NEURONOPATHIC GAUCHER DISEASE

Neuronopathic Gaucher Disease: Case Studies in Challenging Management

CASE 1

The Child with Fits and a Big Abdomen

CLINICAL FOCUS

FOCUS: Recognising type 3 Gaucher disease in a child presenting with epilepsy and hepatosplenomegaly — when GD is not the first diagnosis on your list

CASE 1 | Recognising Neuronopathic Gaucher Disease

CLINICAL PRESENTATION

PATIENT

Age	**7 years**
Sex	**Female**
Origin	**Rural area**
Referred by	**District hospital**
Duration	**4 years**

PRESENTING FEATURES

- Recurrent generalised seizures since age 3
- Increasingly enlarged abdomen
- Progressive gait difficulty
- Frequent infections, poor weight gain
- 2 older siblings died in childhood (cause unknown)

EXAMINATION

- Massive splenomegaly (spleen 22 cm)
- Hepatomegaly (liver 16 cm)
- Squint
- Developmental delay, mild learning difficulties, hyperactive behaviour
- Anaemia, pallor; no lymphadenopathy

INVESTIGATIONS (AVAILABLE LOCALLY)

FBC: Hb 7.1 g/dL, platelets 68×10^9/L, WBC 3.1×10^9/L

Malaria RDT: Negative

LFTs: Mild elevation AST/ALT

Abdominal US: Massive splenomegaly, hepatomegaly

EEG: Generalised slow-wave activity

HIV, TB: Negative

LDHA: Elevated ×4 upper limit

📊 POLL — CASE 1 Q1

A 7-year-old girl presents with 4 years of seizures, massive splenomegaly, and developmental delay/learning difficulties. Which additional clinical sign will you examine for, or which additional investigation will you do, if considering Gaucher as a unifying diagnosis?

A	MRI Brain
B	Horizontal saccadic eye movement impairment (supranuclear gaze palsy)
C	Ataxia
D	Neurocognitive testing

📊 POLL — CASE 1 Q1

A 7-year-old girl presents with 4 years of seizures, massive splenomegaly, and horizontal gaze palsy. The most important single clinical sign pointing AWAY from a purely haematological cause is:

A	MRI Brain	
B	Horizontal saccadic eye movement impairment— a neurological finding specific to gaucher disease	✓ CORRECT
C	Ataxia— non-specific, seen in many other conditions	
D	Neurocognitive testing – likely to be abnormal and non-specific for underlying diagnosis	

Answer B: Horizontal saccadic eye movement impairment (supranuclear gaze palsy (HSGP)) is a hallmark of type 3 (chronic neuronopathic) Gaucher disease. It is not explained by splenomegaly alone and should trigger consideration of a lysosomal storage disorder.

📊 POLL — CASE 1 Q2

You suspect a lysosomal storage disorder. Your laboratory has NO enzyme assay available. What is the MOST accessible next diagnostic step?

A	Bone marrow aspirate
B	MRI brain
C	Whole exome sequencing
D	Empirical enzyme replacement therapy

📊 POLL — CASE 1 Q2

You suspect a lysosomal storage disorder. Your laboratory has NO enzyme assay available. What is the MOST accessible next diagnostic step?

A	Bone marrow aspirate — Gaucher cells may be visible and can be done in most district hospitals	✓ CORRECT
B	MRI brain — essential to confirm neuronopathic disease before any other investigation	
C	Whole exome sequencing — variable availability	
D	Empirical enzyme replacement therapy — a therapeutic trial is acceptable if testing is unavailable	

Answer A: Bone marrow aspirate showing 'crumpled tissue paper' Gaucher cells (lipid-laden macrophages) is a low-cost, widely available test that can strongly support the diagnosis. It is not definitive but is the most practical first step when enzyme assay is unavailable.

📊 POLL — CASE 1 Q3

The family asks about treatment. Enzyme replacement therapy (ERT) with imiglucerase is not available or funded in your country. What is your MOST important immediate management priority?

A	Initiate high-dose anticonvulsant polytherapy immediately to suppress all seizure activity
B	Refer urgently to a specialist centre abroad for ERT initiation, with no local management in the interim
C	Provide supportive care: optimise seizure control, prevent infection, address nutritional deficiency, ensure correct diagnosis, and pursue specialist linkage
D	Advise the family that without ERT nothing can be done and prognosis is universally poor

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D Advise the family that without ERT nothing can be done and prognosis is universally poor

Answer C: ERT does not cross the blood-brain barrier and has limited impact on neurological progression in type 3 GD. Supportive care — seizure management, infection prevention, nutrition, family counselling — is critical and achievable locally. Establishing specialist linkage for confirmation and access programmes is also essential.

📊 POLL — CASE 1 Q4

What other problems might this child face in the future that you should look out for?

A	Spinal deformity
B	Depression & anxiety
C	Bone Disease ✓ CORRECT
D	Hearing loss

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CASE 1 | Type 3 Gaucher Disease

MANAGEMENT APPROACH

MANAGEMENT STEPS

- Confirm diagnosis: bone marrow biopsy ± dried blood spot for enzyme assay (send to specialist lab)
- Optimise seizure control with available
- Treat anaemia: transfuse if Hb <7 g/dL; evaluate iron, folate status
- Monitor for infections; ensure immunisation is up to date
- Nutritional support; involve paediatric dietitian if available
- Establish contact with international Gaucher registry (GOS) and access programmes (compassionate use)
- Regular developmental and neurological assessment every 6 months

KEY CLINICAL POINTS

- ERT improves visceral disease but does NOT halt neurological progression in type 3
- HSGP is diagnostic hallmark — document carefully
- Family history of affected siblings implies autosomal recessive inheritance; offer genetic counselling

In many areas, Gaucher disease is likely under-diagnosed. Any child with massive unexplained splenomegaly + neurological signs should prompt consideration. International patient registries and manufacturer compassionate use programmes may be the only route to therapy. Building regional diagnostic capacity (dried blood spot enzyme assays) is a critical advocacy priority.

CASE 2

An Infant Who Stopped Developing

CLINICAL FOCUS

FOCUS: Acute neuronopathic (type 2) Gaucher disease — recognising a rapidly fatal disorder, supporting families, and navigating ethical decisions when cure is not possible

CASE 2 | Acute Neuronopathic GD — Type 2

CLINICAL PRESENTATION

PATIENT

Age	**5 months**
Sex	**Male**
Origin	**Peri-urban**
Born	**Term, normal delivery**
Feeding	**Formula — poor intake**

PRESENTING FEATURES

- Developmental delay
- Feeding difficulties from 2-3mo
- Opisthotonus
- History of rash in the newborn period
- Frequent aspiration episodes

EXAMINATION

- Low body weight infant (growth faltering)
- Peripheral hypertonic with retroflexed neck posture
- Splenomegaly – hard
- Hepatomegaly
- Squint

INVESTIGATIONS (AVAILABLE LOCALLY)

FBC: Hb 8.6 g/dL, plt 65×10^9/L

BM aspirate: Gaucher cells present

CXR: Aspiration changes bilateral

Glucocerebrosidase (DBS, ref lab): Severely deficient — 1.2 nmol/h/mg (NR >4)

Chitotriosidase: Markedly elevated

GBA gene: Pending (L444P/L444P suspected)

📊 POLL — CASE 2 Q1

A 5-month-old presents with growth faltering, feeding difficulties, opisthotonus and hepatosplenomegaly. Bone marrow shows Gaucher cells and a dried blood spot sent to a reference lab shows severely reduced glucocerebrosidase activity. What is your diagnosis?

A	Niemann-Pick disease type A
B	Gaucher disease type 2 (acute neuronopathic)
C	Neonatal tetanus
D	Bilateral subdural haematomas from non-accidental injury

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A	Niemann-Pick disease type A — clinically indistinguishable from GD type 2, requires sphingomyelinase assay	
B	Gaucher disease type 2 (acute neuronopathic) — consistent clinical picture with biochemical confirmation	✓ CORRECT
C	Neonatal tetanus — trismus and opisthotonus are characteristic and common in unvaccinated infants	
D	Bilateral subdural haematomas from non-accidental injury — commonest cause of infant regression	

Answer B: The combination of confirmed glucocerebrosidase deficiency, Gaucher cells on BM, and the clinical triad of early-onset neurological regression with opisthotonus and trismus is diagnostic of type 2 (acute neuronopathic) Gaucher disease. Niemann-Pick A is a valid differential but enzyme assay here is confirmatory for GD.

📊 POLL — CASE 2 Q2

The family has heard ERT exists and is asking you to start treatment. ERT (imiglucerase) is available via compassionate use. What is the MOST accurate statement about ERT in type 2 Gaucher disease?

A	ERT reliably halts neurological progression in type 2 GD if started before 6 months of age
B	ERT significantly improves visceral disease but does not cross the blood-brain barrier and does not alter neurological decline — prognosis remains poor
C	ERT is contraindicated in infants under 12 months due to severe infusion reactions
D	ERT combined with miglustat has been shown in RCTs to improve survival beyond 2 years in type 2 GD

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C ERT is contraindicated in infants under 12 months due to severe infusion reactions

D ERT combined with miglustat has been shown in RCTs to improve survival beyond 2 years in type 2 GD

Answer B: Type 2 GD is uniformly fatal, usually within the first 2 years of life. ERT does not penetrate the CNS and does not alter the neurological trajectory. While visceral improvement may occur, this does not change overall prognosis. Honest family counselling is essential.

📊 POLL — CASE 2 Q3

The parents are devastated. You have confirmed type 2 GD and explained the prognosis. Which approach to family support and clinical management is MOST appropriate in this setting?

A	Recommend immediate transfer to a paediatric intensive care unit for ventilatory support to maximise life expectancy
B	Advise the family that nothing more can be done and discharge home without follow-up
C	Initiate palliative care: prioritise comfort, manage aspiration risk, support feeding, provide family counselling, and discuss end-of-life planning sensitively
D	Recommend a repeat bone marrow biopsy monthly to track disease progression and guide therapy decisions

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Answer C: Palliative and supportive care is the appropriate, compassionate response. Goals should include comfort, aspiration prevention (positioning, nasogastric feeding if appropriate), seizure palliation, and emotional/spiritual support for the family. Intensive invasive care is generally not appropriate and may prolong suffering without benefit.

📊 POLL — CASE 2 Q4

What aspects of their condition may you want to counsel families on?

A Risk of bone disease and fractures

B Risk of haematological malignancy

C Progressive swallowing and feeding difficulty, seizures, laryngospasm and apnoea.

D Ataxia and eye movement problems

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CASE 2 | Type 2 Gaucher Disease — Palliative & Supportive Management

MANAGEMENT APPROACH

MANAGEMENT STEPS

- Confirm diagnosis with enzyme assay (dried blood spot to reference lab) and GBA genotyping if accessible
- Explain diagnosis and prognosis clearly and compassionately to family — involve community support
- Initiate comfort-focused care: tone management, anti-seizure medication when needed, positioning, pain management, feeding assessment and interventions
- Optimise nutrition
- Avoid aggressive interventions (ICU ventilation) that do not alter disease course
- Offer prenatal counselling for future pregnancies
- Refer to social work, bereavement counselling

KEY CLINICAL POINTS

- Uniformly fatal — median survival <2 years from symptom onset
- ERT is not beneficial for neurological disease and should not be prioritised over comfort care – practicalities of delivering can be prohibitive
- Autosomal recessive — 25% recurrence risk; prenatal diagnosis possible

Families may have strong beliefs around doing everything possible. Culturally sensitive communication is essential. Carrier testing of parents using dried blood spot enzyme assay (where feasible) can inform family planning. Establishing regional referral networks for lysosomal storage disorders remains an urgent need.

CASE 3

An Adult on Treatment — or Are They?

CLINICAL FOCUS

FOCUS: A young adult with known type 3 Gaucher disease — monitoring neurological progression, making treatment decisions when ERT supply is interrupted, and managing bone disease without specialist imaging

CASE 3 | Type 3 GD in a Young Adult — Monitoring & Interruption of ERT

CLINICAL PRESENTATION

PATIENT

Age	**23 years**
Sex	**Male**
Origin	**Urban**
Known GD	**Since age 9**
ERT	**Interrupted 14 months ago**

PRESENTING FEATURES

- Known type 3 GD, previously on imiglucerase (compassionate supply now stopped)
- Increasing bone pain — left hip and lower back
- Two 'bone crises' in past year (severe pain episodes)
- Increasing fatigue and breathlessness on exertion
- Partner reports increasing memory difficulties

EXAMINATION

- Splenomegaly (15 cm, previously 10 cm on ERT)
- Hepatomegaly (13 cm)
- HSGP still present — stable vs. baseline?
- Mild proximal myopathy
- Kyphosis; pain on hip internal rotation
- No jaundice; no lymphadenopathy

INVESTIGATIONS (AVAILABLE LOCALLY)

FBC: Hb 9.8 g/dL, plt 52×10^9/L, WBC 2.7×10^9/L

Plain X-ray hips: 'Erlenmeyer flask' deformity; subchondral sclerosis Lt hip

Chitotriosidase: Markedly elevated (was low on ERT)

Ferritin: 2,840 µg/L (elevated)

ECG: Normal

LFTs/coag: PT mildly prolonged; albumin 31 g/L

📊 POLL — CASE 3 Q1

This patient's ERT supply has been interrupted for 14 months. His spleen has grown from 10 cm to 15 cm, Hb dropped from 11.2 to 9.8 g/dL, and chitotriosidase is markedly elevated. What does this clinical picture confirm?

A	He has developed a new secondary diagnosis (e.g. lymphoma)
B	Disease reactivation and progression consistent with ERT interruption
C	The previous response to ERT was a placebo effect
D	Bone crisis episodes are unrelated to Gaucher disease and should be investigated independently for sickle cell disease

📊 POLL — CASE 3 Q1

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A	He has developed a new secondary diagnosis (e.g. lymphoma) — spleen growth cannot be attributed to GD alone after 14 months
B	Disease reactivation and progression consistent with ERT interruption — worsening of visceral disease is expected when ERT stops ✓ CORRECT
C	The previous response to ERT was a placebo effect — GD does not respond reliably to enzyme replacement
D	Bone crisis episodes are unrelated to Gaucher disease and should be investigated independently for sickle cell disease

Answer B: ERT interruption in GD may lead to disease reactivation — re-expansion of spleen and liver, fall in haemoglobin, and rise in disease biomarkers (chitotriosidase, ferritin). This is the expected clinical trajectory and underscores the need for uninterrupted supply. Bone crises are a known Gaucher complication.

📊 POLL — CASE 3 Q2

You have no MRI available locally to assess bone disease. Plain X-rays show Erlenmeyer flask deformity and subchondral sclerosis. The patient has severe hip pain. What is the MOST appropriate next step for bone management without advanced imaging?

A	Prescribe high-dose NSAIDs long-term as definitive therapy for Gaucher bone disease
B	Perform immediate hip joint replacement surgery without further imaging or haematological optimisation
C	Optimise analgesia, supplement vitamin D and calcium, urgently advocate for ERT resumption, and refer to orthopaedics
D	Reassure the patient that Erlenmeyer flask deformity is a benign radiological finding requiring no action

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B	Perform immediate hip joint replacement surgery without further imaging or haematological optimisation
C	Optimise analgesia, supplement vitamin D and calcium, urgently advocate for ERT resumption, and refer to orthopaedics — avascular necrosis must be excluded and early surgery may be needed ✓ CORRECT
D	Reassure the patient that Erlenmeyer flask deformity is a benign radiological finding requiring no action

Answer C: Plain X-ray cannot exclude avascular necrosis (AVN) which requires MRI — however clinical suspicion and orthopaedic referral are appropriate. Subchondral sclerosis on plain film may indicate early AVN. Vitamin D/calcium supplementation, analgesia, haematological optimisation, and urgent ERT advocacy are all appropriate. Erlenmeyer flask deformity reflects bone remodelling failure and is not benign.

CASE 3 | Type 3 GD in Adults — ERT Interruption, Bone Disease, and Monitoring

MANAGEMENT APPROACH

MANAGEMENT STEPS

- Document disease reactivation formally: spleen size (US or clinical cm), FBC, chitotriosidase, ferritin
- Urgently advocate for ERT reinstatement via manufacturer ,international GD networks
- Analgesia: paracetamol ± codeine for bone pain; avoid long-term NSAIDs (haematological risk)
- Vitamin D and calcium supplementation; treat iron deficiency if confirmed
- Orthopaedic referral: evaluate for avascular necrosis and fracture risk
- Neurological assessment every 6 months: document HSGP, cognitive screening, gait

KEY CLINICAL POINTS

- ERT interruption causes predictable visceral relapse — must be advocated against strongly
- Bone disease in GD is progressive and largely irreversible — prevention is far better than treatment
- Chitotriosidase is an excellent, relatively accessible biomarker for monitoring
- Type 3 adults may reach adulthood with near-normal function — protect that function

Physicians should document disease burden carefully to support access applications. International advocacy tools include the IWGGD and manufacturer Patient Access Programmes. Regional haematology societies have an important role in lobbying national health ministries for lysosomal storage disorder treatment funding.

KEY LEARNING POINTS

Neuronopathic Gaucher Disease

🔍 **Recognise the neurological hallmark:** Horizontal supranuclear gaze palsy (HSGP) + hepatosplenomegaly = think lysosomal storage disorder

🧪 **Diagnose practically:** Bone marrow biopsy + dried blood spot enzyme assay (sent to reference lab) = accessible pathway

💊 **ERT is visceral, not neurological:** It improves spleen, liver, blood counts — but does NOT halt CNS progression in type 2/3

🕊️ **Type 2 GD is a palliative diagnosis:** Honest prognosis + comfort care + family support is the right framework

📋 **Monitor with available tools:** Clinical spleen size, FBC, chitotriosidase, plain X-ray — MRI is ideal but not always essential

🌍 **Advocate:** Use international registries, compassionate access programmes, and ministry-level advocacy to secure treatment