrome as Lokesh has already mentioned. In this condition, you can also get myopathy and short stature and short limbs. X-ray, would show widened metaphysis and actually, it might not be a metaphyseal dysplasia. Another syndrome which can be considered is Zimmermann laband syndrome, in which also you can find a similar constellation of findings. The third possibility is Coffin-Siris syndrome, which has similar findings, cardiac defects, and coarse facies. He has also kept the possibility of glutaric aciduria because of macrocephaly and some abnormality on imaging and hypoglycemia; these children usually have lactic acidosis in case of GA, and there may be non-specific abnormalities on TMS. If it is, Costello syndrome one can find an excess of muscle spindles on muscle biopsy. Some intrauterine infection like CMV could contribute to recurrent respiratory findings.

Professor D. Behera: Please focus here, what is your possibility, please tell, what happens in different syndrome you need not say.

Dr Inusha: Cystic fibrosis is unlikely because the child had macrocephaly and the recurrent respiratory problem of early onset and there is no evidence of other newborn problems that occur in cystic fibrosis.

Professor Meenu Singh: Sir, this patient who has primarily presented as a respiratory case with respiratory distress, hyperinflation and wheezing, later on, has been detected to have a plethora of other physical findings belonging to different systems. We consider cystic fibrosis when we have ruled out common infections like TB and fungus. I think the sweat chloride test should have been done in this patient but probably was not done because the patient could not be moved for doing that test which is done in the biochemistry department. Otherwise, you can’t think of storage disorder and metabolic disorder in the same patient because you know they are two diverse conditions. I would consider some kind of storage disorder in this patient, which could be lipidosis or even pulmonary glycogenosis which can give rise to wheezing, apparent hyperinflation, hepatomegaly, etc., but relatively common conditions like cystic fibrosis would still stay because he has metabolic alkalosis.
Professor D. Behera: These are associated or two separate things?

Professor Meenu Singh: That would be associated because if there is definite hydrocephalus, then you have to consider something other than cystic fibrosis for the CNS manifestations.

Dr Anand: In this 7-month-old baby with underlying cardiac disease started with fever followed by respiratory distress, I would like to consider the possibility of infective endocarditis, although it is very rare in ASD, infective endocarditis of tricuspid valve and the pulmonary valve has been described. Another option is associated with TAPVC or PAPVC with ASD.

Professor D. Behera: With this, I invite Dr Kirti, there are many diverse diagnoses made from storage disease to infective endocarditis, TB and so many things so let us hear from Kirti.

Pathology Findings

A complete autopsy was performed. On opening, the serous cavities were within normal limits.

Heart: Weighed 90 gm; showed marked cardiomegaly with dilated right atrium and right ventricle. There was the presence of right and left ventricular hypertrophy (Figs 1A and B). All the valves were within normal limits. Atrial septal defect (ostium secundum) type (Fig. 1C) was seen. Microscopy showed cardiac myocytes with vacuolation (Fig. 1D) however due to prolonged fixation in formalin, glycogen could not be demonstrated on periodic acid-Schiff’s stain (PAS) despite repeated attempts.

Spleen: Weighed 30 g. Grossly, it was normal, and no infarcts were noted. Microscopy showed preserved white pulp with congestion of red pulp. No storage cells were seen.

Figs 1A to D: (A and B) Gross photograph of heart showing right ventricular and left ventricular hypertrophy; (C) gross photograph of heart showing ostium secundum type atrial septal defect; (D) microscopy depicting cardiac myocytes with vacuolation (PAS, 20x)
Gallbladder and Pancreas: Both the organs were within normal limits, both grossly as well as microscopically.

Brain: Weighed 1060 g. Macrocephaly was seen with patches of subarachnoid hemorrhages involving right frontal (1.5 cm), left occipital lobe (1.0 cm) and right occipital lobe (0.8 cm). The cut surface showed multiple hemorrhages of varying sizes (Fig 2A) on both sides: Genu of the corpus callosum, right inferior frontal gyrus (at 4 x 3 x 2.5 cm), middle frontal gyrus (1 x 1 cm) and pin-head size hemorrhage was seen involving grey and white matter. Both cerebellar lobes showed hemorrhages however medulla was spared. Organized blood clots were noted in the ventricles which were dilated. Microscopy showed hemorrhagic areas bordered by abnormally prominent and swollen endothelial cells throughout the central white matter (Fig. 2B).

Lungs: Weighed 280 g. Grossly, they were heavy, with dull pleura. There was diffuse consolidation with large areas of hemorrhage (Fig. 2C). Microscopy showed extensive areas of fresh alveolar hemorrhage with focal bronchopneumonia and diffuse alveolar damage with the formation of a hyaline membrane (Fig. 2D). Features of aspiration with giant cell reaction were noted. Airways were filled with secretions. No organisms were identified on all special stains.

Kidneys: Weighed 80 g. Grossly, the capsular surface was blotchy with preserved fetal lobulations. Cut surface showed extensive medullary congestion. Bilateral pelvicalyceal system and ureters were normal (Fig. 3A). Microscopy showed few sclerosed and immature glomeruli. Rest of the glomeruli were normal (Fig. 3B inset). Features of acute tubular necrosis were noted. Many tubular epithelial cells showed increased apoptosis. Electron Microscopic examination revealed normal glomeruli and tubules. No inclusions were noted in the podocytes. Tubules show glycogen within the cytoplasm.

Liver: Weighed 290 g. Grossly, it was enlarged for the age with a pale cut surface. The capsular surface was essentially normal (Fig. 3C). Microscopy showed maintained lobular architecture with centrilobular congestion and necrosis of hepatocytes. Portal tracts were essentially normal. Hepatocytes showed fine vacuolation (Fig. 3D), however due to prolonged fixation glycogen could not be demonstrated.

Adrenals: Weighed 5 g. Gross and microscopy were within normal limits. Adrenal cortical cells were normal.

Figs 2A to D: (A) Coronal slice of brain showing multiple hemorrhages of varying sizes on both sides; (B) microscopy showing hemorrhagic areas bordered by abnormally prominent and swollen endothelial cells (H and E, 20x); (C) gross photograph of lung showing dull pleura and diffuse consolidation; (D) microscopy showing extensive areas of fresh alveolar hemorrhage and hyaline membrane formation (H and E, 20x)
Lymph Nodes (LN): Microscopy revealed well preserved T and B cell zones. Bone marrow, thymus, stomach, oesophagus and large intestine, small intestine, testes, skin, and muscle: All these organs did not show any pathology.

FINAL AUTOPSY DIAGNOSIS (PM 27903)

A 7-month-old boy with H/O developmental delay, macrocephaly

- Morphological findings consistent with glycogen storage disease (type 2)/Pompe’s disease
- Cardiomegaly with biventricular hypertrophy and atrial septal defect (ostium secundum)
- Intracerebral hemorrhage with extension to ventricles
- Extensive pulmonary hemorrhage, focal broncho-pneumonia, features of aspiration and diffuse alveolar damage

Final Discussion

Professor D. Behera: Thank you Dr Kirti, Lokesh I think he made storage disease, but his store was something else. Anyways, but the point is the hemorrhage in lung and brain, do you think it is more recent?

Dr Kirti Gupta: It was all fresh hemorrhage, not much of hemosiderin indicating any old hemorrhage neither in lung or brain.

Prof D. Behera: Okay. Dr Pankaj, please.

Dr Pankaj: Thank you mam for showing those beautiful findings, I am still intrigued by the fact that we have done a 12 lead ECG; pome disease shows typical pattern of ECG wherein there is low amplitude, it is attached in the file, but I don’t think the ECG is suggestive of anything like that so I don’t know whether we can conclusively say at what basis that it is Pompe’s.

Dr Kirti Gupta: So the ECG in Pompe’s typically show short PR and tall QR waves which is indicative of hypertrophic cardiomyopathy.

Professor D. Behera: Can anybody see the ECG now retrospectively, it is here. Pediatric cardiologist anybody?? We can review it again.

Professor Meenu Singh: While we are looking at ECG, I remember that I uttered this word glycogenosis when I was giving my list of possibilities in the storage disorders for this patient. The only point against Pompe’s disease is that their presentation would be primarily cardiac. In this patient beside the cardiac presentation, there were
other features. You have shown that all other systems can be involved and especially CNS where enlargement of the head was seen which was due to hydrocephalus secondary to intraventricular hemorrhage glycogenosis as such can affect the lungs and there is something also which is known as pulmonary interstitial glycogenosis, in which you can see glycogen deposits in the interstitium. We had had a case like that before, where cardiomegaly was because of pulmonary hypertension which occurs in these patients, and that would predominately be right sided kind of enlargement. In this patient you have very clearly shown that there was a left-sided enlargement also but the ECHO done in this patient did not show these findings. I think this kind of left-sided hypertrophy of muscle should have been picked up on ECHO?

Professor D. Behera: The only point is that it is not picked up, the point is who is the interpreter was??

Professor Meenu Singh: So that is one thing which may have misled, but storage disorder was always there in mind and patient was being worked up because there was definite cardiomegaly in this patient and glycogen storage disease type 2 can present with features like that.

Dr Vignesh: Ma’am, in the article you have shown about Pompe’s disease, any mention of bony or musculoskeletal involvement??

Dr Kirti Gupta: I did not come across. Muscle is definitely involved in Pompe’s. We did not sample the muscle in this but bone changes I did not come across in the review articles. Cardiomegaly was well evident throughout, X-rays also showing cardiomegaly and respiratory symptoms towards the end of illness were due to the hemorrhages. There is organizing bronchopneumonia also, so there was some underlying respiratory infection that was well controlled and taken care of.

Dr Inusha: Findings of vacuolation or vacuolated cells in liver biopsy or renal biopsy does not indicate that it is glycogen storage disease unless you have demonstrated PAS positivity on the sections and vacuolation can also occur in fatty acid oxidation defect, foam cells can occur in Niemann-Pick disease. Niemann-Pick disease is more likely possibility as you can get CNS, liver manifestations along with renal involvement. Another possibility which Arushi mentioned CP2 deficiency which can also present with myopathy, hypoglycemia, with similar manifestations; so unless you demonstrate PAS positivity and you have not done any lipid staining you cannot categorically say it as Pompe’s disease. In Pompe’s disease, the clue to diagnosis is transaminitis and wide QRS complexes in the ECG and if we don’t have. With these findings, we cannot say it is Pompe’s disease unless you prove by DNA analysis.

Dr Nandita Kakkar: Good morning everyone, I have not seen the case as such, but I feel that this is not Pompe’s disease because we have seen cases of Pompe’s. Reena had presented once a case of Pompe’s, and it is very different. There was no vaculization seen in the heart, and I think there is some other etiology to the heart as well.

Professor Ashim Das: One has to see the whole case together. A child who did not see his first birthday of life presented for the first six months for life with hypotonia of all four limbs and has got cardiomegaly on chest X-ray and high NAC-CK levels, although I know AST, ALT should have raised in LDH increase. I think the differential diagnosis that comes first is the Pompe’s disease. So I don’t think one should be so much dogmatic in this approach, one has to see the whole case. Now why we did not see the glycogen in this case particularly because we have grossed it after 2 months and glycogen is very labile in aqueous fixative. That is why you don’t see glycogen even if you delay it even for 48 hours. So these are the final points which one should see, but I agree with Dr Inusha that the most important thing will be the testing of GA gene and unless we do target sequencing of GA gene that we would have done if we had EDTA blood. Don’t think it has got a different phenotype from Pompe’s disease. So each case is different from the other case. If we see hypertrophic cardiomyopathy with high NAC-CK levels, one should think of Pompe’s disease and this has been advocated for even newborn screening programs considered for the Pompe’s disease.

Dr Lokesh: Sir that isolated CK value was done at the time when the child had hypoglycemia and had features of shock. ECG is normal. ECHO is showing normal findings. Macrocephaly and coarse facies cannot be explained.

Dr Saurav: This child had hypertension requiring diuretics and ACE inhibitors, so are there any known association of Pompe’s. I got to know today that it Pompe’s disease can cause vasculopathy, so could the same process cause hypertension if it involves renal vasculature?

Prof D. Behera: Any other comment before Dr Kirti? So Kirti there is some challenge to your diagnosis. Your point of view, please.

Dr Kirti Gupta: I don’t know how to relate hypertension and the Pompe’s because it generally causes dilative changes in the vessels, so hypertension I do not know however it is just not Niemann Pick disease. Niemann-Pick disease causes the presence of those histiocytes which are filling up the hepatic sinusoids and the spleen which was only not seen in this case. I agree glycogen should have been demonstrated but as Dr Ashim Das said it was because of fixation and prolonged storage in formalin, that the glycogen was lost. So we could not demonstrate glycogen, but there was vaculization which is due to glycogen. Lipid staining is oil red o which again needs a fresh tissue, and we had formalin-fixed tissue.
Dr Inusha: Hypertension can be explained either by the involvement of renal vasculature or by storage disorder like Gaucher and Niemann-Pick. There is endothelial involvement. Pulmonary arterial hypertension is also well known. In Pompe’s, there is no hypertension, and in this case, the cause of hypertension is not clear.

Dr Kirti Gupta: Most of the other features can be explained by this diagnosis except for hypertension.

Prof Kim Vaiphei: I have not seen the case but whatever has been presented one can exclude Gaucher and Niemann-Pick. You may talk about other storage disorders, but in those conditions, you have foam cells. But there are no foam cells here. You cannot keep arguing about when there is very clear cut evidence that they are not there and besides a comment from my side when you have such a hugely enlarged heart why do you sit back and accept normal ECHO and normal ECG? You have to introspect yourself and analyze again where did you go wrong instead of pulling Kirti’s leg.

Dr Pankaj: So we are not pulling anyone’s leg, we are just trying to have good clinicopathological correlation and only for the information of the house that the elder sibling of this child was also neurologically impaired, so he had suffered a birth asphyxia during the time of delivery and this developmental delay may be due to neurological involvement and maybe we can do further evaluation if feasible.

Dr Kirti Gupta: First of all it is an autosomal recessive disease so parents should be screened and evaluated for that and we have a history of elder sibling also showing similar global developmental delay.

Dr Arushi: Thank you ma’am for the interesting discussion, I want to say the important clinical learning from this case is that Pompe’s disease is one disease which is in between neurometabolic and storage disorder and it may be missed on TMS DCMS. So as learning we may keep contesting whether it was Pompe’s or not, and the learning point is where when we have a combination of cardiac and neurological findings and multisystemic involvement maybe we could upfront look for enzyme analysis. Amongst all these disorders which we discussed, Pompe’s is the one which is potentially treatable, and survival of a child can be insured. An important message that we can go for beyond routine screening and can specifically go for enzyme analysis when next time we doubt cardiac involvement besides multisystemic involvement.

Prof D. Behera: How you confirm this? There is a metabolic unit in pediatrics but how you will confirm that is the point!!!

Dr Arushi: Sir, there is enzyme analysis specifically for Pompe’s disease, and then the confirmation is by the genetic analysis, so it requires a different set of metabolic investigations than we routinely do.

Prof D. Behera: Are they available in the department??

Dr Arushi: No sir, Pompe’s enzyme analysis at the moment is not available.

Prof D. Behera: Meenu for the last comment.

Professor Meenu Singh: Sir whether it is a Pompe’s or not, it is a storage disorder. Now, confirmation of storage disorder we know that these are genetically transmitted disorders. We have had our genetics people see this patient during the life, and I think we need to strengthen our genetic diagnosis. We need to have this targeted sequencing which will tell us whether or not this was glycogen storage disorder. So instead of going on discussing things we should also look on ourselves and try to make a genetic diagnosis in these patients because I think in many of our cases this is where our discussion ends that we could not do our gene analysis or we will be doing our gene analysis, so I just would like to finish this.

Prof D. Behera: The point is that the interest should come from the department or the people who are interested, they should start it, and obviously, it should start, and I wholeheartedly agree with you. I am sure that the administration will take it up and if you give a proposal, it can be taken up. Yes, please.

Dr Vivek: We know LCMS and other things, but we are doing untargeted metabolite profiling rather than targeted metabolite profiling. With selective metabolite profiling you are looking for those things that you know of, so that is something that can be very much helpful.

Prof Ashim Das: I want to say that this is only glycogen storage disorder which is a lysosomal storage disorder. The approach should be if you suspect, the targeted sequences by NGS rather than by other methods can be done.

Prof D. Behera: Thank you, everyone. It is worth pursuing.

**SUMMARY**

Pompe’s disease, also known as glycogen storage disease Type 2, is an autosomal recessive disorder caused due to deficiency of acid α-glucosidase (GAA). This results in generalized accumulation of lysosomal glycogen especially in the heart, skeletal and smooth muscle, and the nervous system. Presentation in infancy is associated with respiratory failure, cardiomyopathy, and severe muscle weakness. Juvenile- or adult-onset cases typically present with proximal muscle weakness and are associated with respiratory insufficiency or exertional dyspnea. The presentation of Pompe’s disease in infants is easily recognized by its characteristic hypotonia, generalized weakness, and cardiomegaly. Older patients have a more
nonspecific presentation and can be more challenging to diagnose. The differential diagnosis of Pompe’s disease in infants includes causes of either hypotonia or cardiomyopathy. Serum creatine kinase is usually elevated in infants with Pompe’s disease. In juveniles and adults with Pompe’s disease, it can range from normal to 15 times normal but up to 10% of these patients can have a normal serum creatine kinase. The definitive diagnosis of Pompe’s is done by determining GAA deficiency. This can be performed in blood samples or cultured fibroblasts from a skin biopsy or a muscle biopsy.

Treatment, until recently, was focused on supportive measures, and infants diagnosed with Pompe’s disease usually died within the first year of life. The recent development of recombinant alpha-glucosidase has dramatically improved the life expectancy, and quality of life of infantile-onset disease with improvements in respiratory and motor function observed in juvenile- or adult-onset cases. With this new development, the disease is now amongst few lysosomal storage disorders, for which treatment has become a reality. So the diagnosis of Pompe’s disease should be suspected antemortem for the better patient outcome as well as survival.

In the present case, despite the failure to demonstrate glycogen within the cardiac myocytes and heart, the clinical symptoms of hypotonia and presence of cardiomegaly with biventricular hypertrophy at autopsy are points in strong favor of Pompe’s disease.

SUGGESTED READING