



# Magnetic resonance imaging and symptoms in patients with neurosarcoidosis and central diabetes insipidus

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## Abstract

**Introduction:** In the clinical setting, the diagnosis of neurosarcoidosis in patients with central diabetes insipidus (CDI) is typically based both on symptoms (i.e. polydipsia or polyuria) and brain magnetic resonance imaging (MRI) findings (e.g. pituitary abnormality). However, inconsistent changes in the patient's symptoms and brain MRI findings may occur during the clinical course of the disease.

This review was performed to summarise the relationship between symptoms and brain MRI findings in previously reported cases of neurosarcoidosis with CDI.

**Material and methods:** Case studies of patients diagnosed with neurosarcoidosis with CDI were collected via a PubMed search of studies published through 30 June 2018.

**Results:** Thirteen eligible studies were reviewed (20 patients; 12 men, 8 women; mean age 33 years). Polydipsia or polyuria was the first symptom in 13 patients. The mean duration from disease onset to diagnosis was 3.4 months. Brain MRIs showed abnormal findings in the hypothalamus and pituitary for 17 patients. Immunosuppressive drugs were used in 17 patients. For 14 patients, MRI findings improved, while symptoms did not.

**Conclusion:** Patients with both neurosarcoidosis and CDI symptoms often do not improve, despite the fact that brain MRI findings often improve following treatment. More studies involving detailed pathological analyses and longer follow-up periods are necessary. (*Endokrynol Pol* 2019; 70 (5): 430–437)

**Key words:** neurosarcoidosis; central diabetes insipidus; pituitary; pituitary stalk; prednisolone

## Introduction

Sarcoidosis is a multi-organ, non-caseating, granuloma-forming disorder. Although its aetiology remains unknown, sarcoidosis is thought to be immune-mediated [1]. Nervous system involvement, which can occur in either the central or peripheral nervous system, is observed in 5% to 15% of patients with sarcoidosis [2, 3]. When the hypothalamus-pituitary axis is affected in patients with sarcoidosis, central diabetes insipidus (CDI) is generally also present [4]. CDI is rarely observed, occurring in approximately 2% of patients with neurosarcoidosis, and presents with unique symptoms, such as polydipsia or polyuria [5].

Magnetic resonance imaging (MRI) with gadolinium is the recommended method for the initial assessment of neural pathologies [6]. Brain MRI can be helpful in patients with neurosarcoidosis, although autoimmune

inflammatory, infectious, or malignant diseases can display similar MRI findings as neurosarcoidosis [7]. The MRI findings of neurosarcoidosis typically include infundibular involvement, pituitary stalk thickening, or pituitary gland enlargement; additionally, a loss of the hyperintense signal from the posterior pituitary on T1-weighted images is indicative of an infiltrative process [6].

An earlier report suggested that corticosteroid treatment in patients with neurosarcoidosis effectively ameliorated MRI abnormalities but failed to completely subdue CDI without desmopressin supplementation; however, this study included only four cases [8]. The current review of previously published case studies was performed to summarise the relationship between changes in symptoms and brain MRI findings during the clinical course of neurosarcoidosis with CDI.



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## Material and methods

### Search strategy

We conducted a comprehensive literature search of PubMed to identify studies that reported neurosarcoidosis with CDI. A search of the PubMed database was performed using the terms 'neurosarcoidosis' or 'central nervous system sarcoidosis' and 'diabetes insipidus' to identify any articles published through March 2019.

#### Study selection

Original case reports that included the following data were included in the present review: 1) age and sex; 2) first symptoms; 3) duration of polydipsia or polyuria; 4) affected organs (lungs, eyes, or other organs); 5) anterior pituitary function; 6) brain MRI findings (abnormalities or loss of high signal intensity of the posterior lobe of the pituitary); 7) histological findings; 8) treatment; and 9) clinical course (brain MRI findings and CDI improvement). Review articles and articles written in languages other than English were excluded. After we identified 98 articles, we determined that 13 articles (including 20 patients) were eligible.

## Results

Table I provides a summary and Table II provides a detailed list of the characteristics of the 20 patients who were diagnosed with neurosarcoidosis with CDI. The patients included 12 men [8–12, 14, 15, 17] and eight women [7, 10, 13, 16, 18, 19], with a mean age of 33 years. The first symptom was polyuria in 13 patients [7–9, 11–17] and polydipsia in eight patients [7–9, 11–15]. The mean duration from disease onset to diagnosis was 3.4 months. Isolated neurosarcoidosis was reported in four patients [7, 8, 10, 12]. Brain MRI showed abnormal findings in the pituitary stalk in 10 patients [7, 8, 10–13, 16], abnormal findings in the pituitary gland in nine patients [8–13, 15], and loss of high intensity of the posterior lobe of the pituitary in nine patients [8, 9, 11–13]. Twelve patients were diagnosed through biopsies of the lymph nodes [8, 10, 14, 16, 17], lungs [8–10], and skin [13,15], while only one patient underwent a brain biopsy [8].

Table III provides a detailed list of the clinical treatments, brain MRI findings, and outcomes of patients with neurosarcoidosis and CDI. Steroid therapy was administered to 17 patients [8–12, 14–19], infliximab was administered to two patients [17, 19], cyclophosphamide was administered to one patient [10], and methotrexate was administered to one patient [19]. Desmopressin (1-desamino-8-D-arginine vasopressin) (DDAVP) was used to treat the symptoms of CDI in 19 patients [7–14, 16–19]. Fourteen patients showed improvement in their abnormal brain MRI findings [8–13, 15–17], but no patients showed improvement in the loss of high signal intensity in the posterior lobe of the pituitary. One patient showed spontaneous improvement in CDI symptoms without the use of an immunosuppressive agent [13]. Five patients showed improvement in their anterior pituitary functions, and improvement in the MRI findings were also recognised in these patients [8, 9, 11, 16].

## Discussion

In the current review, complete improvement in CDI symptoms was not observed in most patients diagnosed with neurosarcoidosis with CDI, despite improvements in the abnormal brain MRI findings. These findings suggest that inconsistent changes in symptoms and brain MRI findings occur in most cases during the clinical course of the disease, and reinforce the observation made in the earlier report that included a small number of cases [8]. This result has clinical implications for the use of MRI in the diagnosis of neurosarcoidosis in patients with CDI.

There are several possible reasons for the findings in this review. Once the central nervous system has become involved in sarcoidosis, the pathological changes that occur in the brain may be irreversible. Some studies have reported improvements in the MRI findings for the anterior pituitary after immunosuppressant treatment [8, 9, 11, 16]. In particular, the posterior, rather than anterior, pituitary gland may undergo irreversible damage following granuloma formation. Because the distance from the base of the brain to the sella turcica is greater than that to the pituitary, there has been an assumption that sarcoidosis lesions cannot completely invade the anterior pituitary [16].

Patients with sarcoidosis typically display infundibular involvement, pituitary stalk thickening, or pituitary gland enlargement when examined by MRI, and the loss of the hyperintense signal from the posterior pituitary on T1-weighted images can be indicative of an infiltrative process [6]. Infiltration of sarcoidosis into the infundibulum may jeopardise the production and transport of pituitary-stimulating hormones and induce the direct involvement of the pituitary [2]. This infiltration process may be independent of improvements in CDI symptoms.

The primary treatment option for neurosarcoidosis is steroid therapy [20]. Immunosuppressive agents and antimalarials can also be administered in resistant cases or when glucocorticoids are tolerated [20, 21]. In the current review, immunosuppressants, especially prednisolone, were used in most of the cases, but CDI did not improve, and the use of DDAVP was continued. One report suggested that the early administration (within one month of onset) of prednisolone was effective for the improvement of CDI symptoms; however, not all patients had posterior pituitary lesions in that report [22]. In the current review, the mean duration from disease onset to diagnosis was > 3 months, and the lack of early treatment may have contributed to the inconsistent improvements in symptoms relative to the MRI findings.

**Table I.** Clinical diagnoses, treatments, and outcomes for patients with neurosarcoidosis and central diabetes insipidus

Diagnosis			Treatments		
Age, years	33	(10–77)	Immunosuppressant (n = 20)		
Sex, male	12	(60)	PSL	16	(80)
First manifestations (n = 20)			mPSL	2	(10)
Polyuria	13	(65)	Hydrocortisone	2	(10)
Polydipsia	8	(40)	Infliximab	2	(10)
Duration of polydipsia or polyuria (months)	3.4	(1–12)	Cyclophosphamide	1	(5)
			Methotrexate	1	(5)
Lesion sites (n = 20)			Endocrine (n = 20)		
Lungs	13	(65)	DDAVP	19	(95)
Eyes	3	(15)	Thyroid hormone	3	(15)
Isolated	4	(20)	Gonadotropin hormone	1	(5)
Anterior pituitary dysfunction (n = 20)					
PRL	12	(60)	<b>Symptoms and MRI findings</b>		
LH	9	(45)	Brain MRI abnormality (n = 20)		
FSH	9	(45)	Improved	14	(70)
ACTH	6	(30)	Not improved	3	(15)
TSH	6	(30)	NR	3	(15)
GH	4	(20)	Improvement of loss of high signal intensity* (n = 20)		
Panhypopituitarism	3	(15)	Improved	0	(0)
Brain MRI (n = 20)			No change	4	(20)
Abnormality	18	(90)	NR	16	(80)
Pituitary stalk	10	(50)	Symptoms of CDI (n = 20)		
Pituitary gland	9	(45)	Improved	1	(5)
Hypothalamus	5	(25)	Not improved	15	(75)
Loss of high signal intensity*			NR	4	(20)
Yes	9	(45)	Anterior pituitary dysfunction (n = 16)		
No	1	(5)	Improved	4	(20)
NR	10	(50)	Not improved	4	(20)
Histology (n = 20)			NR	8	(40)
Brain	1	(5)	Other neurological symptoms (n = 14)		
Others	11	(55)	Improved	7	(50)
Lymph node	6	(30)	Not improved	3	(15)
TBLB	3	(15)	NR	4	(20)
Skin	2	(10)			

Data are presented as the mean (range) or n (%); \*posterior lobe of the pituitary gland; PRL — prolactin; LH — luteinising hormone; FSH — follicle stimulating hormone; ACTH — adrenocorticotropic hormone; TSH — thyroid-stimulating hormone; GH — growth hormone; MRI — magnetic resonance imaging; NR — not reported; TBLB — transbronchial lung biopsy; PSL — prednisolone; mPSL — methylprednisolone; DDAVP — 1-desamino-8-D-arginine vasopressin; CDI — central diabetes insipidus

Untreated self-limiting cases and cases with atypical neurosarcoidosis have been reported [10, 13, 23]; additionally, several diseases can present with MRI findings that are similar to those observed for neurosarcoidosis [7]. Substantial experience and cautious judgment appear to be necessary for the accurate diagnosis of neurosarcoidosis in patients with CDI, which could

also explain the inconsistencies observed between CDI symptoms and MRI findings.

The current review has several limitations. The number of reports included in the review was relatively small. Because brain biopsies were very rare (only one case in this review), most patients were clinically but not pathologically diagnosed. None of the reviewed studies

Table II. Clinical diagnoses of patients with neurosarcoidosis and central diabetes insipidus

No.	Authors [Reference]	Year	Age (years, sex)	First symptoms	Duration of polydipsia or polyuria (months)	Lungs	Eyes	Other organs	Anterior pituitary function	Brain MRI	
										Abnormality	Loss of high signal intensity of the posterior lobe of the pituitary
1	Loh et al. [9]	1997	27, M	Polydipsia, polyuria, headache	3	Yes	No	No	Normal	Pituitary	Yes
2	Konrad et al. [7]	2000	10, F	Polydipsia, polyuria	4	No	No	No	Normal	Pituitary stalk, subcortical white matter	–
3	Bullmann et al. [10]	2000	40, F	Amenorrhoea, fatigability	12	No	No	No	PRL ↑	Pituitary stalk	–
			41, F	Amenorrhoea	5	No	No	No	PRL ↑, TSH ↓	Pituitary, pituitary stalk	–
			27, M	Erectile dysfunction	3	Yes	No	Muscle	PRL ↑, LH ↓, FSH ↓	Pituitary stalk, fourth ventricle, brainstem	–
			21, M	Impotence	2	Yes	Yes	GI area, skin, LN	PRL ↑, LH ↓, FSH ↓	Pituitary stalk	–
			26, M	Visual impairment	3	Yes	No	LN	LH ↓, FSH ↓	Hypothalamus, optic nerve	–
4	Tabuena et al. [8]	2004	27, M	Polyuria, fatigability	1	Yes	No	LN	PRL ↑, LH ↓, FSH ↓	Hypothalamus, pituitary stalk, suprasellar region	Yes
			33, F	Polyuria, polydipsia, amenorrhoea, blurred vision, dysarthria, depression	–	Yes	–	–	PRL ↑	Hypothalamus, pituitary	Yes
			26, M	Facial palsy, fatigability, thirst, polyuria, impotence	1	Yes	Yes	No	PRL ↑, LH ↓, FSH ↓, ACTH ↓, TSH ↓	Pituitary	Yes
			18, M	Polyuria, malaise, muscle weakness, diplopia	–	No	No	No	PRL ↑, LH ↓, FSH ↓, ACTH ↓, TSH ↓, GH ↓	Pituitary, third ventricle, optic nerve	Yes
5	Miyoshi et al. [11]	2007	77, M	Fatigability, headache, thirst, polydipsia, polyuria	4	Yes	No	No	PRL ↑, LH ↓, FSH ↓, ACTH ↓, TSH ↓, GH ↓	Pituitary, pituitary stalk	Yes

Table II. Clinical diagnoses of patients with neurosarcoidosis and central diabetes insipidus

No.	Authors [Reference]	Year	Age (years, sex)	First symptoms	Duration of polydipsia or polyuria (months)	Lungs	Eyes	Other organs	Brain MRI			
									Anterior pituitary function	Abnormality	Loss of high signal intensity of the posterior lobe of the pituitary	Histology
6	Jomaa et al. [12]	2009	15, M	Headache, polydipsia, polyuria, diplopia	1	No	No	No	PRL ↑	Hypothalamus, pituitary, pituitary stalk, cavernous sinus, chiasmatic region, cerebral tent, meningeal spaces	Yes	—
7	Inaba et al. [13]	2009	58, F	Polydipsia, polyuria	1	Yes	Yes	Skin	PRL ↑, LH ↓, FSH ↓, ACTH ↓, TSH ↓, GH ↓	Pituitary, pituitary stalk	Yes	Skin
8	Alam et al. [14]	2011	25, M	Polydipsia, polyuria	3	Yes	No	LN	Normal	Normal	Normal	LN
9	Asabella et al. [15]	2011	26, M	Polydipsia, polyuria	—	No	No	Skin	—	Pituitary, white matter, splenium, corpus callosum	—	Skin
10	Tanaka et al. [16]	2012	51, F	Fever, polyuria, visual field defect	4	Yes	No	LN	LH ↓, FSH ↓, GH ↓	Pituitary stalk	Yes	LN
11	O'Reilly et al. [17]	2015	22, M	Polyuria, adipisia	—	No	—	LN	ACTH ↓	Hypothalamus	—	LN
12	Lemuel et al. [18]	2015	45, F	Nausea, vomiting, fatigability, anorexia	—	Yes	—	Cranium	ACTH ↓, TSH ↓	—	—	—
13	Sanghi et al. [19]	2016	40, F	Altered mental status, slurred speech, seizure	—	Yes	No	No	PRL ↑	Subcortical white matter	—	—
	Present case	2012	33, F	Visual field defect, polydipsia, polyuria	1	Yes	No	No	PRL ↑	Pituitary, pituitary stalk	Yes	TBLB

M — male; F — female; GI — gastrointestinal; LN — lymph node; TBLB — transbronchial lung biopsy; PRL — prolactin; LH — luteinising hormone; FSH — follicle-stimulating hormone; ACTH — adrenocorticotropic hormone; TSH — thyroid stimulating hormone; GH — growth hormone; MRI — magnetic resonance imaging

Table III. Clinical treatments, brain magnetic resonance imaging findings, and outcomes of patients with neurosarcoidosis and central diabetes insipidus

No.	Treatment	Brain MRI			Improvement of diabetes insipidus symptom	Other clinical courses
		Abnormality	Loss of high signal intensity in the posterior lobe of the pituitary			
1	DDAVP, PSL 40 mg/day	Improved	No change	No	The patient recovered from his headache, lethargy and weight loss	
2	DDAVP	Not improved	–	No	–	
3	DDAVP, PSL	Improved	–	No	Normal menstrual cycles were re-established	
	DDAVP, PSL	Not improved	–	No	Pituitary dysfunction and radiological results remained unchanged over the course of steroid treatment	
	DDAVP, PSL, cyclophosphamide 150 mg/day	Not improved	–	No	Hydrocephalus developed despite immunosuppressive treatments	
	DDAVP, PSL	Improved	–	No	Prednisone therapy resulted in good remission of the pituitary and abdominal manifestations measured radiologically, although hypogonadism persisted	
	DDAVP, PSL, mPSL	Improved	–	No	Despite improvement in brain MRI, pituitary dysfunction remained unchanged	
4	DDAVP, PSL 55 mg/day	Improved	–	No	Other conditions appeared to be stable with a low dose of prednisolone	
	DDAVP, PSL 0.5 mg/kg/day	Improved	–	No	Amenorrhoea, dysarthria, homonymous haemianopia, and dysphagia improved with corticosteroid treatment	
	DDAVP, PSL 40 mg/day	Improved	–	No	Impotence and uveitis improved	
	DDAVP, gonadotropin, thyroid hormone, PSL 60 mg/day	Improved	–	No	Hormone therapy could not be withdrawn	
5	DDAVP, levothyroxine, hydrocortisone 25 mg/day	Improved	No change	No	The patient recovered from his headache, lethargy and weight loss	
6	DDAVP, mPSL 0.5 g/d, PSL 1 mg/kg	Improved	–	–	Corticosteroid therapy rapidly ameliorated the patient's neurological symptoms	
7	DDAVP 5 µg/day	Improved	No change	Yes	The findings of ophthalmologic sarcoidosis, pulmonary lesions, and cutaneous sarcoidosis remained unchanged throughout the clinical course	
8	Alam et al. [14] DDAVP, PSL	–	–	No	The patient remained well and continued on desmopressin and steroid therapy	
9	Asabella et al. [15] PSL	Improved	–	–	–	

Table III. Clinical treatments, brain magnetic resonance imaging findings, and outcomes of patients with neurosarcoidosis and central diabetes insipidus

No.	Treatment	Brain MRI		Improvement of diabetes insipidus symptom	Other clinical courses
		Abnormality	Loss of high signal intensity in the posterior lobe of the pituitary		
10	DDAVP 7.5 µg/day, PSL 50 mg/day	Improved	No change	No	Anterior pituitary function improved compared with that before treatment
11	DDAVP, PSL, infliximab	Improved	—	—	Infliximab therapy resulted in the successful remission of radiological disease and the complete recovery of osmoregulated thirst appreciation
12	DDAVP, hydrocortisone 100 mg/day, PSL 20 mg/day	—	—	—	The patient required desmopressin for a few weeks, but this was eventually discontinued because of hyponatraemia
13	DDAVP, levothyroxine, mPSL 1g/day, methotrexate, infliximab	—	—	No	The patient's mental status greatly improved
Present case	DDAVP, PSL 30 mg/day	Improved	No change	No	Despite improvements in brain MRI findings, posterior pituitary dysfunction remained unchanged

DDAVP — 1-desamino-8-D-arginine vasopressin; PSL — prednisolone; mPSL — methylprednisolone; MRI — magnetic resonance imaging

included a follow-up period that was long enough to demonstrate improvements in neurosarcoidosis with CDI.

## Conclusion

During the clinical course of neurosarcoidosis and CDI, symptoms frequently do not improve even when improvements are observed in the brain MRI findings following treatment, which highlights the need for vigilance in clinical practice when assessing the progress of neurosarcoidosis and CDI. More studies with detailed pathological analyses and longer follow-up periods are necessary.

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