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Diagnostic Challenges of Hyperviscosity Symptoms: A Case of Concomitant Secondary Polycythaemia and Intracranial Hypotension

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Abstract

A man in his 60s with obstructive sleep apnoea (OSA) and a ventriculoperitoneal (VP) shunt for idiopathic intracranial hypertension (IIH) presented with worsening occipital headache and photophobia, posing a diagnostic challenge between symptomatic secondary erythrocytosis and chronic intracranial hypotension potentially related to shunt over-drainage. Investigations revealed marked erythrocytosis, with haemoglobin 207 g/L and haematocrit 0.640 L/L. Haematology favoured secondary erythrocytosis associated with poor adherence to continuous positive airway pressure therapy and possible medication-related contributions, including testosterone. Neuroimaging demonstrated features suggestive of longstanding intracranial hypotension, raising the possibility of a concurrent shunt-related contributor to headache. Neurosurgical assessment recommended no acute intervention. Neither haematological nor radiological findings established the cause of the headache, and multiple mechanisms may have contributed simultaneously. Testosterone was withheld, respiratory treatment was optimised, and analgesia was increased. Without venesection or shunt intervention, haemoglobin declined to 187 g/L over six days and was 190 g/L before discharge, accompanied by symptomatic improvement. However, the interval between blood samples and concurrent treatment changes prevented attribution of the improvement to a specific intervention. This case highlights the diagnostic challenges of evaluating headache in patients with pre-existing neurosurgical conditions, emphasising the risk of premature diagnostic anchoring and the importance of recognising that intracranial, systemic, and medication-related factors may coexist and contribute to the clinical presentation

Categories: Neurology, Hematology, Endocrinology/Diabetes/Metabolism
Keywords: hyperviscosity syndrome, intracranial hypotension syndrome, obstructive sleep apnoea, persistent headache, secondary polycythaemia

Introduction

Erythrocytosis is characterised by an elevation in circulating red blood cells, typically identified through increased haemoglobin and haematocrit. Contemporary diagnostic thresholds include haemoglobin >165 g/L or haematocrit >0.49 L/L in men, and haemoglobin >160 g/L or haematocrit >0.48 L/L in women [1]. An important distinction is between relative erythrocytosis, which results from reduced plasma volume due to factors such as dehydration, gastrointestinal fluid losses, or diuretic use, and absolute erythrocytosis, which reflects a genuine increase in red cell mass. Differentiation is initially guided by clinical assessment, medication history and serial blood counts, with direct measurement of red cell mass and plasma volume providing confirmation when required and available. In men with a haematocrit >0.60 L/L, absolute erythrocytosis can generally be assumed, although a concurrent reduction in plasma volume may contribute to the measured elevation [1,2]. Absolute erythrocytosis may be primary, most notably polycythaemia vera, or secondary to conditions such as hypoxia, obstructive sleep apnoea (OSA), and testosterone therapy [1].

Beyond identifying the presence and underlying cause of erythrocytosis, determining its clinical significance presents a further challenge. Elevated haematocrit increases blood viscosity and may reduce cerebral blood flow, with headache and visual disturbances recognised as potential manifestations of hyperviscosity [2,3]. Although physiological studies have demonstrated an association between haematocrit values of approximately 0.47-0.58 L/L and reduced cerebral blood flow, no definitive haemoglobin or haematocrit threshold has been established at which hyperviscosity symptoms develop [2]. The occurrence and severity of symptoms vary between individuals, making it difficult to establish whether an elevated haematocrit is directly responsible for headache, particularly when other potential causes coexist.

This diagnostic uncertainty is particularly relevant in secondary erythrocytosis, where several underlying factors may contribute simultaneously. OSA is one recognised contributor, as recurrent episodes of nocturnal hypoxaemia may stimulate erythropoietin production and increase red cell mass. A meta-analysis of 3,654 adults with OSA reported a polycythaemia prevalence of approximately 2% overall, increasing to 6% among those with severe OSA [4]. The same meta-analysis found that continuous positive airway

pressure (CPAP) therapy was associated with modest reductions in haemoglobin (mean 3.76 g/L) and haematocrit (1.1 percentage points), although these findings were predominantly derived from patients without baseline polycythaemia [4]. Testosterone therapy is another recognised contributor, stimulating erythropoiesis through increased erythropoietin production and suppression of hepcidin, thereby enhancing iron availability for red cell production [5]. A systematic review reported testosterone-associated erythrocytosis rates ranging from 0% to 66.7%, particularly with intramuscular formulations, higher doses, and older age [6]. However, substantial differences in study populations, testosterone preparations, treatment regimens, and diagnostic thresholds limit the applicability of these prevalence estimates to individual patients. These overlapping contributors, together with the absence of a reliable threshold for symptomatic hyperviscosity, can complicate the assessment of headache and reinforce the need to consider alternative or coexisting causes rather than attributing symptoms to erythrocytosis alone.

Idiopathic intracranial hypertension (IIH) is characterised by raised intracranial pressure without an identified secondary cause. Headache, transient visual obscurations, pulsatile tinnitus and papilloedema may occur, while progressive visual impairment remains an important clinical concern. Treatment aims to preserve vision and manage headache, with cerebrospinal fluid (CSF) diversion considered when visual function is threatened or deteriorating [7,8].

A ventriculoperitoneal (VP) shunt diverts CSF from a cerebral ventricle through a valve and catheter into the peritoneal cavity, where it is absorbed [9]. Although effective in reducing intracranial pressure, shunting carries risks of obstruction, infection, and excessive CSF drainage, commonly termed shunt over-drainage. Excessive drainage, which may be exacerbated by upright posture and siphoning, can reduce intracranial CSF volume or pressure, potentially resulting in intracranial hypotension. The reported frequency of shunt over-drainage varies considerably according to patient population, valve design, and diagnostic criteria, limiting the applicability of a single prevalence estimate to patients with IIH [9,10].

Intracranial hypotension classically presents with an orthostatic headache that worsens when upright and improves on lying down, sometimes accompanied by nausea, neck pain, or auditory symptoms. However, the positional component may become less pronounced or absent in longstanding cases, making clinical recognition more challenging [10,11]. Neuroimaging may demonstrate slit-like ventricles, reflecting marked narrowing of the ventricular cavities, and subdural hygromas, which are collections of CSF-like fluid between the arachnoid and dura [10]. MRI may additionally reveal diffuse pachymeningeal enhancement, venous engorgement, or downward displacement of intracranial structures [11]. Nevertheless, these findings are neither universally present nor sufficient to establish symptomatic shunt over-drainage, and their significance must be interpreted alongside the clinical presentation [10,11].

Assessment of headache in patients with a VP shunt should include careful characterisation of the headache phenotype, neurological examination, fundoscopy and evaluation of visual function [7,8]. Importantly, headache in patients with IIH frequently has a migraine-like or tension-type phenotype, while primary headache disorders and medication-overuse headache may coexist with IIH [7,8,12]. Worsening headache should therefore not automatically be attributed to raised intracranial pressure or shunt dysfunction. IIH consensus guidelines advise against routine diagnostic lumbar puncture in shunted patients without papilloedema, and note that routine CT imaging and shunt-series radiographs are unlikely to be informative in the absence of papilloedema, unless other clinical concerns warrant investigation [7]. Specialist intracranial pressure monitoring may be considered in selected cases where diagnostic uncertainty persists [7,9]. Management of established shunt over-drainage may involve anti-siphon devices, adjustment of programmable valve settings or shunt revision [9,10]. Unlike programmable valves, fixed-pressure valves cannot be adjusted non-invasively and may require surgical replacement if alteration of drainage characteristics is necessary [9].

This case describes a patient with a history of IIH treated with VP shunting who presented with worsening headache in the presence of marked erythrocytosis and neuroimaging findings suggestive of chronic intracranial hypotension. These findings raised two potential, and possibly coexisting, explanations for his symptoms: erythrocytosis-associated hyperviscosity and intracranial hypotension potentially related to shunt over-drainage. However, neither the degree of erythrocytosis nor the radiological abnormalities could independently establish the cause of his headache. The case highlights the challenges of distinguishing clinically significant abnormalities from incidental or chronic findings, particularly when multiple mechanisms may contribute to symptom deterioration. It also emphasises the importance of avoiding premature diagnostic anchoring on shunt-related pathology in patients with a neurosurgical history, while maintaining a broad assessment of systemic, medication-related and intracranial contributors.

Case Presentation

A man in his 60s presented to the emergency department with a several-week history of worsening occipital headache and photophobia against a background of chronic headache. The headache was continuous and non-postural, without morning predominance or exacerbation by coughing, straining, or bending. He also reported nausea. There was no associated fever, vomiting, seizure activity, new limb weakness, sensory disturbance, or speech difficulty. There was no pain, redness, or swelling along the shunt tract, abdominal pain, or previous episodes of shunt malfunction. Antibiotics and antiemetics prescribed by his general

practitioner had not improved his symptoms. A productive cough and bibasal crackles were also noted, although chest radiography showed no consolidation.

His neurological history included IIH treated with a right-sided Medtronic medium fixed-pressure VP shunt (Medtronic plc, Galway, Ireland) seven years earlier and bilateral optic nerve sheath fenestration on two occasions. No recent shunt assessment was available, and he reported no recent shunt-related intervention. Other comorbidities included OSA, hypertension, type 2 diabetes mellitus, chronic kidney disease recorded as stage 4, ischaemic heart disease, peripheral venous disease, chronic liver disease, cervical degenerative disease, peripheral neuropathy and depression. Erythrocytosis had reportedly been present since three years prior to presentation, with haemoglobin approximately 190 g/L six months before presentation.

His regular medications included intramuscular testosterone undecanoate (Nebido), empagliflozin, indapamide and furosemide. Other medications comprised aspirin, atorvastatin, bisoprolol, irbesartan, isosorbide mononitrate, metformin, insulin glargine, rivaroxaban, gabapentin, venlafaxine, finasteride, tamsulosin, omeprazole, ferrous fumarate and modified-release morphine (Zomorph) 10 mg twice daily. The testosterone dose and date of the last injection were not available. He reported poor adherence to CPAP, although the frequency and duration of use were not quantified. No sleep study report or measure of OSA severity was available.

At the first recorded emergency department observations, blood pressure was 134/88 mmHg, pulse 85 beats/minute, respiratory rate 20 breaths/minute, temperature 35.9 °C, and oxygen saturation 97% on room air. Glasgow Coma Scale was 15/15. He appeared plethoric but was alert and oriented. Visual fields were full on confrontation, pupils were equal and reactive to light, and eye movements were normal. Fundoscopy showed no papilloedema or optic atrophy. The remaining cranial nerve examination was normal, with normal limb power, sensation, coordination, and gait. There was no neck stiffness. Visual acuity was not measured. Mucous membranes were moist and peripheral perfusion was normal. Jugular venous pressure was not elevated, and there was no peripheral oedema, cyanosis or clubbing. Cardiovascular examination was unremarkable. Respiratory examination noted bibasal crackles. The abdomen was soft and non-tender, without palpable hepatomegaly or splenomegaly. The shunt tract showed no redness, swelling, tenderness, or wound abnormality. Weight and a quantified fluid balance were not documented.

Postural (orthostatic) blood pressure measurements were 112/73 mmHg after five minutes lying, 99/63 mmHg after one minute standing, and 105/70 mmHg after three minutes standing. Subsequent blood pressure fluctuated: it reached 168/97 mmHg the next day (Day 1), with several lower readings during the next three days, including 113/58 mmHg on Day 3 and 128/55 mmHg on Day 5. Hypertension recurred near discharge, with readings of 188/94 mmHg at 23:38 on Day 8 and 186/95 mmHg at 04:51 on Day 9, followed by 120/63 mmHg at 14:22 that day.

The initial full blood count, collected on the day of presentation (Day 0), showed haemoglobin 207 g/L, haematocrit 0.640 L/L, and red blood cell count 7.08×10^{12}/L. White blood cell count was 11.6×10^{9}/L, platelet count 162×10^{9}/L, mean corpuscular volume 90 fL, and mean corpuscular haemoglobin 29.2 pg. The accompanying renal profile showed sodium 134 mmol/L, potassium 5.0 mmol/L, urea 9.7 mmol/L, and creatinine 157 µmol/L, with estimated glomerular filtration rate 38 mL/minute/1.73 m^2. Additional available results, including liver biochemistry and coagulation tests, are presented with the laboratory reference intervals in Table *1*.

Investigation	Result	Reference range
Haemoglobin	207	130-180 g/L
Haematocrit	0.640	0.400-0.540 L/L
Red blood cells	7.08	4.50-6.50 $\times 10^{12}$/L
White blood cells	11.6	4.0-11.0 $\times 10^{9}$/L
Platelets	162	140-400 $\times 10^{9}$/L
MCV	90	80.0-99.0 fL
MCH	29.2	27.0-32.0 pg
Sodium	134	133-146 mmol/L
Potassium	5.0	3.5-5.3 mmol/L
Urea	9.7	2.5-7.8 mmol/L
Creatinine	157	60-120 µmol/L
eGFR	38	-
Erythropoietin	19.6 IU/L	4.3-29 IU/L
JAK2 V617F	Not detected (ARMS-PCR; ipsogen JAK2 RGQ PCR Kit (QIAGEN N.V., Venlo, Netherlands))	Negative
Ferritin/iron studies	Not performed	Not performed
Red cell mass/plasma volume	Not measured	Not measured
Total protein	78 g/L	57-82 g/L
Albumin	46 g/L	35-50 g/L
Alkaline phosphatase	60 U/L	30-130 U/L
Alanine aminotransferase	46 U/L	10-49 U/L
Total bilirubin	10 µmol/L	0-21 µmol/L
INR	1.4	1-2
Prothrombin time	18.7 seconds	12.0-15.0 seconds
APTT	45.8 seconds	26.1-36.6 seconds

TABLE 1: Initial laboratory investigations and laboratory reference intervals.

MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; eGFR, estimated glomerular filtration rate; *JAK2*, Janus kinase 2; ARMS-PCR, amplification refractory mutation system-polymerase chain reaction; INR, international normalised ratio; APTT, activated partial thromboplastin time

Serum erythropoietin was 19.6 IU/L (reference range, 4.3-29 IU/L). Analysis of codon 617 in exon 14 of *JAK2* by amplification-refractory mutation system (ARMS)-polymerase chain reaction (PCR) using the ipsogen *JAK2* RGQ PCR Kit (QIAGEN N.V., Venlo, Netherlands) detected no V617F variant. No arterial blood gas analysis was performed. The repeat full blood count on Day 6 showed haemoglobin 187 g/L and haematocrit 0.569 L/L, representing reductions of 20 g/L and 0.071 L/L, respectively, from Day 0. No intervening results were available to establish when within that interval the fall occurred. In the last available blood count done on Day 8, before self-discharge on Day 9, haemoglobin was 190 g/L and haematocrit 0.585 L/L.

Initial laboratory investigations demonstrated marked erythrocytosis with a haemoglobin of 207 g/L, haematocrit of 0.64, and red blood cell count of 7.08 $\times 10^{12}$/L (Table *2*). Mean corpuscular volume and mean corpuscular haemoglobin were within normal limits. Serum erythropoietin was within the normal range (19.6 IU/L), and *JAK2* mutation testing was negative, supporting a diagnosis of secondary polycythaemia.

Sample day, time	Hb (g/L)	Hct (L/L)	Clinical context
Day 0, 10:32	207	0.640	Initial presentation
Day 6, 12:48	187	0.569	First available repeat; substantial fall documented by this date
Day 8, 12:41	190	0.585	Last available result before self-discharge on Day 9
Two-month follow-up, 10:35	193	0.584	Persistent erythrocytosis after discharge
~1.4-year-follow-up, 11:14	158	0.487	Later follow-up; Lower than initial values

TABLE 2: Serial haemoglobin (Hb) and haematocrit (Hct) measurements.

Neuroimaging

Serial neuroimaging was reviewed for possible shunt-related pathology. CT three months prior to presentation described bilateral convexity subdural collections measuring up to 7 mm on each side. The shunt tip lay within the right lateral ventricle, which was smaller than the left but unchanged compared with the MRI done one month prior to presentation (Figure *1a*). There was no midline shift. The initial report raised the possibility of over-drainage, and a consultant addendum noted that the collections might be slightly deeper than on the MRI done two years prior. Streak artefact from a necklace limited posterior fossa assessment and prevented evaluation of cerebellar tonsillar position.

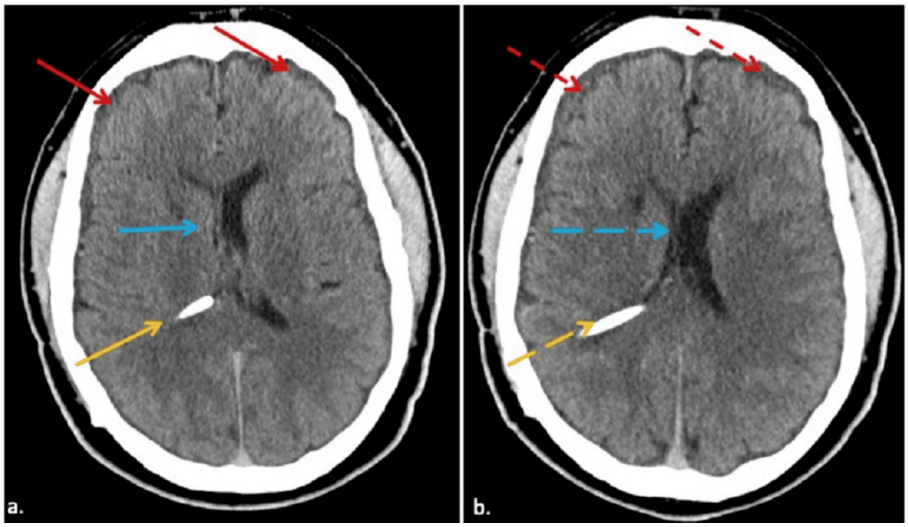


FIGURE 1: Axial CT soft tissue window

(A) Two months prior to presentation, demonstrating bilateral subdural hygromas (red arrows), an effaced right lateral ventricle (blue arrow), and the ventriculoperitoneal shunt (orange arrow). (b) At presentation, demonstrating unchanged bilateral subdural hygromas (dashed red arrows), an effaced right lateral ventricle (dashed blue arrow), and the ventriculoperitoneal shunt (dashed orange arrow).

CT at presentation showed no significant interval change in the subdural collections or ventricular dimensions compared with the scan done three months prior (Figure *1b*). Neither CT report identified acute haemorrhage, a mass lesion, or infarction.

Contrast-enhanced MRI on Day 5 showed shallow, fairly balanced bilateral subdural collections on axial T1- and T2-weighted imaging (Figures *2a*, *2b*), with smooth circumferential dural enhancement on post-contrast T1-weighted imaging (Figure *2c*). The collections were described as longstanding but slightly deeper than on the MRI two years prior. Ventricular appearances remained stable: the third and right lateral ventricles were slit-like, whereas the left lateral ventricle was normally sized. No midbrain sagging, cerebellar tonsillar descent, or obvious dural venous sinus distension was reported. The overall radiological impression favoured longstanding intracranial hypotension, while acknowledging that not all classical features were present. Figure *2d* provides a sagittal post-contrast T1-weighted view.

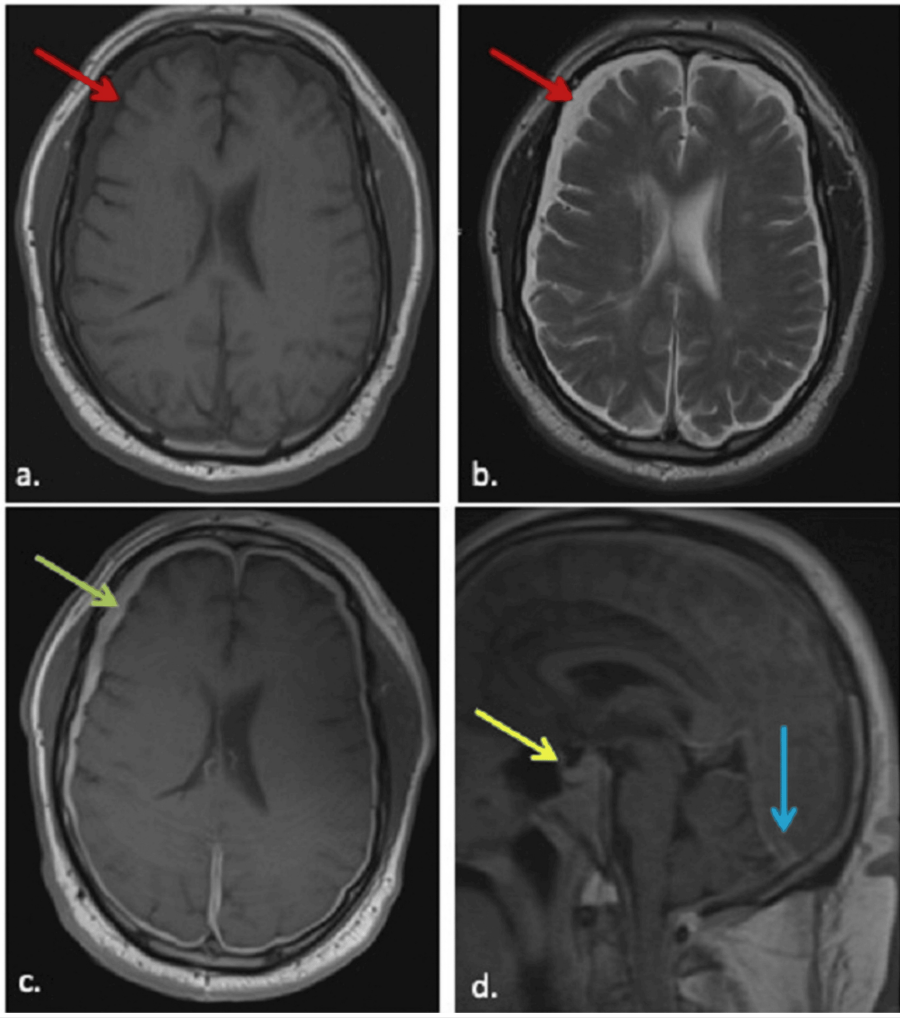


FIGURE 2: MRI of the brain at presentation.

(a) Axial T1-weighted image and (b) axial T2-weighted image demonstrating bilateral subdural hygromas (red arrows). (c) Axial T1-weighted image with contrast demonstrating smooth circumferential dural enhancement (green arrow). (d) Sagittal T1-weighted image with contrast demonstrating a normal pituitary gland (yellow arrow) and normal-appearing venous sinuses (blue arrow).

Differential diagnosis

The differential diagnosis included shunt malfunction, chronic shunt over-drainage, primary headache disorders such as migraine, medication-overuse headache and symptomatic erythrocytosis-associated hyperviscosity. The marked erythrocytosis raised the possibility of a systemic contribution to his headache, while the longstanding subdural collections and pachymeningeal enhancement were suggestive of chronic intracranial hypotension, potentially related to shunt over-drainage. However, neither finding independently established the cause of his symptoms.

Neurosurgical review recommended no acute intervention. Shunt-series imaging and intracranial pressure measurements were not performed, and a formal valve assessment was not documented. Given the coexistence of significant haematological abnormalities, radiological features of intracranial hypotension and a history of chronic headache, the recent symptomatic deterioration was considered likely multifactorial, with potentially overlapping contributions from erythrocytosis-associated hyperviscosity and altered CSF dynamics. Nevertheless, the available clinical and investigative findings did not allow the relative contribution of each mechanism to be determined.

Treatment

Management addressed potentially modifiable systemic factors alongside neurosurgical assessment. Testosterone was withheld because of its association with erythrocytosis. Endocrinology advised continuing to withhold testosterone until haemoglobin was below 175 g/L. Haematology initially recommended

venesection, but this was deferred because the patient's symptoms improved; haemoglobin was 190 g/L on 20 March. Zomorph was increased from 10 mg to 20 mg twice daily.

CPAP was used regularly at night during admission, although nightly usage hours, device settings, and residual respiratory events were not quantified. Supplemental oxygen was administered at 2-4 L/minute through nasal cannulae during the inpatient course. The exact start dates and durations of these interventions were not documented. Blood pressure was monitored but remained variable, including elevated readings shortly before discharge.

Outcome and follow-up

Headache improvement was noted during admission despite persistent erythrocytosis. Haemoglobin had fallen to 187 g/L by Day 6 and was 190 g/L on Day 8, without venesection. The temporal association between symptom improvement and the changes in treatment does not establish which intervention was responsible or exclude a contribution from chronic intracranial hypotension. He self-discharged on Day 9, limiting further inpatient assessment. Neurosurgical and haematology follow-up were arranged.

Repeat blood tests at presentation showed haemoglobin 193 g/L and haematocrit 0.584 L/L. At haematology review four months later, the clinical impression was secondary erythrocytosis associated with OSA and presumed chronic hypoxia, with possible contributions from testosterone and empagliflozin. Ferrous fumarate was noted in the medication review, but iron studies and the indication for supplementation had not been investigated. No primary haematological cause was identified on the available assessment, which included negative *JAK2* V617F and exon 12 testing. Haemoglobin and haematocrit levels were considered consistent with his values over the preceding two years. Empagliflozin was continued for diabetic control.

Abdominal ultrasonography three months after presentation described an enlarged liver with diffusely increased echogenicity, suggestive of fatty infiltration, without focal lesions or intrahepatic duct dilatation. A 2.1 cm simple right renal cyst was also reported, with no other renal abnormality described. Splenic findings were not documented. His headache had improved, and he was discharged from haematology follow-up.

Later blood tests at the 1.4-year follow-up showed haemoglobin 158 g/L and haematocrit 0.487 L/L. Testosterone had not been resumed, empagliflozin had been continued, and neither venesection nor shunt intervention had occurred during follow-up. Longer-term CPAP adherence was not quantified. Neurosurgical review four months after presentation reportedly documented resolution of the headache and discharge from follow-up. The clinical and investigation timeline is shown in Table *3*.

Time Point	Event / investigations	Clinical significance
~ Two months prior to presentation	CT: bilateral convexity subdural collections up to 7 mm; reduced right ventricular size	Pre-admission comparison
Day 0	ED presentation with continuous non-postural headache; Hb 207 g/L, Hct 0.640; CT without significant interval change	Index presentation
Day 5	MRI: bilateral collections, pachymeningeal enhancement and slit-like right/third ventricles	Suggestive of chronic intracranial hypotension
Day 6	Hb 187 g/L, Hct 0.569	First repeat sample; no intermediate samples
Day 8	Hb 190 g/L, Hct 0.585	Last documented inpatient full blood count
Day 9	Self-discharge after symptomatic improvement	No venesection or shunt intervention
~Two-month follow-up	Hb 193 g/L, Hct 0.584	Persistent erythrocytosis
~Four-month follow-up	Haematology review: multifactorial secondary erythrocytosis considered	OSA, testosterone and empagliflozin considered
~1.4-year follow-up	Hb 158 g/L, Hct 0.487	Subsequent reduction; headache resolution reported at later neurosurgical review

TABLE 3: Clinical and investigation timeline.

Hb, haemoglobin; Hct, haematocrit; OSA, obstructive sleep apnoea

Discussion

The principal diagnostic challenge in this case was determining whether the patient's worsening headache was attributable to marked erythrocytosis, chronic intracranial hypotension potentially associated with VP shunt over-drainage, or a coexisting headache disorder. Although each represented a plausible explanation, the coexistence of haematological and radiological abnormalities did not establish their clinical significance. The headache was therefore considered likely multifactorial, with potentially overlapping mechanisms contributing to symptom deterioration. However, the available findings could not establish the relative contribution of each mechanism, and the subsequent improvement did not resolve this uncertainty.

The marked erythrocytosis was an important finding because of its potential contribution to cerebral hyperviscosity. At presentation, haemoglobin was 207 g/L and haematocrit was 0.640 L/L. In men, a haematocrit exceeding 0.60 L/L strongly supports absolute erythrocytosis without requiring direct red cell mass measurement, although concurrent plasma volume contraction may accentuate the measured elevation [1,13]. Increased blood viscosity has been associated with reduced cerebral blood flow, providing a plausible physiological mechanism for headache; however, Humphrey et al. examined relative polycythaemia and did not establish a haemoglobin or haematocrit threshold at which headache develops [2]. Consequently, although the degree of erythrocytosis was clinically significant, its contribution to the patient's symptoms could not be determined from the blood count alone.

Establishing the cause of the erythrocytosis introduced further complexity, as several potential contributors were present. The haematology team favoured secondary erythrocytosis, with OSA, poor reported adherence to CPAP therapy, testosterone treatment and empagliflozin considered plausible contributors [1,6]. Negative *JAK2* V617F and exon 12 testing, together with an erythropoietin concentration within the laboratory reference interval, supported this working diagnosis without definitively excluding all primary marrow disorders [1,13]. Nevertheless, the relative importance of the individual secondary factors remained uncertain. Meta-analyses indicate that erythrocytosis occurs in a minority of patients with OSA, with a pooled polycythaemia prevalence of approximately 2% overall and 6% among those with severe disease [4,14]. Furthermore, nocturnal oxygen saturation may be more closely associated with secondary erythrocytosis than the apnoea-hypopnoea index in some populations, although neither measurement was available in this case [15]. Testosterone-associated erythrocytosis is also well recognised, but reported prevalence varies substantially with formulation, dosage and patient characteristics [6]. These findings support the possibility of several interacting contributors rather than allowing the marked erythrocytosis to be attributed confidently to OSA or any single medication.

Although erythrocytosis offered one plausible explanation for the headache, the patient's neurosurgical history and neuroimaging findings raised a separate concern. Longstanding bilateral subdural collections, pachymeningeal enhancement, and slit-like ventricular appearances were suggestive of chronic intracranial hypotension, potentially related to shunt over-drainage [10,11]. However, radiological features of over-drainage do not necessarily indicate symptomatic intracranial hypotension [10]. In this case, the headache was continuous rather than clearly orthostatic, and CT appearances remained unchanged between the two scans done three months prior to presentation and at presentation. These findings made a newly developed shunt-related cause of the deterioration less certain, although stable ventricular size does not reliably exclude shunt dysfunction in patients with IIH [9]. The presence of a fixed-pressure valve also did not establish over-drainage, despite limiting the option of non-invasive valve adjustment [9,10].

Neurosurgical assessment recommended no acute intervention. This was consistent with the need to interpret radiological abnormalities alongside the clinical presentation rather than treating imaging findings in isolation. IIH consensus guidance discourages routine shunt revision for headache without papilloedema or threatened visual function and recommends a clinically directed approach to further investigations [7]. Although fundoscopy demonstrated no papilloedema, formal visual acuity and perimetry assessments were unavailable. Intracranial pressure was not measured, limiting physiological confirmation of over-drainage or another pressure-related disturbance. Nevertheless, the absence of pressure monitoring did not necessarily represent an omitted investigation, as its use must be guided by the clinical circumstances [7,9]. Taken together, the imaging findings supported chronic intracranial hypotension as a possible contributor but did not establish that it was responsible for the recent worsening of headache.

The diagnostic uncertainty was further compounded by the possibility of a coexisting primary or medication-related headache disorder. Photophobia and nausea were compatible with a migraine-like phenotype, which is common among patients with IIH [7,8,12]. Medication-overuse headache has also been described in patients with CSF shunts [16]. However, the International Classification of Headache Disorders, third edition (ICHD-3), requires headache occurring on at least 15 days per month in a patient with regular medication overuse for more than three months, with opioid overuse defined as use on at least 10 days per month [17]. The available analgesic history was insufficient to establish these criteria. Accordingly, migraine and medication-overuse headache remained potential overlapping mechanisms rather than confirmed diagnoses. Their consideration was nevertheless important because worsening headache in a patient with a VP shunt should not automatically be attributed to intracranial pressure abnormalities [7].

The subsequent clinical course provided an opportunity to assess these competing explanations, although the response to treatment remained difficult to interpret. During admission, haemoglobin decreased from 207 g/L on Day 0 to 187 g/L on Day 6 without venesection, before measuring 190 g/L, with a haematocrit of 0.585 L/L, on Day 8. As no intervening blood counts were available, the precise timing of the decline within the six-day interval could not be established. During this period, nocturnal CPAP and supplemental oxygen were provided, testosterone was withheld, and morphine was increased. The patient also experienced symptomatic improvement. However, because these interventions occurred concurrently, neither the haematological response nor headache improvement could be attributed confidently to a particular treatment.

Several mechanisms could have contributed to the reduction in haemoglobin. CPAP therapy has been associated with modest average reductions in haemoglobin and haematocrit, although pooled findings do not establish that it could account for the magnitude or timing of the decline observed over six days in this patient [4]. Withholding testosterone was also appropriate, as Endocrine Society guidance recommends interrupting testosterone therapy when haematocrit exceeds 0.54 L/L and evaluating contributing factors such as hypoxia and sleep apnoea [18]. However, the erythropoietic effects of testosterone do not necessarily reverse immediately. A systematic review reported that haemoglobin and haematocrit returned to normal approximately three months after testosterone discontinuation in one study [6]. This observation cannot be directly extrapolated to intramuscular testosterone undecanoate because of differences in formulation, pharmacokinetics and duration of action. Consequently, the six-day reduction in haemoglobin observed in this patient cannot be confidently attributed to withholding testosterone. Although treatment of OSA and cessation of testosterone may have contributed to the overall improvement, neither intervention could independently explain the observed short-term response.

Changes in plasma volume represented another potential influence on the haematological trajectory. The patient was receiving indapamide, furosemide and empagliflozin, which could potentially contribute to haemoconcentration through their effects on fluid balance. Nevertheless, haematocrit decreased while these medications were continued, and the absence of formal fluid-balance records or serial plasma-volume measurements prevented assessment of whether changing hydration status contributed to the decline. Given the patient's coexisting heart failure and ischaemic heart disease, established diuretic treatment was maintained during admission while other potentially reversible contributors were addressed. If erythrocytosis had persisted, reassessment of the medication regimen alongside volume status and cardiovascular risk could have been considered. However, this remains a retrospective clinical consideration rather than evidence that diuretic treatment caused the erythrocytosis or its subsequent improvement.

Despite the reduction in haemoglobin and improvement in headache, the erythrocytosis had not resolved by discharge. Venesection was initially recommended but subsequently deferred following symptomatic improvement. This decision should not be interpreted as evidence that venesection was unnecessary, particularly as haematocrit remained markedly elevated at 0.585 L/L. British Society for Haematology guidance recommends considering venesection in patients with hypoxic pulmonary disease who have symptoms attributable to hyperviscosity or a haematocrit above 0.56 L/L, with a suggested target of 0.50-0.52 L/L (Grade 2C) [19]. However, its applicability in this case required individualised judgement because the degree of hypoxia had not been objectively established and the erythrocytosis was potentially multifactorial. The persistence of an elevated haematocrit despite symptomatic improvement further demonstrated that the relationship between erythrocytosis and headache was not straightforward. Serial full blood counts, symptom assessment and reassessment of the underlying contributors therefore remained important.

The longer-term clinical course reinforced this uncertainty. Haemoglobin remained elevated at 193 g/L at the three-month follow-up but had decreased to 158 g/L by the four-month follow-up, when headache resolution was also reported. Testosterone had remained withheld, and empagliflozin was continued, while neither venesection nor shunt revision had been performed. These findings were compatible with a reversible component of secondary erythrocytosis but did not establish that the shunt-related radiological abnormalities were clinically insignificant. The limited number of follow-up blood counts, unknown timing of headache resolution, unquantified long-term CPAP adherence and absence of repeat neuroimaging prevented a direct relationship between haematological normalisation and headache resolution from being established. Important additional limitations included the absence of nocturnal oxygenation and blood gas measurements, detailed testosterone administration records, systematic headache severity assessments and complete visual function testing. Smoking and carbon monoxide exposure, iron status and changes in plasma volume were also insufficiently characterised.

Ultimately, this case illustrates the difficulty of distinguishing clinically significant abnormalities from findings that may be chronic, incidental or only partially responsible for a patient's symptoms. Marked erythrocytosis provided a plausible mechanism for hyperviscosity-associated headache, while neuroimaging suggested chronic intracranial hypotension potentially related to shunt over-drainage. A coexisting primary or medication-related headache disorder could also have contributed. Although the headache was considered likely multifactorial, the relative contribution of these mechanisms could not be established. Importantly, symptomatic improvement occurred without venesection or neurosurgical intervention and while the haematocrit remained substantially elevated, demonstrating that treatment response alone could

not resolve the diagnostic ambiguity. The case therefore emphasises the importance of avoiding premature diagnostic anchoring on either haematological or neurosurgical findings, favouring a multidisciplinary assessment that considers systemic, intracranial and headache-related mechanisms together, supported by serial blood counts, clinical reassessment and appropriate longer-term follow-up. One limitation is that the full discharge letter was unavailable, limiting verification of the detailed assessment and plan.

Conclusions

This case highlights the diagnostic challenges of evaluating worsening headache in patients with pre-existing neurosurgical conditions when multiple potentially contributory abnormalities coexist. Marked erythrocytosis raised the possibility of hyperviscosity-associated headache, while neuroimaging suggested chronic intracranial hypotension potentially related to VP shunt over-drainage. A coexisting primary or medication-related headache disorder may also have contributed, suggesting a multifactorial aetiology. However, neither the haematological nor radiological findings established causation, and symptomatic improvement following concurrent interventions could not be attributed to any single treatment. Importantly, headache improved despite persistent erythrocytosis and without neurosurgical intervention, further illustrating the uncertainty surrounding the relative contribution of these mechanisms. This case emphasises the importance of avoiding premature diagnostic anchoring on either shunt-related pathology or systemic abnormalities, recognising that multiple mechanisms may coexist, and adopting a multidisciplinary approach supported by careful clinical assessment and longitudinal follow-up.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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