

Pituitary Sarcoidosis in a Pediatric Patient Successfully Treated With Adalimumab and Methotrexate

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D. Sofia Villacis-Nunez, MD¹  and Amit Thakral, MD¹ 

Abstract

Neurosarcoidosis is a rare phenomenon in the pediatric population, with only a few cases reported in the literature worldwide. While hypothalamo-pituitary involvement is known to occur, direct infiltration of the pituitary gland and isolated anterior pituitary dysfunction without diabetes insipidus is seldom observed. A high index of suspicion is required for diagnosis of neurosarcoidosis, and treatment can be challenging due to lack of standardized guidelines. We present the case of a 17-year-old female with known sarcoidosis of the lacrimal glands, who developed severe headache and neurologic symptoms secondary to granulomatous infiltration of the pituitary gland and infundibulum due to neurosarcoidosis. She was successfully treated with corticosteroids, methotrexate, and adalimumab, with complete radiologic resolution. This is the first documented pediatric case of neurosarcoidosis with radiologic granulomatous infiltration of the pituitary gland, manifesting as partial anterior hypopituitarism, in the form of central hypothyroidism, without diabetes insipidus.

Keywords

pediatric, sarcoidosis, neurosarcoidosis, pituitary

Introduction

Sarcoidosis is a chronic disease characterized by noncaseating granulomatous inflammation that can occur in virtually any organ.¹ Its pathogenesis is not fully understood, and patterns of organ involvement can vary from patient to patient. Nervous system involvement in sarcoidosis, namely, neurosarcoidosis, can affect 2% to 26% of patients of all ages. Pediatric-specific epidemiology is unknown.^{2,3} This is usually a diagnosis of exclusion, and biopsy is often required for confirmation.⁴ Moreover, once the diagnosis is established, the choice of a therapeutic agent poses a challenge, as no standardized guidelines for management are currently available. We present an unusual case of an adolescent female with known sarcoidosis of the lacrimal gland, who later developed neurosarcoidosis with pituitary gland involvement manifested as central hypothyroidism, and describe the treatment strategy utilized in this patient.

Case Report

The patient is a 17-year-old obese (body mass index = 37.82 kg/m²; 98.58th percentile), African American female, with sarcoidosis of the lacrimal glands diagnosed at the age of 15 years. At that time, she presented with a 3-week history of bilateral upper eyelid edema. Laboratory evaluation revealed an elevated erythrocyte sedimentation rate (29

mm/h; normal range = 0-20 mm/h), and slightly elevated immunoglobulin (Ig) G. Angiotensin-converting enzyme (ACE) and lysozyme levels were normal. A maxillofacial and sinus computed tomography (CT) with contrast showed a diffuse nonspecific enlargement of the bilateral lacrimal glands. Histology of the right lacrimal gland identified granulomatous inflammation, consistent with sarcoidosis. She received a 6-month prednisone taper, with resolution of palpebral swelling.

Two years later, she developed sharp, right frontal intermittent headaches. Over 4 months, the headaches progressively worsened, becoming constant and intermittently waking her from sleep. These headaches were accompanied by blurry vision, nausea, dizziness, and subjective occasional gait instability. At the time, she was taking combined oral contraceptive pills, started 20 months earlier for polymenorrhagia, which she discontinued when her

¹Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA

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Corresponding Author:

D. Sofia Villacis-Nunez, Department of Pediatric Rheumatology, Children's Healthcare of Atlanta, Emory University, 1400 Tullie Road, Atlanta, GA 30329, USA.
Email: dvillac@emory.edu



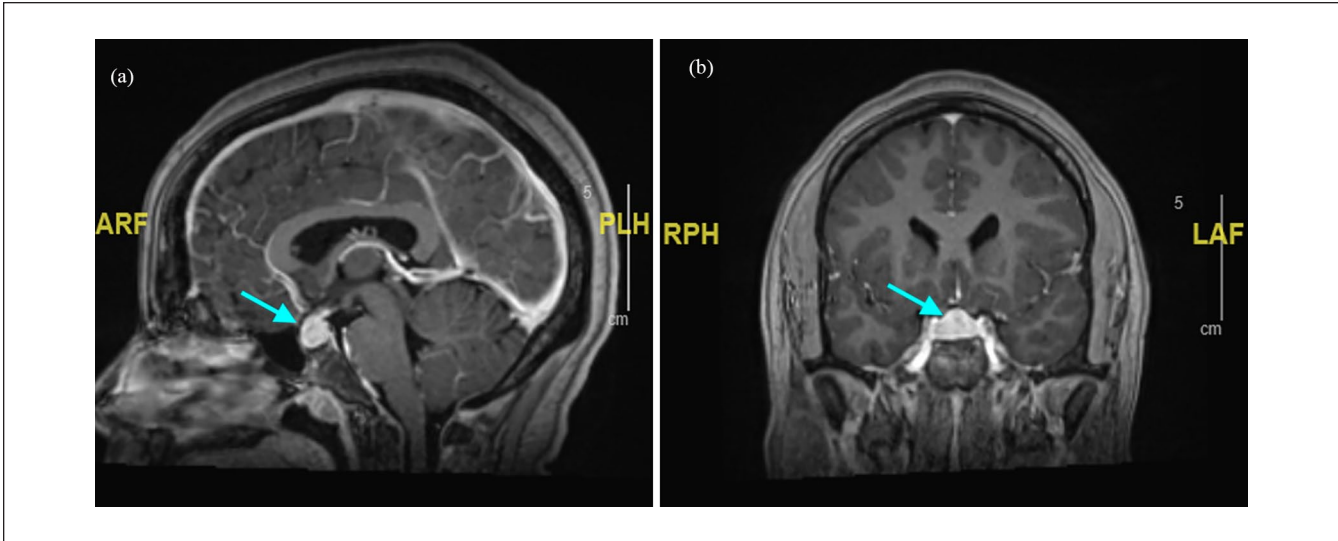


Figure 1. Initial brain magnetic resonance imaging (MRI) with and without contrast: Postcontrast sagittal (a) and coronal (b) images of homogeneously enhancing diffuse enlargement of the pituitary gland, with somewhat irregular boundaries, measuring up to 1.8 cm in size, and a mild smooth thickening with enhancement involving the pituitary infundibulum. No associated hemorrhage.

headaches became persistent; this was followed by amenorrhea. Therapy for migraine headaches was attempted, without response. Consequently, the patient presented to the emergency room for evaluation of severe headaches. Physical examination, including neurologic assessment, was unremarkable. The patient had fully developed secondary sexual characteristics. Ophthalmologic evaluation revealed no intraocular inflammation, no optic disc abnormalities, no retinal pathology, and normal visual field testing. A brain magnetic resonance imaging (MRI) with and without contrast was obtained (Figure 1a and b), showing diffuse granulomatous involvement of the pituitary gland consistent with sarcoidosis, and prominence of the bilateral lacrimal glands, reduced in size compared with previous CT, with increased T2 signal within the right lacrimal gland. Serologic studies showed sedimentation rate elevation (24 mm/h [normal range = 0-20 mm/h]). ACE and lysozyme levels were normal. Cerebrospinal fluid (CSF) analysis revealed mild pleocytosis (7/ μ L [normal range = 0-5/ μ L]) with lymphocyte predominance (91.7%), and elevated Ig G to albumin index (0.23 [normal range = <0.21] [vs 0.41 in serum]); oligoclonal bands were absent and no malignant cells were observed in cytology. CSF glucose, protein, and ACE level were within normal range.

Infectious workup was negative. A high-resolution chest CT showed a solitary 2 to 3 mm pulmonary nodule in the left lower lobe without lymphadenopathy. Results of hormonal studies (Table 1) demonstrated low free thyroxine (T4), borderline low triiodothyronine (T3), and normal thyroid-stimulating hormone (TSH), consistent with central hypothyroidism. These had been within normal limits 2 years earlier. The diagnosis of neurosarcoidosis involving the adenohypophysis was made.

The patient was started on intravenous (IV) pulse methylprednisolone 1 g daily for 3 days, followed by oral prednisone 60 mg daily, methotrexate 25 mg subcutaneous weekly, and adalimumab 40 mg subcutaneous every 2 weeks, with symptomatic improvement. Therapy with levothyroxine 100 μ g (~1 μ g/kg) daily was also initiated. Six months later, a follow-up brain MRI with and without contrast (Figure 2a and b) showed complete resolution of the pituitary and infundibular lesions. The patient continues on stable doses of methotrexate and adalimumab. Her prednisone dose was tapered to off uneventfully.

Thyroid function normalized after 3 months of therapy (free T4: 1 ng/dL [normal range = 0.8-1.4 ng/dL]; TSH: 3.02 mIU/L [normal range = 0.50-4.30 mIU/L]). Her menstrual periods restarted, but remained irregular, which along with her obesity, hirsutism, and elevated free testosterone 3 months after hospitalization (6.5 pg/mL [normal range = 0.5-3.9 pg/mL]), led to the diagnosis of polycystic ovarian syndrome. A hormonal intrauterine device has been inserted to address her persistent menstrual irregularity.

Discussion

Neurosarcoidosis, affecting the peripheral and/or central nervous system, is rare in pediatrics. It can occur in the setting of systemic sarcoidosis, or as an isolated phenomenon. A review conducted in 2016 documented 53 reported cases of neurosarcoidosis in pediatric patients.⁵ We identified 13 additional cases (counting ours) not listed in that review.⁶⁻¹⁷ Symptoms tend to differ based on the age of presentation; seizures are more common in younger children, whereas cranial nerve palsies predominate in older children and adolescents.² Hypothalamic/pituitary dysfunction, headaches,

Table 1. Hormonal Studies (in Blood).

Test	Result
ACTH	38.9 (normal range = 7.2-63.3 pg/mL)
Cortisol	Initial = 5.3 µg/dL (collected at 7:30) (normal range = 3.7-19.4) ACTH stimulation test: Pretest (collected at 8:00): 4.4 µg/dL 1 hour post-stimulation: 15.5 µg/dL
IGF-I	272 ng/mL (normal range = 120-479 ng/mL, z score = 0.1)
FSH	5.78 mIU/mL (normal range for Tanner stage V = 0.41-8.59)
LH	2.49 mIU/mL (normal range for Tanner stage V = 0.40-21.23)
Prolactin	18.1 ng/mL (normal range = 4.2-23 ng/mL)
Free T4	0.67 ng/dL (normal range = 0.79-1.34 ng/dL)
Total T3	83 ng/dL (normal range = 83-215 ng/dL)
TSH	3.2 uIU/mL (normal range = 0.5-3.6 uIU/mL)
Free testosterone	4.4 pg/mL (normal range = 1.2-9.9 pg/mL)
Hemoglobin A1C	5.7% (normal range = <6%)

Abbreviations: ACTH, adrenocorticotropic hormone; IGF- I, insulin-like growth factor I; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

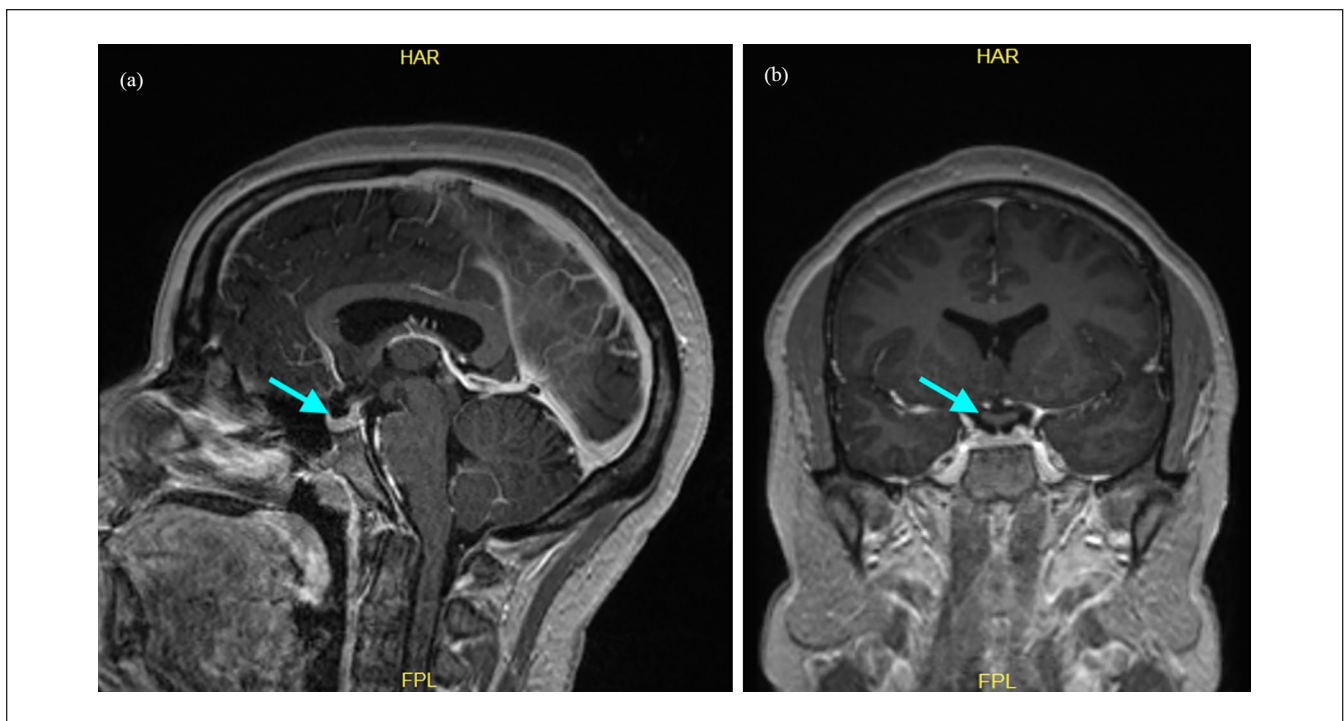


Figure 2. Brain magnetic resonance imaging (MRI) with and without contrast post-therapy: Postcontrast sagittal (a) and coronal (b) images showing pituitary lesion resolution, with no new lesions. Pituitary measures 4 mm in height in the midline and approximately 6 mm along the lateral aspects, with a broad 1.3 cm transverse dimension.

meningismus, central nervous system mass lesions, and peripheral neuropathies are other manifestations that can occur across all ages.^{1,2,18} Our patient had chronic, unremitting headaches with poor response to oral analgesics, vision changes, and gait instability, which were concerning for an intracranial process, and her amenorrhea hinted at an underlying hormonal dysfunction, later confirmed by

biochemical testing. Even though decreased levels of free T4 with normal TSH can be observed in obese individuals, she had normal studies in the setting of similar weight 2 years earlier. Taking this into consideration, the diagnosis of central hypothyroidism was established on the basis of a new onset inappropriately normal TSH and low free T4, and the presence of amenorrhea. Furthermore, her menstrual

cycles restarted after initiating thyroid hormone replacement, supporting the role of decreased thyroid function on her menstrual dysregulation. Although her sex hormones were within normal limits initially, she was later found to have elevated levels of free testosterone, and hirsutism, prompting an additional diagnosis of polycystic ovarian syndrome; thus, her menstrual irregularities were most likely multifactorial.

As proved by this case, the diagnosis of neurosarcoidosis can be challenging as it is based not only in identifying typical symptomatology but also relies on radiologic findings, and histologic evidence of noncaseating granulomas, while excluding other potential etiologies.⁴ Serologic and CSF studies are often nonspecific. Careful investigation of extraneural manifestations is critical, as it can both increase the diagnostic suspicion, as well as provide a site amenable for biopsy. Proposed diagnostic criteria classify the diagnosis of neurosarcoidosis as definite, probable, and possible.³ Our patient met the definition of a probable case, by showing evidence of central nervous system inflammation in CSF (lymphocytic pleocytosis, elevated IgG to albumin ratio in CSF) and brain MRI (granulomatous pituitary enlargement), with a chest CT demonstrating a pulmonary nodule (pulmonary involvement), and available histology proving lacrimal gland granulomas.

Hypothalamic and pituitary involvement by granulomatous mass lesions has been documented in 6% to 9% of neurosarcoidosis cases, with a wide spectrum of endocrine abnormalities.^{3,4} Specific data for the pediatric population are not available. We identified 18 pediatric patients with neurosarcoidosis involving the hypothalamus and/or pituitary gland documented in the literature, including our case. The majority of these patients had posterior (9 patients), or combined anterior and posterior (4 patients) pituitary involvement; one patient reportedly had sarcoid pituitary infiltration on imaging without hormonal derangements.^{5-7,19-21}

Anterior pituitary dysfunction without diabetes insipidus (DI), as evidenced in our patient, is the least common pattern of hypophyseal involvement in neurosarcoidosis, with only 3 previously reported cases.⁵ As opposed to our patient's limited endocrine dysfunction, all 3 previously documented cases had disruption of several hormonal axes (growth failure, lack of sexual maturation, with or without deficient adrenocorticotropic hormone secretion).^{5,21,22} Among these cases, only our patient has neuroimaging showing direct sarcoid pituitary infiltration; of the remaining 3 cases, one had involvement of the pituitary stalk and hypothalamus, without true pituitary enlargement on imaging, and 2 cases were reported prior to the advent of advanced neuroimaging.^{5,21,22} This makes our case the first to document direct pituitary infiltration from sarcoidosis causing partial anterior hypopituitarism manifested as central hypothyroidism, in a pediatric patient.

Once the diagnosis of neurosarcoidosis is established, the choice of therapy constitutes another challenge. Due to the paucity of data specific to pediatric neurosarcoidosis, there

are no standardized protocols and treatment is largely based on case series, most oriented to adults with systemic disease.^{5,18} Corticosteroids and other immunosuppressive agents have been used for disease management with variable response. A stepwise approach has been proposed, starting with oral corticosteroids (IV for severe disease) as first-line therapy.⁴ These are usually tapered slowly for months; 80% of patients of all ages are reported to fail steroid therapy due to progression of disease or toxicity.^{4,18} In contrast, many pediatric cases have been reported to have long-term resolution (up to 8 years) on steroid monotherapy; a few patients did not receive any immunosuppression.⁵ The timing and indications of steroid-sparing agents are less clear. Methotrexate, mycophenolate mofetil, azathioprine, and leflunomide are considered second-line agents, with methotrexate being the most widely used. Infliximab is proposed as a third-line agent, while adalimumab, cyclophosphamide, and rituximab are considered fourth line.^{4,18} In our patient, an aggressive treatment approach aiming at complete lesion resolution was taken, given the potential for long-term morbidity from central nervous system lesions. Accordingly, she received high doses of IV followed by oral corticosteroids, and was simultaneously started on methotrexate and adalimumab. Of note, adalimumab offers the advantage of subcutaneous administration and less allergenic potential, which increases its tolerability over Infliximab. The role of each individual medication in disease control for this patient is difficult to discern at the moment. Nonetheless, the combination of methotrexate and adalimumab appears to be effective for disease maintenance in our patient, as she had full resolution of the pituitary lesion on imaging and there has been no evidence of relapse while off steroids.

Conclusion

This case highlights the wide variety of manifestations of pediatric neurosarcoidosis, including pituitary gland infiltration and hormonal deficiencies. Detailed exploration for extraneural disease should be undertaken as this can increase the diagnostic suspicion, as well as provide viable sites for biopsy. It is important to consider that organ involvement can be asynchronous. Notably, our case demonstrated full regression of a pituitary lesion with the combination of corticosteroids, methotrexate, and adalimumab, without significant side effects. This regimen could be considered for future cases of pediatric neurosarcoidosis.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ORCID iDs

D. Sofia Villacis-Nunez  <https://orcid.org/0000-0001-9182-6067>

Amit Thakral  <https://orcid.org/0000-0003-0476-4721>

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