Case Number 2
GM1 Gangliosidosis

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Case summary:

Demographic details:
Mr. JB, male, Xaghra
Referred from: Home due to family history

Mr. JB is a two-year-fourth-month old Caucasian boy from Xaghra. He is a known case of GM1 gangliosidosis. This child is a type 1, meaning early onset (presenting in the early months of life). The condition is characterised mainly by neurodegeneration and regression of achieving milestones, decreasing muscle activity and seizures. He was breastfed during his first year of life but he then started demonstrating oral feeding problems and began losing weight, necessitating nasogastric tube feeding. A soft silicone nasogastric tube was inserted in his right nostril, and requires changing every 6 weeks. This ensures adequate hydration and nutrition. He is now suffering from recurrent respiratory tract infections and was thus admitted for hospitalisation. Medications are also administered through the nasogastric tube in order to reduce the risk of aspiration pneumonia.

Presenting complaint:

The child presented with signs and symptoms suggestive of a lower respiratory tract infection:
Tachypnoea
Fever
Yellowish sputum production
Tachycardia

History of presenting complaint:

For the last 6 months, he has had recurrent episodes of respiratory tract infections requiring antibiotics and recurrent hospitalisations especially after the age of 23 months.

Past medical and surgical history:

Past medical history:

Given the family history, when the patient was born, there was a high index of suspicion for GM1 gangliosidosis and the diagnosis was confirmed by one week after gene testing for the enzyme beta-galactosidase. As a baby, he was asymptomatic. He appeared normal in the first three months during regular surveillance checks. In fact, after being diagnosed with this condition there was a period of denial in which the parents could not believe that their child had this condition. But on subsequent monthly check-ups, it was observed by the paediatricians who examined him regularly that he failed to achieve the expected skills in important developmental milestones including head lag by 3-4 months, lack of ability to roll over by 7-8 months and lack of ability to sit unsupported by 10 months. Also, after the age of 9 months, there was gradual increasing hypotonia and decreased interaction with his carers. He lost his eyesight after 17 months of age due to progressive accumulation of toxic metabolites in the cerebral cortex.

Drug history:

No known drug allergies. Compliant with the National Immunisation Service; the child was vaccinated against Diphtheria, Tetanus, Pertussis, Polio, Haemophilus and Hepatitis B. He also received the Pneumococcus vaccine and last year was vaccinated against Influenza.

Drug	Dosage	Frequency	Type	Reason
Cephalexin	125mg	8 hourly for 7 days	Cephalosporin antibiotic	To eradicate bacterial infection

Co-amoxiclav was also given to eradicate Pseudomonas aeruginosa.

Family history:

His brother died from cardio-respiratory failure resulting from GM1 gangliosidosis at the age of 2 years and 3 months. The condition was much more severe in his brother and the symptoms were present earlier. He had head lag from the very beginning and made no eye contact with carers; he never smiled or reacted socially. He spent almost all his life in hospital, suffering from recurrent respiratory tract infections. Both parents were referred for genetic testing and counselling and both were shown to be carriers of this condition.

Social history:

The patient has three older brothers. In the beginning, he used to smile at them and laugh but his social interactive skills began regressing after 6 months of age.

Systemic inquiry:

- General health: Healthy skin but cachectic and lethargic.
- Cardiovascular system: Tachycardia at 160 beats per minute.
- Respiratory system: Respiratory distress with chest wall recessions, expiratory wheeze, inspiratory crackles and respiratory rate of 55 breaths per minute.
- Gastrointestinal System: Feeds given via nasogastric tube.
- Genitourinary system: Nil to note.
- Central nervous system: Generalised decreased movement.
- Musculoskeletal system: See above.
- Endocrine System: Nil to note.

Current therapy:

Non-pharmacological treatment:
Physiotherapy is the mainstay of therapy focusing on facilitating clearance of upper respiratory tract secretions. This is done twice a day by a physiotherapist and more frequently by the caring mother.

When the patient is short of breath, particularly during prolonged seizures, which cause the oxygen saturation to decline below 90%, oxygen is administered via nasal prongs or facemask in order to improve oxygenation.

When there are rattling breathing sounds, a sterile suction catheter is passed from the mouth and oropharynx so as to clear out secretions. The mother applies external tracheal pressure at times to encourage the cough reflex. The patient is at times placed in a 20^{o} head down position for postural drainage of lung

secretions. This is carried out around three times daily.

A soft silicone 8mm nasogastric tube is replaced every 6 weeks for feeding. Food is given in liquidised form. The patient is fed 90ml every 3 hours, skipping the 3am feed. Medication is also administered through this tube.

In order for the nasogastric tube to be inserted, the distance between the bridge of the nose to earlobe and the distance from the bridge of the nose to the xiphoid process are measured and added. The distance in this case is around 31cm, however to ensure that the tube inserts well in the stomach, 33cm of tubing is used. Before feeding, a syringe is attached to the free end of the tube and gastric contents are aspirated. Subsequently a pH indicator is used which should turn red due to gastric acidity, thus ensuring that the nasogastric tube been appropriately positioned in the stomach.

Blood was obtained from the infant either during cannula insertion or in the first few days from the cannula itself or via the 'Broken Needle Technique' (i.e. breaking the hub off the needle).

In order to perform the latter, the catheter was secured by applying light finger pressure on the catheter beyond the cannula. Then, the cannula was withdrawn slowly. The cannula was peeled apart whilst maintaining forward pressure on the catheter, taking care not to dislodge the catheter from the vein. Following venipuncture, the catheter was advanced through the breakaway needle and the needle was withdrawn from the vein. The needle wings were pinched firmly together to initiate breaking of the needle. Then, the needle was peeled smoothly until the needle halves were held together only at the tip. Finally, the catheter was carefully lifted out of the needle lumen.

This technique is ideal because the venipuncture hole is smaller than a cannula, thus preserving the infant's tiny veins.

Drugs:

Drug Name (Generic)	**Dosage**	**Frequency**	**Type**	**Reason**
Clonazepam	0.25mg	Once daily	Anticonvulsant	To regulate seizures
Sodium Valproate	8ml	12-hourly	Anticonvulsant	To regulate seizures
Lactulose	2-5ml	PRN	Osmotic laxative	To reduce constipation
Salbutamol (nebulizer)	0.4ml	PRN	Bronchodilator	To treat bronchospasm
Nebulized Hypertonic Saline (3%)	4ml	12-hourly prior to physiotherapy	Mucolytic	To enhance mucus clearance from chest
Bromhexine	2ml	8-hourly	Mucolytic	To enhance mucus clearance from chest

Discussion of results of general and specific examinations:

On observation, the skin of the patient appeared healthy but he was cachectic. On examination, he had significant head lag and a retracted right tympanic membrane (chronic). With regards to facial features, he had frontal bossing and a flat nasal bridge. Paucity in movements was noted in his face, upper and lower limbs. Generalised seizures were observed which mostly consisted of eye and mouth twitching and occasional increased tone in his upper and lower limbs. For the past few days, he also had fever and

yellow respiratory tract secretions.

Unlike 50% of the infants with lysosomal storage diseases, this particular child showed no macular cherry-red spot on fundoscopy.

Hepatosplenomegaly – liver and spleen measure 7cm and 3cm respectively.

Heart rate increased at 160 beats/minute (normal <120).

Breathing rate of 55 breaths/minute (normally <30), chest wall recessions and respiratory distress.

Differential diagnosis:

- GM1 Gangliosidoses
- GM 2 Gangliosidoses
- I-cell Disease (Mucolipidosis Type II)
- Mucopolysaccharidosis Type IH
- Mucopolysaccharidosis Type IV
- Sialidosis (Mucolipidosis I)
- Wilson disease

Diagnostic procedures:

For GM1 gangliosidosis:

Laboratory exams:
Test: Peripheral blood film.
Justification for test: To test for a lysosomal storage disease.
Result: Vacuolated lymphocytes were observed under the microscope.
Conclusion: A lysosomal storage disease is highly probable.

GM1 gangliosidosis is suspected because Morquio type B syndrome has a later age of onset.

Test: DNA testing on newborn venous sample (This is a specific test for this condition.).
Justification for test: To identify the gene deletion that leads to a deficiency of beta-galactosidase.
Result: GLB1 gene deletion is observed on the short arm of chromosome 3 of white blood cells.
Conclusion: This gene that provides instructions for beta-galactosidase enzyme synthesis is lacking, hence GM1 gangliosidosis is confirmed.

For the respiratory tract infection:

Test: Complete Blood Count.
Justification for test: As a baseline; repeated on several days afterwards to monitor progression.
Result: See next page.

Test	*Result*	*Reference interval*	*Units*
Sodium, serum	132	135-145	mmol/L
Potassium, serum	4.5	4.1-5.3	mmol/L
Albumin, serum	34	35-55	g/L
Urea	1.6	4.0-8.2	mmol/L
WBC	6100	4000-10,500	x109/L
Neutrophils	3600	3000-5800	x106/L
Lymphocytes	1600	1500-3000	x106/L
Platelets	284	150-400	x109/L
Haemoglobin	10.9	13.0-18.0	g/dL

Conclusion: Low white blood cell count lead showed that there was a high risk of infection. This low white blood cell and platelet count was due to splenomegaly. Low haemoglobin indicates anaemia. Slightly low sodium indicates fluid retention.

Test: C-reactive protein test.
Justification for test: To assess if there is an inflammatory process.
Result: 36mg/L (normal: <13mg/L).
Conclusion: The elevated concentration of C-reactive protein confirms the presence of an inflammatory process.

Test: Blood Cultures.
Justification for test: To detect the presence of bacteria or fungi in the blood.
Result: No bacteria or other organisms were grown.
Conclusion: No bacteraemia is present.

Test: *Sputum Culture.*
Justification for test: To identify the microorganism causing the infection.
Result: *Haemophilus influenzae* was cultivated.
Conclusion: This is probably the cause of fever so antibiotics could be used.
Beforehand, *Pseudomonas aeruginosa* was cultivated in his tracheal secretions.

Therapy:

The physiotherapy sessions are not tolerated since the child is severely affected by the chest infection. At the moment, in view of the respiratory distress, feeds are decreased to 75 ml and might be stopped to minimise gastric distension and splinting of the diaphragm.

Drugs:

Drug	**Dosage**	**Frequency**	**Type**	**Reason**
Ceftazidime	275mg	8 hourly for 7 days	Antibiotic	To eradicate *Haemophilus influenzae*

Diagnosis:

The medical team is also discussing with the parents whether to give the child the influenza vaccine while he is feeling a bit better or to make use of cocooning i.e. vaccinating the people in close contact with the child instead of vaccinating the child himself. Moreover he was not given the MMR vaccine, which is usually given at 16 months of age, because it might constitute as extraordinary treatment given that he

will not be attending school.

Final treatment and follow up:

He was given a 2 week course of intravenous benzyl penicillin and gentamicin and was advised to continue benzyl penicillin for 2 weeks prophylaxis. The patient was given an appointment to be followed up at 'Grown-ups with congenital heart defects' clinic.

Diagnosis:

The patient was diagnosed with infantile GM1 gangliosidosis. This subtype combines the features of a neurolipidosis (i.e. neurodegeneration, macular cherry-red spots) with those of a mucopolysaccharidosis (i.e. visceromegaly, dysostosis multiplex, coarsened facial features). This form of GM1 gangliosidosis most frequently presents in early infancy and may be evident at birth. Once these symptoms and signs are identified, the patient is referred for genetic testing and counselling which is specific for this particular condition.

A current respiratory tract infection was diagnosed through positive sputum cultures, an elevated CRP and response to intravenous antibiotics.

Final treatment and Follow-up:

Currently no effective medical treatment is available for the underlying disorder in patients with GM1 gangliosidosis. Patients with this condition normally die with pneumonia or cardio-respiratory failure. The life expectancy is between 18-24 months. However, luckily enough, due the continuous care of his parents, this child is now 28 months old. Unlike Gaucher's disease which is also a lysosomal storage disease, there is no enzyme therapy for GM1 gangliosidosis. Reportedly a girl with infantile/juvenile GM1 gangliosidosis successfully underwent a bone marrow transplant as soon as she was diagnosed with the condition before any symptoms started to occur. However, it was shown that this transplant was of no long-term benefit.

Fact Box 2:

Name of Condition: Infantile GM1 Gangliosidosis

Infantile GM1 Gangliosidosis is an autosomal recessive disease in which the enzyme β–galactosidase is deficient. This disease is quite rare, and its prevalence at birth is thought to be 1: 100,000–200,000 live births[5], however an unusually high prevalence of one per 3700 live births has been reported in Malta [3, 5]. The cause of infantile GM1 gangliosidosis is a mutation in the gene GLB1 located on the chromosome band 3p21.33 [3].
β–galactosidase is an enzyme which is found in lysosomes. Its action is to remove the terminal galactose subunit from compounds which have it attached to them. These compounds include GM1 gangliosides (commonly found in neurones) and keratan sulfate[3]. This leads to the accumulation of these compounds since they will not be degraded, leading to the various symptoms of the disease.

Signs and symptoms:
Symptoms of infantile GM1 gangliosidosis include hepatosplenomegaly, generalised skeletal dysplasia, coarse facial features and progressive central nervous system degeneration. Macular cherry–red spots have also been reported in about 50% of cases [6, 3].

Risk factors:
Once the parents have a child with this condition, they will be referred for genetic testing and a positive result would confirm that they have a recurrence risk of 1 in 4 (25%) for each unborn child. Males and females are equally likely to be affected. There is also a 2 in 4 (50%) chance for each child to be heterozygous for the condition i.e. they will not be affected by the condition but are carriers, and a 1 in 4 (25%) chance that the child will be neither affected nor a carrier.

Diagnosis and management:
GM1 gangliosidosis can be diagnosed by analysing the activity of β–galactosidase using biochemical analysis. The enzyme is obtained from leukocytes in the blood. However this diagnosis cannot be used to diagnose carriers of this condition. Molecular sequence analysis of the GLB1 gene is another technique used to diagnose GM1 gangliosidosis patients [4, 1]. Amniotic fluid may also be used to diagnose this condition antenatally [2].

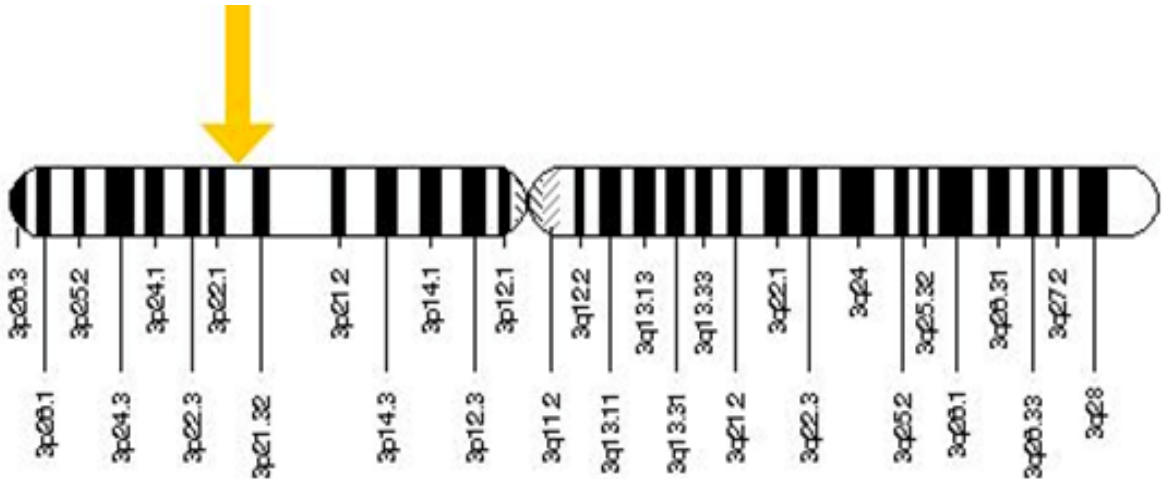

Figure 1: This shows the location of the GLB-1 gene

Unfortunately there is no curative treatment for this disorder. Bone marrow transplantation in an individual showed no long–term benefit. Presymptomatic cord-blood haematopoietic stem-cell transplantation has been suggested as a possible treatment as it has shown success with other lysosomal storage disorders [3].

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