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*Case report*

# Hypopituitarism—A rare manifestation in Joubert syndrome: about 4 cases

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**Abstract:** Joubert syndrome (JS) is a complex medical condition characterized by a pathognomonic midbrain-hindbrain malformation visible on brain imaging, which is known as the "molar tooth sign" (MTS). The presence of the MTS in the brain is the defining diagnostic criterion for JS. Individuals with JS commonly exhibit a developmental delay, hypotonia, and abnormal eye movements. In addition, neonatal breathing dysregulation is observed in about half of the cases. Midline brain defects associated with JS can lead to pituitary hormone abnormalities, thereby manifesting as multiple pituitary insufficiencies in the neonatal period, such as hypoglycemia and, in male patients, a micropenis with undescended testes. Although JS is a well-researched genetic condition, there is minimal information on the endocrinological aspects of JS. This manuscript aims to emphasize the spectrum of endocrinologic findings in JS through the retrospective evaluation of four cases characterized by combined pituitary dysfunctions, including secondary hypothyroidism, growth hormone deficiency, and panhypopituitarism. Highlighting these treatable aspects of JS is crucial, as continuous endocrinological monitoring can positively impact a patient's well-being, particularly in managing secondary adrenal and thyroid insufficiencies.

**Keywords:** Joubert syndrome; hypopituitarism; endocrine

**Abbreviations:** ACTH: Adrenocorticotropic hormone; CAI: Central adrenal insufficiency; CPAP: Continuous positive airway pressure; DHEA-S: Dehydroepiandrosterone-sulfate; FSH: Follicle stimulating hormone; fT3: Free triiodothyronine; fT4: Free thyroxine; GC/MS: Gas chromatography–mass spectrometry; GHD: Growth hormone deficiency; IGF-1: Insulin-like growth factor 1; IGFBP-3: Insulin-like growth factor binding protein 3; IM: Intramuscular injection; JS: Joubert syndrome; LH: Luteinizing hormone; MRI: Magnetic resonance imaging; MS: Mass spectrometry; MTS: Molar tooth sign; NA: Not applicable; PSIS: Pituitary stalk interruption syndrome; rhGH: Recombinant human growth hormone; TE: Testosterone enanthate; TSH: Thyroid stimulating hormone; THs: Thyroid hormones

## 1. Introduction

Joubert syndrome (JS) is a recessive multisystem disease caused by different variants in at least 43 genes (OMIM) that cause dysfunction of the primary cilium. This nearly ubiquitous, multiple sensory organelle converts external stimuli into intracellular signaling cascades and simultaneously mediates several well-known signaling pathways [1]. Primary cilia dysfunction in JS leads to a broad spectrum of clinical manifestations. The hallmark features of JS include "molar tooth sign" (MTS), cerebellar ataxia, hypotonia, and a developmental delay. Additionally, the syndrome exhibits the highly variable involvement of other organ systems, with some patients experiencing liver, renal, visual, oculomotor, respiratory, and skeletal abnormalities.

Due to high clinical heterogeneity and multiorgan involvement, JS has been classified into eight clinical subgroups: JS with pure neurological features, JS with a retinal defect, JS with renal involvement, JS with an oculorenal defect, JS with a hepatic defect, JS with an orofaciodigital defect, JS with acrocallosal features, and JS with Jeune asphyxiating thoracic dystrophy. On axial magnetic resonance imaging (MRI), the radiologic triad of thick and straight superior cerebellar peduncles, deep interpeduncular fossa, and either hypoplastic or dysplastic superior cerebellar vermis create the MTS, which is a hallmark of JS. Subsequent to this midbrain defect, an association with pituitary dysfunction may be present.

Despite extensive research on JS, endocrine abnormalities have not been discussed in detail in the literature. Several studies have documented pituitary anomalies and hormone dysfunctions in patients with JS, though these aspects are not always the primary focus. Published studies indicated that endocrine dysfunctions can range from isolated thyroid or growth hormone deficiencies to panhypopituitarism. Among these, growth hormone deficiency appears to be the most common. Studies by Stephen et al. [2] and Niceta et al. [3] specifically reported cases of growth hormone deficiency, while others have highlighted instances of multiple pituitary hormone deficiencies, including central hypothyroidism, adrenal insufficiency, and hypogonadism [4–6]. This underscores the importance of recognizing and managing endocrine issues in JS.

This study presents four cases which exhibit psychomotor delay, hypotonia, and the characteristic brain malformations and breathing abnormalities observed in JS. These cases were found to be associated with endocrine abnormalities, including central hypothyroidism and panhypopituitarism. Given the variability in endocrine dysfunction among JS patients, we aim to contribute to

understanding these treatable aspects and underscore the importance of regular endocrinological monitoring in this population.

## 2. Patients and methods

We report three boys and a girl with JS and endocrine dysfunction from three clinical centers, who were hospitalized between September 2021 and September 2023. All patients are Polish, and their parents are nonconsanguineous. The diagnosis of JS was primarily based on the presence of the MTS on brain MRI scans, which is the definitive criterion for diagnosing JS. Additionally, the clinical status, including neurological examinations and typical features such as hypotonia, developmental delay, and abnormal eye movements, supported the diagnosis.

We performed a retrospective analysis of medical data, focusing on the following: perinatal and neonatal patient characteristics, including gestational age, birth weight, Apgar score, and respiratory problems. We primary focused on the endocrine manifestations of JS including hypopituitarism, hypoglycemia, micropenises, and cryptorchidism.

Additional evaluations to analyze JS symptoms included ophthalmological examinations that covered oculomotor function. We did not systematically collect data on retinal findings, colobomas, and liver and renal involvements. In this study, genetic testing was not performed on any of the individuals.

Investigations included a physical examination, an endocrine evaluation, height standard deviation scores (SDS), and penile development in boys. Assessments of adrenal function included monitoring the morning serum cortisol, adrenocorticotropic hormone (ACTH), and glucose levels. Thyroid function was estimated by measuring the serum thyroid stimulating hormone (TSH) concentration and the free triiodothyronine (fT3) and free thyroxine (fT4) thyroid hormones (THs). Central hypothyroidism was determined based on lower fT3 and fT4 levels with simultaneously inappropriately normal TSH levels. Diagnostic pathways concerning a growth hormone deficiency (GHD) consisted of serum levels of insulin-like growth factor 1 (IGF-1), IGF binding protein 3 (IGFBP-3), GH secretion during hypoglycemia, and the measurement of spontaneous GH levels during sleep. We defined GHD as the peak GH level of <10 ng/mL while asleep or during hypoglycemia accompanied by lowered IGF-1 levels.

Male patients were assessed for cryptorchidism and a micropenis by endocrinologists and urologists. Additionally, the serum levels of gonadotropins and testosterone were measured. Central hypogonadism was suspected in case of low LH, FSH, and testosterone levels during the mini puberty period.

We performed MRI scans on all patients, which involved assessing the superior cerebellar peduncles, the interpeduncular fossa, and the superior cerebellar vermis. In addition, we analyzed midline brain defects, the anterior pituitary size, the posterior pituitary location, and the shape.

Genetic testing was not performed on any of the individuals in this study.

## 3. Case presentation

### *3.1. Patient I*

Patient I is a 1.5-year-old boy born at 35 weeks' gestation with a birth weight of 2.98 kg (0.98 SD), length of 51 cm (2.6 SD), and Apgar score of 8. His mother has one healthy daughter and a history of two miscarried pregnancies (one fetus had confirmed trisomy 2).

As a neonate, the patient presented with breathing difficulties and required respiratory support. On the second day after birth, he developed necrotizing enterocolitis, which resolved with treatment. Based on the tandem mass spectrometry (MS) and the gas chromatography–mass spectrometry (GC/MS) profile, metabolic defects were excluded. The MRI revealed the following pathognomonic features of JS, including the presence of the MTS: vestigial, dysmorphic cerebellar vermis, thickened and elongated superior cerebellar peduncles, and a distorted, elongated fourth ventricle with a rounded ceiling (Figure 1). Investigations in the neonatal period confirmed a central adrenal insufficiency (CAI) and central hypothyroidism (Table 1), for which hydrocortisone and levothyroxine were prescribed. He had a lowered serum IGF-1 level but no hypoglycemia; therefore, a recombinant human Growth Hormone (rhGH) treatment was not initiated.

On examination, a micropenis and partially divided scrotum (hypoplastic) were noted. The testicles were located high at the openings of the inguinal canals. Gonadotropins tested during the mini-puberty period were found to be lowered, thus indicating hypogonadism. The patient was administered three intramuscular injections of testosterone enanthate at a monthly interval, starting at the age of 3 months. This procedure led to penile enlargement. The patient required oral motor exercises and sensory stimulation due to weak oral reflexes, ophthalmological care concerning strabismus, and rehabilitation for muscle atrophy.

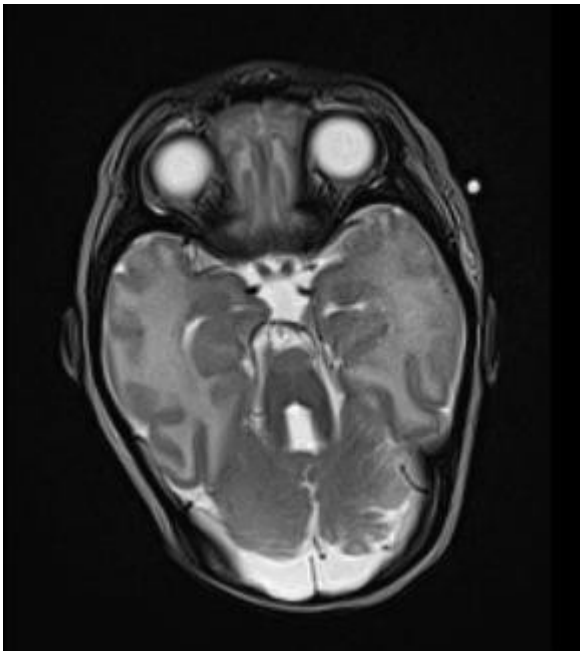

**Figure 1.** Axial brain MRI showing features of JS: thick, elongated and abnormally oriented superior cerebellar peduncles and deepened interpeduncular fossa compose a MTS (Patient I).

**Table 1.** Summary of endocrine deficiencies in a studied group of patients.

| Patient no. | Sex | Central adrenal insufficiency | GHD | Hypoglycemia | Secondary hypothyroidism | Micropenis | Cryptorchidism | Hypogonadotropic hypogonadism |
|---|---|---|---|---|---|---|---|---|
| I | M | + | + | − | + | + | + | + |
| II | M | − | + | − | + | + | − | NA |
| III | F | + | + | − | + | NA | NA | + |
| IV | M | + | + | + | + | − | − | + |

Note: F: Female; M: Male; GHD: Growth hormone deficiency; NA: Not applicable.

### *3.2. Patient II*

Patient II is currently a 6-year-old male, born to a mother with a history of one miscarriage and one healthy child. Prenatally, ultrasonography indicated Dandy-Walker syndrome. The boy was born at 40 weeks' gestation, with a birth weight of 3.4 kg (0.75 SD), length of 55 cm (2.12 SD), and Apgar scores of 4-3-5-6. Within the first hours of life, the infant developed convulsions, required respiratory support, and remained intubated until 11 days old; he remained on a continuous positive airway pressure (CPAP) until 15 days old. The brain MRI showed pituitary stalk interruption syndrome (PSIS), which is indicative of ectopy of the posterior pituitary, as well as features of JS—MTS, reduced midbrain and part of the pons, and an "indentation" in the upper cerebellar peduncles.

A hormonal evaluation was performed within the first month. An adrenal insufficiency and hypothyroidism were ruled out based on the sufficient levels of fT3, fT4, and morning cortisol. An initial physical assessment revealed a micropenis. Starting at 3 months of age, he was administered three intramuscular injections of testosterone enanthate at a monthly interval, and significant penile growth was observed following treatment. At the age of 3 months, he was reevaluated for thyroid function, which revealed central hypothyroidism (TSH 2.05 uIU/mL, fT4 0.85 ng/dL) that was managed with L-thyroxine. An endocrine assessment disclosed a lowered serum IGF-1 level and GHD; thus, the rhGH treatment was introduced at the age of 5 months with a good response. At the most recent visit, at the age of 5.7 years, his height was 124.7 cm (Z score −0.3; 40th centile) and his weight was 27.5 kg (Z score 0.2; 60th centile). Motor delay and balance disorders were noticed. He was diagnosed with a mild intellectual disability.

### *3.3. Patient III*

Patient III is a 6-year-old female born from a second pregnancy (after one miscarriage) at 39 weeks' gestation, with a birth weight of 3.53 kg (0.4 SD), length of 55 cm (3.3 SD), and Apgar scores of 3-5-4-4. As a neonate, she presented with respiratory failure, metabolic acidosis, laryngeal edema that required an administration of corticosteroids, jaundice due to neonatal hyperbilirubinemia, and hypotonia. She was dependent on mechanical ventilation for two weeks. A diagnosis of JS was made based on the brain MRI findings of PSIS and a MTS.

The patient was screened for pituitary deficiencies, which led to diagnoses of adrenal insufficiency, central hypothyroidism, and central hypogonadism. At 3 weeks of age, hydrocortisone treatment was initiated, followed by L-thyroxine supplementation, both of which resulted in a positive response: she was more active, her adrenal function improved, and her thyroid hormone levels normalized. Due to lowered IGF-1 and GHD, the rhGH treatment was initiated at the age of 2 months.

Now, at age 6, she is non-verbal but interacts through a communicator. She remains non-ambulatory due to her severe hypotonia.

### *3.4. Patient IV*

Patient IV is a 2-year-old male born at 40 weeks' gestation, with a body weight of 3.9 kg (0.39 D), length of 57 cm (3.3 SD), and Apgar scores of 7–8. The pregnancy was complicated by gestational hypertension. After birth, he immediately presented with irregular breathing and signs of laryngeal flaccidity, which required passive oxygen therapy. Hypoglycemia occurred in the first hours of life,

with the lowest glucose level being 22 mg/dL; he was given an intravenous glucose infusion. From the second day of life, hyperbilirubinemia with cholestasis was observed, most probably due to panhypopitutarism.

A physical examination revealed skin jaundice, swelling in the parieto-occipital area, and dysmorphic features including a flat bridge of the nose, upward slanting palpebral fissures, thickened auricular rims, and a micropenis. The brain imaging confirmed an MTS (Figure 2). In addition, a defect of the hypothalamic-pituitary region was observed, alongside hypoplastic sella turcica, an ectopic position of the posterior lobe of the pituitary gland within the hypothalamus (glandular part not detected), a narrow linear structure that may correspond to a hypoplastic pituitary stalk, and a defect of the craniocervical junction in the form of a closed meningeal hernia at the level of C1, C2 of the spinal cord.

Laboratory tests showed an insufficient fT4 level (0.59 ng/dL) with a TSH of 1.0 uIU/L and a low cortisol concentration (<0.3 mg/dL). Hormonal substitutions, first with hydrocortisone and then with L-thyroxine, were introduced at the age of 7 weeks. Due to emesis and a feeding intolerance, an enteral tube was inserted to achieve an adequate caloric requirement. Despite the treatment and adequate nutrition, hypoglycemic episodes were still observed (glucose level: 42–47 mg/dL). At a glucose level of 54 mg/dL, a low GH (0.46 ng/dL) and IGF-1 concentration (<7 ng/mL) were found. Moreover, the maximal level of growth hormone at night was 0.62 ng/mL. The rhGH treatment was started at the age of 4 months, which resulted in the resolution of hypoglycemia. Now, at 2 years of age, the boy requires constant hormone substitutions with the following: hydrocortisonum, L-thyroxine, and rhGH. He is under neurological care due to the delay in psychomotor skills.

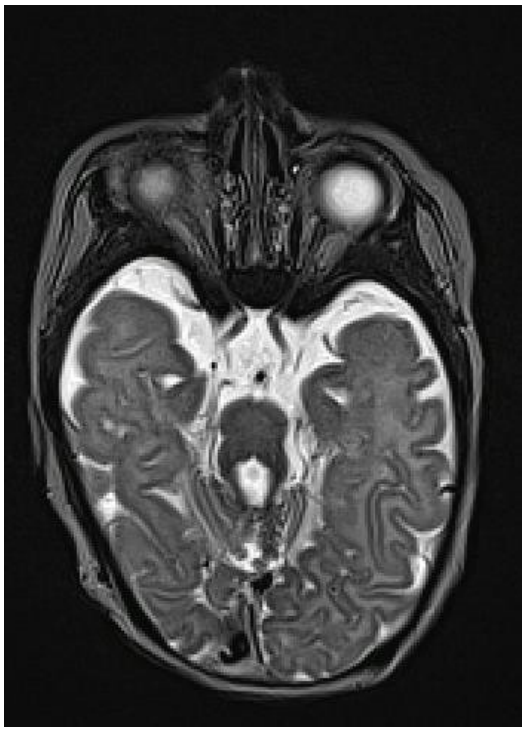

**Figure 2.** Axial brain MRI with features of JS: thickened, excessively horizontally positioned superior cerebellar peduncles (MTS), hypoplastic and dysplastic cerebellar vermis (Patient II).

## 4. Results

Table 1 shows a summary of the clinical features of the subjects. Table 2 lists the hormonal findings in the studied patients before replacement therapy. In all cases, MRI revealed the characteristic MTS and a batwing appearance of the fourth ventricle, which led to the diagnoses of JS. The assessed pituitary function showed secondary hypothyroidism with lowered fT4 and fT3 and an inadequate TSH in all four patients. They needed L-thyroxine administration to normalize the THs. In three out of the four patients, an adrenal insufficiency was detected: in two within the first month and in one in the third month. The diagnoses were established based on reduced levels of ACTH and cortisol. Hypoglycemia was observed in one of the patients. The initiation of steroid (hydrocortisone) replacement therapy led to improved functioning of the patients.

In all subjects, the levels of IGF-1 and IGFBP-3 were measured, which revealed biochemical signs of GHD. Laboratory investigations, including GH during sleep, were performed in two patients, which showed GHD. The rhGH therapy was provided only to two individuals.

In three out of the four individuals assessed, biochemical indicators were definitive for central hypogonadism. In two of them with micropenises, replacement treatment with TE was given, which led to increase in penile length and diameter.

**Table 2.** Hormonal findings in studied patients before replacement therapy.

| Patient no. | Age | TSH [uIU/mL] | fT4 [ng/dL] | Cortisol [ug/dL] | ACTH [pg/mL] | FSH [mIU/mL] | LH [mIU/mL] | Testosterone [ng/dL] | IGF-1 [ng/mL] |
|---|---|---|---|---|---|---|---|---|---|
| | Normal ranges | 0.87–6.15 | 0.94–1.44 | 5.0–25.0 | 10.0–60.0 | 0.16–4.1 | 0.02–7.0 | 60.0–400.0 | 30.0–70.0 |
| I | 3 weeks | 7.03 | 0.7 | <1 | <2.7 | <0.11 | <0.12 | <12.98 | <7 |
| II | 1–3 months | 2.05 | 0.85 | 8.69 | 71.5 | X | X | X | <15 |
| III | 3 weeks | 1.41 | 0.69 | 8.8 | 4.4 | <0.30 | <0.07 | NA | X |
| IV | 7 weeks | 1.0 | 0.59 | <0.3 | 9.67 | 0.465 | 0.32 | X | 16.5 |

Note: ACTH: Adrenocorticotropic hormone; FSH: Follicle stimulating hormone; fT4: Free thyroxine, IGF-1: Insulin-like growth factor 1; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; X: Data not available; NA: Not applicable.

## 5. Discussion

We aimed to analyze and describe the role of endocrine system disorders in JS as the awareness of this condition is essential for an appropriate intervention. The most common disorders presented in the studied case series were central hypothyroidism and GHD. Our observation regarding GHD aligns with other reports, where GHD was noted as the most prevalent hormonal deficit in patients with JS [7]. The underlying mechanism of this deficiency is not fully understood. However, Stephen et al. described a variety of hormonal deficits, including GHD, in two siblings with JS caused by a KIAA0753 variant [2]. Both patients had undetectable GH levels and responded well to the rhGH therapy. Additionally, a partial GH deficiency and precocious puberty were reported in JS children with a confirmed pathogenic variant in the ciliary gene RPGRIP1L [8]. While these cases suggest a

potential link between specific genetic variants and pituitary dysfunction, further studies across a broader cohort of patients with JS are needed to determine whether dysfunction in either KIAA0753 or RPGRIP1L directly contributes to pituitary anomalies. The possibility of GHD should be considered early in the neonatal stage, particularly in the presence of hypoglycemic episodes. GHD necessitates a prompt initiation of treatments with rhGH and the ruling out of additional pituitary deficits. Throughout childhood, regular height measurements and growth tracking using a standardized growth chart are essential. If there's a clinical indication of growth issues, laboratory tests should be conducted. The endocrine assessment for patients with JS should include standard evaluations, such as measuring levels of IGF-1 and IGFBP-3, conducting growth hormone stimulation tests, and determining bone age progression. However, there are specific considerations in the context of JS that may necessitate a tailored approach. For instance, due to the potential involvement of multiple pituitary hormones and the complex genetic background in JS, a more comprehensive and cautious approach may be required. This includes the careful monitoring for atypical presentations and additional complications associated with JS, such as hypoglycemia, which may be more pronounced in these patients. While standard GHD treatment protocols are generally applicable, clinicians should be aware of potential complications unique to JS, such as scoliosis, which can be exacerbated by the rhGH therapy. Therefore, starting the rhGH treatment in JS patients requires a close collaboration with orthopedic specialists to monitor for scoliosis progression, which is in line with the currently published management guidelines [9].

In light of the minimal endocrinologic workup recommended by these sources, our experience suggests that a more proactive and thorough endocrine evaluation could be beneficial to manage the diverse and potentially severe manifestations of GHD in JS. This includes regular follow-ups and a multidisciplinary approach to address the unique challenges presented by this condition.

Central hypothyroidism, which is caused by the insufficient stimulation of an otherwise normal thyroid gland by TSH, was present in all the described cases. A prompt diagnosis is crucial, as a delay in treatment can lead to irreversible neurological deficits. Moreover, central hypothyroidism may be asymptomatic or present with subtle signs such as reduced activity and feeding difficulties, which could be mistakenly attributed to the ciliopathy itself. Given these findings, universal thyroid screening may be advisable for all patients diagnosed with JS, particularly in the neonatal and early childhood stages. The early detection and treatment of thyroid dysfunction are essential to prevent potential long-term complications. Levothyroxine substitution therapy stands as the primary approach for treatment. However, the introduction of levothyroxine in JS patients should be preceded by the assessment of the hypothalamus-pituitary- adrenal axis. For individuals diagnosed with CAI, or when the possibility of its existence cannot be ruled out, initiating levothyroxine should be preceded by proper a glucocorticoid therapy to avert triggering an adrenal crisis.

In three out of our four patients, the laboratory results were consistent with CAI, although this deficiency has been documented in only about 4% of individuals with JS [9]. While this relatively small percentage may be underestimated, it highlights the importance of vigilant monitoring for endocrine abnormalities in patients with JS, given the potential severity of these conditions.

The manifestations of this condition are diverse and hinge on the timing of onset, as well as the presence and severity of any accompanying pituitary anomalies. Symptoms can include a low blood pressure, difficulties in feeding hypoglycemia, drowsiness, extended periods of jaundice, convulsions, and low sodium levels. The diagnosis is based on an assessment of the morning cortisol levels and, once indicated, conducting an ACTH stimulation test. This procedure was undertaken in a few JS cases,

which showed a normal adrenal function [3]. Nevertheless, once CAI is diagnosed, it is crucial to administer hydrocortisone to prevent an adrenal crisis.

Previous studies have hinted at possible connections between JS and hypogonadism and micropenis [3,10]. A case of multiple pituitary hormone deficiency in a 13-day-old baby with a micropenis, hypoglycemia, and JS was reported by Akcan et al. [4]. The penile length and diameter increased following a dihydrotestosterone treatment. In our clinical cohort, two individuals diagnosed with micropenis and hypogonadism were administered TE, which led to penile enlargement.

Among our patients, there was a case of undeveloped sella turcica, an ectopic location of the nervous part of the vertex in the hypothalamus without visualization of the glandular part of the pituitary, as well as PSIS. Two siblings reported by Stephen had pituitary malformations: an ectopic posterior pituitary gland and an absent pituitary stalk and a small pituitary gland [2]. Other features mentioned included a pituitary malformation, an ectopic posterior pituitary, and pituitary agenesis which led to panhypopituitarism [3,6].

The literature data support our findings that a pituitary insufficiency may occur in JS [3,5,10]. The management of JS with pituitary hormone deficiencies requires a multidisciplinary approach, which involves regular monitoring and tailored hormonal replacement therapies to address the specific deficiencies identified in each case.

## 6. Conclusions

JS is a clinically and genetically heterogeneous disorder identified in children presenting with episodic hyperpnea, hypotonia, abnormal eye movements, and MTS in MRI scans. Based on our findings, it is evident that the prevalence of endocrine dysfunction in our cohort was significantly higher than the 4% reported in the current literature. This discrepancy suggests that hormone deficiencies, which are treatable aspects of JS, might often go undiagnosed due to the multisystemic nature of the condition. Once diagnosed with JS, it is crucial to evaluate pituitary functions and to follow them longitudinally. An awareness of possible pituitary insufficiency may be crucial to the well-being of the patients, especially when it concerns secondary adrenal and thyroid insufficiencies.

Therefore, we emphasize the importance of routine and comprehensive endocrine evaluations for all patients diagnosed with JS to ensure the early detection and management of potential hormonal deficiencies.

## Author contributions

Elżbieta Marczak: conceptualized the study and designed the research methodology, interpreting the results and writing the original draft, collected the clinical data and performed data analysis, contributed to reviewing and editing the manuscript for intellectual content, supervised the entire project and provided funding; Maria Szarras-Czapnik: contributed to reviewing and editing the manuscript for intellectual content; Małgorzata Wójcik: contributed to reviewing and editing the manuscript for intellectual content; Agnieszka Zachurzok: contributed to reviewing and editing the manuscript for intellectual content; Elżbieta Moszczyńska: contributed to reviewing and editing the manuscript for intellectual content; Jerzy Starzyk: contributed to reviewing and editing the manuscript for intellectual content; Agata Zygmunt-Górska: collected the clinical data and performed data analysis; Karolina Czyżowska: collected the clinical data and performed data analysis; Anna Szymańska:

collected the clinical data and performed data analysis; Katarzyna Gołąb-Jenerał: collected the clinical data and performed data analysis.

## Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

## Ethics approval of research and informed consent

The study protocol was approved by the Research Ethics Committee of The Children's Health Memorial, Warsaw, Poland on 27.03.2024 (7/KBE/2024). Written informed consent was obtained from the parents or legal guardians of underage patients.

## Conflict of interest

The authors declare no conflict of interest.

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