

# Heerfordt's Syndrome Presenting with Recurrent Facial Nerve Palsy

## Case report and 10-year literature review

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### متلازمة هيرفوردز المصاحبة لتكرار شلل العصب الوجهي تقرير حالة ومراجعة أدبيات عشرة أعوام

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**ABSTRACT:** Heerfordt's syndrome is defined as a combination of facial palsy, parotid swelling, *uveitis* and fever in sarcoidosis cases. Heerfordt's syndrome as a cause of facial palsy is very rare. We report a case of alternating facial nerve palsy in a 52-year-old female initially treated for Bell's palsy. The patient was referred to the All India Institute of Medical Sciences, Bhubaneswar, India, in January 2013 for clinical evaluation. She was found to have a parotid swelling and anterior intermediate *uveitis*. A pathoradiological evaluation suggested sarcoidosis and a final diagnosis of Heerfordt's syndrome was made. Steroid treatment was initiated which led to an improvement in the facial palsy and *uveitis* as well as the disappearance of the parotid swelling with a corresponding decrease in angiotensin-converting enzyme levels. An English literature review was carried out to analyse the varied presentation of this syndrome. The analysis focused on presenting symptoms, biochemical markers and radiological findings of Heerfordt's syndrome cases.

**Keywords:** Heerfordt Syndrome; Sarcoidosis; Facial Palsy; Case Report; India.

**الملخص:** تعرف متلازمة هيرفوردز بأنها مزيج من الأعراض التي تتمثل في شلل في الوجه، تورم الغدة النكافية، التهاب القزحية والحمى في حالات الساركويد. متلازمة هيرفوردز المسببة للشلل الوجهي حالة نادرة جدا. نقدم هنا حالة شلل العصب الوجهي لامرأة تبلغ من العمر 52 عاما عولجت مبدئيا لشلل بيل. أحيلت المريضة إلى معهد عموم الهند للعلوم الطبية، بوبانسوار، الهند، في يناير 2013 للتقييم السريري. وجد عندها تورم في الغدة النكافية والتهاب العينية الأمامية المتوسطة. أشار التقييم الإشعاعي لمرض الساركويد وتم التشخيص النهائي لمتلازمة هيرفوردز. وقد بدأ العلاج بالستيرويد والتي أدت إلى تحسن في شلل الوجه والتهاب القزحية وكذلك اختفاء تورم النكفية مع انخفاض في مستويات أنزيم المحول للأنجيوتنسين. تم استعراض الأدبيات الإنجليزية لتحليل العرض المتنوع لهذه المتلازمة. وركز التحليل على الأعراض، العلامات البيوكيميائية والنتائج الإشعاعية من حالات متلازمة هيرفوردز.

**مفتاح الكلمات:** متلازمة هيرفوردز: مرض الساركويد؛ شلل العصب الوجهي؛ تقرير حالة؛ الهند.

**H**EERFORDT'S SYNDROME IS DESCRIBED as part of the spectrum of sarcoidosis, occurring in approximately 0.3% of sarcoidosis cases.<sup>1</sup> It is defined as a combination of *uveitis*, parotid gland enlargement, fever and facial nerve palsy.<sup>2</sup> A typical case of Heerfordt's syndrome is rare and patients usually have atypical presentations. Unilateral facial nerve palsy without a specific cause is most commonly diagnosed as Bell's palsy. Although it is a diagnosis of exclusion, a comprehensive analysis is usually performed only for patients who do not respond to treatment. Heerfordt's syndrome as a cause of unilateral facial palsy is rare, thus invariably delaying diagnoses and increasing morbidity for patients with this condition.<sup>3</sup> The case presented below establishes the need for a comprehensive analysis in specific cases of idiopathic facial palsy

that do not respond to treatment or are recurrent in nature. A review of published literature from 2003 to 2013 in the MEDLINE database was also carried out, based on a search for Heerfordt's syndrome and its clinicopathological presentations.

### Case Report

A 52-year-old Indian female was referred for an evaluation of her bilateral facial palsy to the All India Institute of Medical Sciences in Bhubaneswar, India. She had a history of right-sided facial palsy dating from January 2013, which was diagnosed as Bell's palsy and treated with short-term oral steroids. However, recovery was only partial. In May 2013, she subsequently developed left-sided facial palsy and was referred for further evaluation. A history of swelling in

the parotid region on the left side and undocumented low-grade fever was elicited.

On physical examination, the patient had House-Brackmann grade IV bilateral lower motor neuron facial nerve palsy. A diffuse ill-defined swelling was noted in the left parotid region with no palpable lymphadenopathy, while the right parotid gland was normal. An examination of her chest, lungs and cardiovascular system was unremarkable. Other cranial nerves, motor and sensory physical examinations were normal. Cytology from the left parotid gland was suggestive of non-suppurative chronic granulomatous disease. Her serum angiotensin-converting enzyme (ACE) levels were significantly elevated (129 U/L; normal range: 8–65 U/L). Serum, urinary calcium levels and erythrocyte sedimentation rate were all within normal limits. A computed tomography scan of the thorax revealed mediastinal and hilar lymphadenopathy. Except for occasional irritation of the eyes, the patient had no other significant ophthalmological history. On a slit-lamp examination, features of anterior intermediate *uveitis* were detected.

A diagnosis of Heerfordt's syndrome was made and the patient was initiated on long-term steroid therapy. After two months of treatment with oral steroids, the left facial palsy had completely improved although there was still residual palsy on the right side (grade III). Her ACE levels were 45 U/L.

## Discussion

Heerfordt's syndrome was first described in 1909 by the Danish ophthalmologist, Christian Frederick Heerfordt.<sup>4</sup> A case of unilateral facial palsy with no evident cause is usually diagnosed as Bell's palsy and treated empirically.<sup>5</sup> The lack of typical symptomatology in cases of Heerfordt's syndrome is a diagnostic hurdle for the treating physician. The incidence of cranial nerve palsy in sarcoidosis is about 5%,<sup>6</sup> with the facial nerve followed by the optic nerve being the most common nerves involved.<sup>7</sup> Facial nerve palsy forms an important defining component of Heerfordt's syndrome. The approximate incidence of facial nerve palsy in this syndrome is 25–50%.<sup>8</sup> Sharma *et al.* analysed the rare manifestation of sarcoidosis in an Indian population and, according to their results, Heerfordt's syndrome was present in 1.2% of cases.<sup>9</sup>

The aetiology of this syndrome is still ambiguous and, as a result, so is the pathogenesis. The pathology of neurosarcoidosis is due to a non-caseating epithelioid granuloma. There is an accumulation of cluster of differentiation 4 cells at the sites of inflammation. Generally, these granulomas resolve

spontaneously or with treatment. Persistence of the inflammatory process induces fibrotic changes, resulting in irreversible tissue damage.<sup>10</sup> Nerve root and cranial nerve involvement is either caused by the compressive effect of an adjacent granuloma or because of perivascular and intraneural lymphocytic infiltration.<sup>11,12</sup> The sarcoid granuloma involves the peripheral nerves and is responsible for the varied clinical presentation of the syndrome. Neurosarcoidosis has no definite modality of treatment. Spontaneous remission has been observed, but in progressive or non-resolving cases, such as the one observed in the current report, steroid treatment is required.

Head and neck manifestations of Heerfordt's syndrome are non-specific and a high index of suspicion is required to diagnose the condition early. Common otological manifestations include sensorineural hearing loss, facial nerve paralysis, labyrinthine involvement with vestibular dysfunction and temporal bone involvement.<sup>13</sup> Nasal symptoms include obstruction, *epistaxis*, pain and anosmia. The characteristic finding of a yellow-coloured sub-mucosal nodule is not always found. However, involvement of the airway and salivary gland is frequently noted.<sup>14</sup> Non-caseating epithelioid cell granulomas do not always indicate sarcoidosis; diseases such as tuberculosis, fungal and parasitic infections, Wegener's granulomatosis or leptomenigeal lymphoma may also have such granulomas and should be excluded by the appropriate clinical and pathoradiological investigations.<sup>15</sup>

The symptoms of the current case correspond with the typical diagnosis for Heerfordt's syndrome—bilateral facial palsy, parotid gland enlargement, anterior intermediate *uveitis* and a low-grade non-specific fever. Although elevated calcium levels were not seen, elevated levels of ACE, mediastinal and hilar lymphadenopathy and evidence of non-caseating granulomas on the cytology of the left parotid gland substantiated the diagnosis. The decline in ACE levels after steroid treatment further confirmed the diagnosis. Unfortunately, the right facial nerve palsy still persisted at follow-up, with only partial improvement.

To analyse the varied presentation of Heerfordt's syndrome, a search of the MEDLINE database of literature published between 2003 and 2013 to yielded 31 articles. After excluding articles lacking online abstracts and those not specifically dealing with Heerfordt's syndrome, a total of 14 articles were reviewed.<sup>2,3,16–27</sup> The findings of these articles have been tabulated [Table 1]. The seventh cranial nerve was most commonly involved,<sup>16</sup> followed by the trigeminal nerve.<sup>6</sup> Polyradiculopathy was observed

**Table 1:** Literature review of Heerfordt's syndrome cases and their varied findings

Author	Findings							
	Facial palsy	Ophthalmological	Parotid swelling	Fever	Cytology	Bio-chemistry	Radiology	Other
Denny <i>et al.</i> <sup>3</sup>	UL	Anterior uveitis	BL	Present	Pre-auricular lymph node NCG	Increased ACE levels	CXR showing prominent hilar marking	Coughing, night sweats and weight loss
Fieß <i>et al.</i> <sup>24</sup>	UL	<i>Panuveitis</i>	BL	Present	Turbinectomy specimen NCG	-	-	Refractory sinusitis, fever and poor general condition
Otani <i>et al.</i> <sup>20</sup>	BL	BL granulomatous uveitis	BL	-	Parotid NCG	-	CXR showing BL hilar lymphadenopathy	Paralysis of the left second branch of the fifth cranial nerve
Kato <i>et al.</i> <sup>18</sup>	BL	Anterior uveitis	BL	Present	Parotid NCG	-	-	GBS
Shimizu <i>et al.</i> <sup>25</sup>	UL	Anterior uveitis	BL	Present	Parotid NCG	-	-	Pericardial infarction and a family history of sarcoidosis
Fukuhara <i>et al.</i> <sup>17</sup>	BL	Anterior uveitis	BL	Present	Parotid NCG	-	-	Radiculopathy in the trunk and trigeminal area
Fieß <i>et al.</i> <sup>21</sup>	Right	Anterior and posterior uveitis	BL	Present	Parotid NCG	-	-	Poor general condition
Yagi <i>et al.</i> <sup>23</sup>	BL	Anterior uveitis	-	-	-	-	Present	Progressive multifocal leukoencephalopathy
Petropoulos <i>et al.</i> <sup>2</sup>	Left	Anterior and posterior uveitis	BL	Present	Transbronchial lymph node biopsy	-	-	Night sweats, weight loss, headaches and left <i>otalgia</i>
Tamme <i>et al.</i> <sup>27</sup>	Right	BL swelling of eyelids	BL	Present	Parotid NCG	-	Bihilar lymphadenopathy	-
Ishiwata <i>et al.</i> <sup>16</sup>	Right	Myodesopsia	Present	-	Parotid NCG	-	-	Involvement of the fifth cranial nerve
Ishimatsu <i>et al.</i> <sup>19</sup>	Right	Anterior uveitis	Right	Present	Lung biopsy NCG	Increased ACE and lysozyme levels	CXR showing bihilar lymphadenopathy	Increased serum TNF-alpha levels
Braido <i>et al.</i> <sup>26</sup>	BL	Anterior uveitis	BL	Present	Parotid NCG	-	Present	BL sarcoid involvement of the Gasser's ganglion <i>cisternae</i>
Walter <i>et al.</i> <sup>22</sup>	BL	Anterior uveitis	BL	-	Parotid NCG	-	-	-
Current case	BL	Anterior uveitis	Left	Present	Parotid NCG	Increased ACE levels	Chest CT showing hilar lymphadenopathy	-

UL = unilateral; BL = bilateral; NCG = non-caseating epithelioid granuloma; ACE = angiotensin-converting enzyme; CXR = chest X-ray; GBS = Guillain-Barré syndrome; TNF = tumour necrosis factor; CT = computed tomography.

in one instance.<sup>17</sup> Furthermore, the literature review demonstrated that bilateral facial nerve palsy can be confused with other differential diagnoses, such as Lyme disease, Guillain-Barré syndrome or syphilis.<sup>18,28</sup> Kato *et al.* depicted this potential ambiguity in their report of a case of Heerfordt's syndrome which was initially misdiagnosed and treated as Guillain-Barré syndrome.<sup>18</sup> In sarcoidosis, involvement of the eye reportedly occurs in 11–83% of patients.<sup>29</sup> The most common manifestation described is anterior *uveitis*, with symptoms of increased lacrimation, photophobia, *myodesopsia* (seeing 'floaters') and blurred vision.<sup>29</sup>

Parotid gland involvement reportedly has a documented incidence of 6%.<sup>30</sup> It is usually bilateral in up to 73% of cases, but unilateral involvement has been reported.<sup>19,31</sup> The majority of patients with Heerfordt's syndrome experience some degree of fever; only four patients in the literature review had no documented evidence of fever.<sup>16,20,22,23</sup> Histological examinations of tissue exhibiting non-caseating granulomas are highly suggestive of Heerfordt's syndrome. In the majority of cases in the review, fine needle aspiration cytology of the parotid gland exhibited pathognomic findings. In one patient with refractory sinusitis, Fieß *et al.* found non-caseating granulomas in a turbinectomy specimen.<sup>24</sup> Granulomas were also observed in lymph node and pulmonary tissue.<sup>23,19</sup> ACE levels and hilar lymphadenopathy, though not important on their own, become highly suggestive of Heerfordt's syndrome when found in association with multiple symptoms since these features are found in sarcoidosis.

Although facial nerve involvement is commonly described, few reports suggest the involvement of other cranial nerves. Two case reports indicated involvement of both the fifth and seventh cranial nerve while one patient in the literature review had involvement of only the fifth cranial nerve.<sup>17,29,31</sup> Other noteworthy presentations of Heerfordt's syndrome included pericardial effusion,<sup>25</sup> progressive multifocal leukoencephalopathy,<sup>23</sup> ear pain,<sup>2</sup> involvement of the bilateral Gasser's ganglion,<sup>26</sup> pre-auricular lymphadenopathy,<sup>3</sup> poor general condition,<sup>21</sup> bilateral swelling of the eyelids<sup>27</sup> and elevated serum tumour necrosis factor-alpha levels.<sup>30</sup>

## Conclusion

The presentation of Heerfordt's syndrome is rare and varied. In the current case, symptoms of bilateral facial palsy, parotid gland enlargement, anterior intermediate *uveitis* and a low-grade non-specific fever corresponded with the typical diagnosis for Heerfordt's syndrome. A literature review suggested that eye involvement is the most consistent finding

in patients presenting with Heerfordt's syndrome, along with unilateral or bilateral facial nerve palsy or parotid gland swelling. It is recommended that cases of unilateral facial palsy which do not respond to treatment or are recurrent in nature be evaluated for any systemic involvement. In suspected cases, further analyses such as blood investigations, radiology and a parotid gland assessment should be performed to rule out Heerfordt's syndrome.

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