CASE REPORT

Reversible brain lesion following growth hormone replacement therapy in an adolescent

Adamos Hadjipanayis,¹ Elisavet Efstathiou,² Leda Theophilou,³ George Chrousos⁴

¹School of Medicine, Larnaca General Hospital, European University Cyprus, Larnaca, Cyprus

²Pediatric, Larnaca General Hospital, Larnaca, Cyprus

³St George's University of London, University of Nicosia, Nicosia, Cyprus

⁴Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece

Correspondence to
Dr Adamos Hadjipanayis,
adamos@paidiatros.com

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SUMMARY

A 12.6-year-old girl presented with a 2-month history of headache, recurrent vomiting and 5 kg weight loss. She had been receiving recombinant human growth hormone (rhGH) replacement therapy at a dose of 0.035 mg/kg for the past 10 months, due to short stature. Investigations before initiating rhGH, including brain MRI, had been normal. Physical examination revealed a nystagmus and a mildly elevated arterial blood pressure. Brain MRI revealed a lesion in the posterior aspect of the medulla oblongata, adjacent to the foramen of Magendie. rhGH therapy was discontinued, followed by a gradual resolution of the symptoms. At follow-up 3 months later, she was asymptomatic and physical examination was unremarkable. A subsequent repeat brain MRI showed complete resolution of the lesion, supporting the diagnosis of a variant of reversible posterior leucoencephalopathy syndrome. This is the first case report of a reversible brain lesion linked to rhGH replacement therapy.

BACKGROUND

Recombinant human growth hormone (rhGH) has been approved for use in growth hormone deficiency (GHD) as well as a number of other non-GHD conditions associated with growth impairment, such as chronic renal failure, Turner syndrome, small-for-gestational age without height catch-up, Prader-Willi syndrome, idiopathic short stature, *SHOX* gene haploinsufficiency and Noonan syndrome.¹

The incidence of short stature associated with GHD has been estimated to be about 2.5 per 10 000.² Non-GHD such as found in idiopathic short stature has an incidence of up to 120 per 10 000 children. In adults, the annual incidence of GHD has been estimated to be 1:10 000, in line with the incidence of pituitary tumours, and its prevalence rises to 3:10 000 if adult patients with childhood-onset GHD are included.³ Despite the benefits of rhGH treatment in adults with hypopituitarism, there is still substantial inconsistency worldwide regarding the practice of rhGH therapy in this group.^{4,5}

The diagnosis and management of patients eligible for rhGH replacement treatment with a variety of conditions involve a wide range of specialties such as paediatric endocrinologists, adult endocrinologists, paediatricians, internal medicine specialists, neurologists and radiologists.

Several acute and long-term side effects may be related to the use of rhGH such as headache, rash, pain at injection site, transient fever, idiopathic intracranial hypertension, pseudotumour cerebri, increased intraocular pressure, slipped upper femoral epiphysis and deterioration of existing scoliosis.⁶ A recent position paper concerning the safety of rhGH derived from the Endocrine Society, Pediatric Endocrine Society and Growth Hormone Research Society concluded that growth hormone (GH) continues to have a good safety record when used for approved indications and at the recommended doses. However, the statement highlighted the necessity of ongoing and long-term surveillance of the increasing number of adults who were treated with rhGH in childhood.⁷

To our knowledge, there is no published article in the literature to date presenting a reversible brain lesion as a possible side effect of rhGH replacement therapy. Touching the backdrop of interest in the safety of rhGH replacement treatment, we believe this case report sheds more light in this important area and commands reporting.

CASE PRESENTATION

A 12.6-year-old girl was presented to the emergency department with a 2-month history of constant, generalised headache, nausea and recurrent vomiting. She also reported loss of appetite and a weight loss of 5 kg over the same period, equivalent to 18% of the patient's body weight. She was previously assessed at the age of 10.3 years for short stature by the Department of Paediatric Endocrinology. Her height and weight were below the third percentile (Z-scores -3.3 and -2.7 , respectively). Initial investigations included glucagon stimulation test (GH peak $8.7 \mu\text{g/L}$) and Insulin-like growth factor 1 (IGF1) which was 160 ng/mL . Clonidine test was also performed but was discontinued due to hypotension. Her arterial blood pressure before performing the clonidine test was $111/68 \text{ mm Hg}$. MRI of the brain was unremarkable (figure 1A,B). Additional screening investigations for chronic diseases, including coeliac disease, were negative. Karyotype was $46, XX$. Following this assessment, rhGH replacement therapy was initiated at a dose of 0.035 mg/kg per day. She was followed up at the paediatric endocrinology department every 3 months after the initiation of GH treatment. IGF1 level (165 ng/mL) was measured only at the first follow-up visit. She had been on this treatment for a total duration of 10 months before the symptoms began to occur, which led up to her admission. The

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Figure 1 Sagittal and axial MRI images of the brain before the initiation of the recombinant human growth hormone (rhGH) therapy (A,B), followed by sagittal and coronal MRI images, at admission, showing the hyperintense lesion in the posterior aspect of the medulla oblongata, adjacent to the foramen of Magendie (arrows) (C,D). The images of the repeat MRI of the brain (E,F), 3 months after discontinuation of rhGH therapy, show complete resolution of the lesion in the same area.

growth velocity on GH treatment at 6 and 9 months was 8 cm and 8.6 cm per year, respectively. She was not taking any other concurrent medications during this period, nor was there any indication in the social and family history of recreational drug use or suspicion of poisoning or other accidental or deliberate drug ingestion.

At evaluation during acute presentation at 12.6 years old, her height and weight Z-scores had declined further to -4.2 and -3.0 , respectively (<3 rd percentile). She was afebrile, with a normal heart rate and an elevated arterial blood pressure for height and age (119/93 mm Hg). Physical examination, including funduscopy, was unremarkable apart from the finding of a mixed nystagmus. The neurological examination was unremarkable. She was prepubertal, with Tanner staging I.

It is worth noting that 3 weeks before her admission to the hospital, the patient was presented to the emergency department with a history of chest pain, generalised weakness, limb incoordination, confusion and agitation. She also reported that she was unable to open her right eyelid. Physical examination was unremarkable and her arterial blood pressure was 102/73 mm Hg. She stayed at the emergency department for a few hours and was discharged home with the diagnosis of ‘panic attack’.

INVESTIGATIONS

MRI of the brain at the time of her admission revealed a high-intensity lesion on fluid-attenuated inversion recovery (FLAIR) images in the posterior aspect of the medulla oblongata adjacent to the foramen of Magendie (figure 1C,D). The lesion retained high signal on T2-weighted sequence in the posterior aspect. It measured 10.2 mm $\times$ 7.4 mm transaxially and had a cephalocaudal extent of 19.6 mm. It had a central intense high T2 signal core with less intense, but still high, signal rim. There was minimal loss of diffusion restriction within the lesion. The

lesion was low signal on T1-weighted images with no significant contrast enhancement. There was no mass effect being exerted by the lesion. The remainder of the brain parenchyma including the pituitary gland was normal with no other signal abnormalities seen. The myelination pattern was age-appropriate and complete.

The laboratory investigations including full blood count, renal function (creatinine, urea), plasma electrolytes (sodium, potassium, chlorine), liver function tests (aspartate transaminase, alanine transaminase), C reactive protein and erythrocyte sedimentation rate were normal.

DIFFERENTIAL DIAGNOSES

On the basis of the MRI of the brain findings, the differential diagnoses included an inflammatory condition, such as myelitis or an evolving demyelinating condition, a diffuse neoplastic lesion or a variant of reversible posterior leucoencephalopathy syndrome (RPLS).

The position of the lesion posed a challenge for invasive neurosurgical procedures to be carried out in order to exclude a neoplastic tumour, and this was anyhow deemed unnecessary as it did not correlate well with the clinical picture and investigations, and was thought to be an extremely remote possibility. Furthermore, the clinical signs and MRI findings were not compatible with a demyelinating condition at that point.

TREATMENT

After her second presentation to the emergency department, the patient was admitted to the hospital. rhGH therapy was discontinued and she was kept under close observation on the paediatric ward, following a conservative approach to her management.

She remained stable and made good progress with gradual resolution of her symptoms. The systolic blood pressure, which was in the upper limit of the reference range for her height and age before admission, gradually returned to normal. At her discharge from hospital 2 weeks later, she was asymptomatic.

OUTCOME AND FOLLOW-UP

She continued to be asymptomatic at follow-up 3 months after her discharge from hospital, and her physical examination was entirely normal. Her weight was 35 kg (3rd percentile, Z-score -2.0) and her height was 134 cm (<3 rd percentile, Z-score -3.3). A subsequent MRI of the brain, carried out 3 months after discharge (figure 1E,F), showed complete resolution of the lesion, supporting the diagnosis of a variant of RPLS. Currently she continues to have yearly reviews as paediatric outpatient, and at the latest review 5 years after this incident, she remains well and symptom-free. Her weight is 40 kg (<3 rd percentile, Z-score -2.7) and her height is 147 cm (<3 rd percentile, Z-score -2.7).

DISCUSSION

The clinical presentation, the radiological findings and the outcome of this case are consistent with a diagnosis within the spectrum of RPLS, a term that was first used by Hinchey *et al* in 1996.⁸ Since then, many other terms have been used for the same entity, including posterior reversible encephalopathy syndrome, reversible occipital-parietal encephalopathy, posterior leucoencephalopathy syndrome, hyperperfusion encephalopathy, reversible encephalopathy, occipital-parietal encephalopathy and reversible posterior cerebral oedema syndrome.

Even though the classic presentation of RPLS includes headaches, seizures, visual disturbance and altered mental function, there are many published cases stating milder presentations.^{9 10}

The incidence of RPLS is unknown because it is probably an underdiagnosed entity.

It has been reported in all age groups, including very rarely, younger children.^{11 12} It is commonly associated with hypertensive encephalopathy, pre-eclampsia, renal failure, sepsis, chemotherapy, sickle cell disease, severe hypertension, acute renal failure, solid organ and bone marrow transplantation, tumour lysis syndrome, disrupted metabolic state, shock, autoimmune disorders and the use of immunosuppressive therapy. Up to present, it has never been reported to be associated with rhGH replacement therapy.

Typical findings of MRI of the brain in RPLS include potentially reversible bilateral focal lesions of parietal and occipital subcortical white matter with vasogenic oedema and increased intensity on T2-weighted images and FLAIR signals. However, there are also reports of atypical presentations with variable distributions of vasogenic oedema and restricted diffusion-cytotoxic oedema in the frontal lobes, inferior temporal lobes, cerebellum, basal ganglia, brainstem and deep white matter.^{13 14} Interestingly, there are two published adult RPLS cases with involvement only of the medulla oblongata, which appear similar to our case.¹⁵

The pathophysiology of RPLS remains unclear. Two theories have attempted to give an explanation. According to the original theory, sudden elevations in arterial blood pressure exceeding the autoregulatory capacity of the brain combined with cytotoxic effects of medicines, which in our case might have been the rhGH, on the vascular endothelium might be the culprits. Both may lead to a breakdown of the blood-brain barrier with transudation of fluid and local oedema. Vascular endothelial damage seems to be the key feature. Predilection of the white matter rather than grey matter has been hypothesised due to the tight packing of the axons of the former, which allows water accumulation. A recent popular theory, based on findings in animal models, proposes that hypertension leads to impaired vascular autoregulation and hyperperfusion, which leads to endothelial injury in the capillary bed. As a result, vasogenic oedema may develop in the affected brain areas. The posterior cerebral circulation is more prone to impaired autoregulation and vasogenic oedema than the anterior cerebral circulation. Therefore, in classic RPLS the lesions are mainly in the posterior area.

Since many cases of RPLS (20%–40%) are described without any evidence of hypertension, some researchers have rejected both of the above theories.^{13 14} The most recent and widely accepted mechanism is now the theory of endothelial injury rather than hyperperfusion/hypertension. This mechanism is also supported by the increased contrast enhancement seen in MRI of the brain in patients with RPLS.^{13 16}

In the majority of cases, RPLS is reversible. Its prognosis depends mainly on the underlying cause. Most of the patients show complete or near-complete resolution of both clinical and radiological abnormalities within days to weeks. However, it may progress to irreversible neurological deficits and even death, depending on the severity of the primary disease and possible diagnostic and treatment delay. In our case, the lesion was no longer present 3 months after discontinuation of rhGH therapy. MRI of the brain findings of restricted diffusion have been reported to be associated with a poor prognosis.¹⁷

One may attempt to challenge the diagnosis of RPLS in this case. However, the evidence speaks for itself in that the brain lesion that was demonstrated on MRI of the brain at the time of the patient's initial presentation had undoubtedly resolved

a few weeks after discontinuation of rhGH therapy. Moreover, in conjunction with the MRI of the brain findings, there was a complete resolution of the symptoms and an impressive recovery in the patient's clinical condition within days after cessation of rhGH therapy.

In conclusion, the wider use of rhGH replacement therapy in recent years continues to unveil new, important and unusual side effects. rhGH must therefore be used cautiously and under strict current recommendations in patients meeting the required criteria. Physicians involved in the use of rhGH replacement therapy should be aware that it could cause, among other known side effects, a reversible brain lesion in adolescents, and possibly other age groups also. More research is needed to ascertain the exact pathophysiology of the occurrence of RPLS in rhGH replacement therapy as well as the incidence rate in this group of patients.

Learning points

- ▶ Recombinant human growth hormone (rhGH) replacement therapy may cause reversible brain lesions such as reversible posterior leucoencephalopathy syndrome (RPLS) in adolescents.
- ▶ rhGH replacement therapy must be used cautiously in patients who fulfil the relevant evidence-based criteria.
- ▶ MRI of the brain is the most appropriate imaging modality to demonstrate the central nervous system changes in RPLS and should be performed in a timely manner when such clinical suspicion arises from the patient's presentation.
- ▶ Children on growth hormone therapy developing any new symptom should have urgent consultation with the treating endocrinologist.
- ▶ Blood pressure monitoring is important for children on rhGH replacement therapy during each follow-up consultation.

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