ORIGINAL ARTICLE

Sensory Ganglionopathy and the Blink Reflex: Electrophysiological Features

Taimour Alam, Alexander StJ.E. Barker, James J.P. Alix, Marios Hadjivassiliou, Dasappaiah G. Rao

ABSTRACT: ***Background:*** Sensory ganglionopathy (SG) is characterised by asymmetrical sensory fibre degeneration, with the primary pathology occurring at the level of the dorsal root ganglion. It is seen in the context of autoimmune, paraneoplastic, and degenerative disorders. There is limited literature examining the electrophysiological correlate of the trigeminal ganglion and associated pathways, the blink reflex (BR), in cases of SG. Previous work has suggested that the BR is preserved in cases of SG associated with paraneoplasia. ***Methods:*** The local clinical neurophysiology database was searched for patients diagnosed with SG from peripheral nerve conduction studies in whom the BR was performed. Twenty-six patients were included in the final analysis. ***Results:*** Sjögren's syndrome constituted the most common SG aetiology (8/26), followed by idiopathic cases (7/26) and paraneoplasia (5/26). BR abnormalities were seen in 9 of the 26 patients (34.6%) across all aetiologies. No patients reported sensory disturbance in the distribution of the trigeminal nerve, indicating that the changes noted are subclinical. Three patients showed abnormality of the R1 response; in the remaining six patients, only R2 responses were affected. ***Conclusions:*** Subclinical abnormalities of both R1 and R2 can be seen in the context of SG of varying aetiologies, including paraneoplasia. Performing the BR in patients with suspected of having SG may be helpful in providing additional evidence of patchy sensory fibre involvement that is characteristic of the disease.

RÉSUMÉ: Gangliopathie sensitive et réflexe de clignement : caractéristiques électrophysiologiques. ***Contexte:*** La gangliopathie sensitive (GS) est caractérisée par une dégénérescence asymétrique des fibres sensitives, la pathologie primaire étant localisée au niveau du ganglion spinal. On la rencontre dans le contexte de maladies autoimmunes, paranéoplasiques ou dégénératives. Il existe peu de littérature qui examine les caractéristiques électrophysiologiques du ganglion du trijumeau et les voies qui y sont associée ainsi que le réflexe de clignement (RC) chez les patients présentant une GS. Selon des études antérieures, le RC est conservé chez les cas de GS associée à une paranéoplasie. ***Méthode:*** Nous avons identifié dans la base de données de neurophysiologie clinique locale des patients ayant reçu un diagnostic de GS basé sur des études de conduction au niveau du nerf périphérique et chez qui le RC a été recherché. Vingt-six patients ont été inclus dans l'analyse finale. ***Résultats:*** Le syndrome de Sjögren était l'étiologie la plus fréquente de GS (8/26), suivi de cas idiopathiques (7/26) et de paranéoplasies (5/26). Des anomalies du RC ont été constatées chez 9 des 26 patients (34,6%), toutes étiologies confondues. Aucun patient n'a rapporté de problèmes sensitifs dans le territoire du nerf trijumeau indiquant que les changements notés sont subcliniques. Trois patients présentaient une réponse R1 anormale. Chez les 6 autres patients, seulement les réponses R2 étaient touchées. ***Conclusions:*** Des anomalies subcliniques de R1 et R2 peuvent exister dans le contexte de GS d'étiologies variées, dont la paranéoplasie. Chez les patients chez qui on soupçonne une GS, le RC peut aider à fournir des indices additionnels d'une atteinte asymétrique des fibres sensitives, ce qui est caractéristique de la maladie.

Keywords: electrodiagnostic studies, paraneoplastic conditions, sensory neurons

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Introduction

Sensory ganglionopathy (SG) is a disorder characterised by damage and dysfunction of the sensory neuronal cell bodies lying in the dorsal root ganglion.[1] It may be seen in degenerative conditions such as Friedreich's ataxia[2] and is well recognised in the context of paraneoplastic disorders.[3] We and other authors have also reported SG in the context of autoimmune disorders such as Sjögren's syndrome and gluten sensitivity.[4,5] Diagnosis can be difficult, and a set of diagnostic criteria, using both clinical and electrophysiological features, has been proposed.[6]

The trigeminal ganglion is easily assessed with electrical stimulation of the supraorbital nerve with recording electrodes placed over the orbicularis oculi muscles bilaterally. The recorded responses are termed the Blink Reflex (BR). Responses used most often in clinical practice consist of an initial response ipsilateral to the stimulus, termed R1, followed by a later response seen both ipsilaterally and contralaterally, known as R2. Fibres conducting the R1 synapse within the main trigeminal nucleus in the pons, forming a circuit with the facial nucleus via interneurons that then lead back to the facial muscles. The pathway for the R2 response is polysynaptic, with afferent fibres

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passing through the spinal trigeminal tract to the spinal trigeminal nucleus. From there, connections exist to ipsilateral and contralateral facial nuclei giving rise to bilateral R2 responses following unilateral stimulation.[7] Abnormalities of the latencies for R1 and R2 responses are used most frequently in clinical practice.

In the context of sensory ganglionopathy, clinical evidence of sensory involvement of the trigeminal nerve innervated territory is well established in various aetiologies, including Sjögren's syndrome, paraneoplasia, and acute autonomic and sensory neuropathy.[8-10] There are, however, few previous reports documenting the electrophysiological features of the BR in association with SG.[11,12] In the largest case series, paraneoplastic disorders were not associated with any abnormalities.[11] The BR has also been used to delineate subclinical cranial nerve involvement in patients with diabetes mellitus.[13,14] The purpose of the present study was to determine if there was evidence of subclinical involvement of trigeminal fibres in the context of SG diagnoses made in association with a variety of conditions and to characterise any abnormalities present.

Methods

We reviewed the local electromyography database in the Department of Clinical Neurophysiology, Royal Hallamshire Hospital, Sheffield, England, over an 11-year period. We performed a search for patients diagnosed with SG, or possible SG, in whom BR data were available. This resulted in 27 patients being identified. One patient was subsequently excluded because of an interim clinical episode of Miller-Fisher syndrome, which could have accounted for abnormalities in the BR responses. The included cases were scrutinised for the information displayed in Table 1. Based on the information obtained, the diagnostic criteria scoring system for SG proposed by Camdessanche et al was completed for all patients.[6]

Electrophysiological examinations were performed using Nicolet EMG machines and Viking select software. Recording technique and normative data were taken from established departmental normative values that are very similar to published reference values.[15] Maximum latency is 13 ms for R1, 41 ms for ipsilateral R2, and 44 ms for contralateral R2. The maximum side-to-side difference in latency is 1.8 ms for R1 and 5.7 ms and 9.4 ms for ipsilateral and contralateral R2, respectively.

Sensory responses were recorded from the median, ulnar, radial, lateral antebrachial, and medial antebrachial nerves in the upper limbs and sural and peroneal nerves in the lower limbs. Motor studies were performed on the median, ulnar, peroneal, and tibial nerves. The number of peripheral nerves examined varied between patients, depending upon how quickly asymmetrical, non-length dependent and/or exclusively sensory involvement could be established. All patients had sensory responses from at least three limbs recorded, with 17 patients having all four limbs examined. Motor responses were recorded from a minimum of two limbs, with 17 patients having more than two limbs examined.

Results

Analysis of the clinical examinations of all patients revealed that all but three were ataxic. Asymmetrical sensory loss at the time of initial medical assessment was documented in 13 patients. Five individuals had clinical involvement of the lower limbs only, three suffered upper limb involvement only, and the remaining group had both upper and lower limb involvement. No patients reported sensory disturbance to the face or intraorally. Pain in the distal upper limbs was reported by two patients early in the course of the disease, but was otherwise not noted to be a prominent feature. Sjögren's syndrome was recognised as the most common aetiology for SG (Table 1). No sensory responses were recordable from either the upper or lower limbs during nerve conduction studies in seven patients (Table 1). The SG diagnostic criteria scores, postulated aetiologies, and BR abnormalities are given in Table 2. All but two patients scored higher than 6.5 on the diagnostic criteria score for a diagnosis of SG. The two patients that did not achieve a score higher than 6.5 had clinical involvement of the lower limbs only, with one patient not clearly having clinical asymmetry and one not fulfilling criteria for Sensory Nerve Action Potential abnormality in the upper limbs.

Analysis of the BR recordings revealed abnormal responses in 9 of 26 patients (34.6%). In two patients, isolated abnormality of the R1 response was noted (Table 2). One patient showed abnormality of the R1 and R2. In the remaining six patients, only R2 abnormalities were seen. Four of nine patients with abnormal BR studies had magnetic resonance imaging of the brain performed. No evidence of brainstem pathology was apparent in any of the cases. In one additional patient with an abnormal BR, full-body positron emission tomography scan was normal. Interestingly, the BR was normal in five of seven patients in whom no sensory responses could be recorded from the limbs.

Discussion

In our cohort, six of 26 patients had abnormalities of R2 and three patients had R1 abnormalities. The R1 response is generally regarded as the more robust response in terms of both latency and resistance to modulation from external factors. Our data suggest that subclinical involvement of trigeminal fibres can be seen in patients with SG, with variable involvement of the R1 and R2 responses.

Overall, our most frequent observation was that of disturbance to R2, with abnormalities ranging from mild prolongation of R2 latency to absence of the R2 response. The pathologic correlate of this finding would appear to be either the more selective involvement of cell bodies of fibres conducting the R2 response within the Gasserian ganglion, or in the multisynaptic central pathways responsible for R2 generation. Previous work looking at cranial reflexes in patients with Sjögren's syndrome and SG postulated that the likely site of pathology was at the level of the Gasserian ganglion.[16] We suspect that the abnormalities seen in our cohort are also more likely to be secondary to involvement of the Gasserian ganglion.

It is interesting to note that five patients had no sensory responses recordable from the limbs, but had a normal BR. This disparity could be explained by the fact that the fibres conducting both R1 and R2 are thought to be of thin- to medium-thickness myelinated fibres,[7,17] unlike the large A-alpha fibres responsible for sensory nerve action potential generation on examination of the limbs. There is some suggestion that the A-delta fibres in the limbs are relatively spared in patients with SG[18]; this disparity in fibre type could explain why the BR appears relatively preserved or shows modest abnormality in the context of severe involvement of the limbs.

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Table 1: Etiological, clinical, and electrophysiological data used in calculating the diagnostic criteria score for all patients

					Clinical features			Electrophysiology				
								(Upper limb)	(Upper limb)	(Lower limb)		
Patient	Age	Sex	Etiology	Duration of symptoms in years	Ataxia present?	Asymmetry in sensory loss?	Upper/lower limb involvement?	At least 1 SNAP unrecordable?	3 SNAPs <30% of LLN?	<2 motor nerve conduction studies abnormal?	Any SNAPs recordable?	Diagnostic criteria score
1	69	M	Gluten/celiac	29	Yes	Yes	Both	Yes	–	Yes	No	12.7
2	41	F	Gluten/celiac	1	No	Yes	Both	No	No	Yes	Yes	6.8
3	61	M	Gluten/celiac	1	Yes	Yes	Both	No	No	Yes	Yes	9.9
4	20	M	Friedreich's	5	Yes	No	Both	Yes	–	Yes	No	11
5	24	M	Friedreich's	10	Yes	No	Both	Yes	–	Yes	No	11
6	20	F	Friedreich's	13	Yes	No	Both	Yes	–	Yes	No	11
7	76	F	Idiopathic	4	Yes	Yes	Lower only	Yes	–	Yes	No	10.7
8	67	F	Idiopathic	6	Yes	Yes	Both	Yes	–	Yes	Yes	12.7
9	73	F	Idiopathic	20	Yes	No	Both	Yes	–	Yes	Yes	11
10	73	F	Idiopathic	7	Yes	Yes	Lower only	No	No	No	Yes	4.8
11	54	M	Idiopathic	16	Yes	Yes	Both	No	Yes	Yes	Yes	12.7
12	65	F	Idiopathic	16	Yes	No	Both	Yes	–	Yes	Yes	11
13	72	F	Idiopathic	5	Yes	Yes	Both	Yes	Yes	No	Yes	9.6
14	79	M	Paraneoplastic	4	Yes	No	Lower only	Yes	–	Yes	Yes	9
15	76	M	Paraneoplastic	5	Yes	No	Lower only	Yes	–	Yes	Yes	9
16	71	M	Paraneoplastic	6	Yes	No	Lower only	Yes	–	No	Yes	5.9
17	77	M	Paraneoplastic	1	Yes	Yes	Both	Yes	–	Yes	Yes	12.7
18	68	F	Paraneoplastic	2	Yes	No	Both	Yes	Yes	Yes	No	11
19	60	F	Sjögren's	6	Yes	Yes	Both	No	No	Yes	Yes	9.9
20	65	F	Sjögren's	5	Yes	No	Upper only	Yes	–	Yes	Yes	11
21	51	F	Sjögren's	12	Yes	Yes	Both	Yes	–	Yes	Yes	12.7
22	71	F	Sjögren's	27	Yes	No	Both	Yes	–	No	Yes	7.9
23	73	F	Sjögren's	21	Yes	No	Both	Yes	–	Yes	No	11
24	65	F	Sjögren's	7	No	Yes	Upper only	No	No	Yes	Yes	6.8
25	67	M	Sjögren's	1	Yes	Yes	Both	Yes	–	Yes	Yes	12.7
26	75	M	Sjögren's	7	No	No	Upper only	Yes	–	Yes	Yes	7.9

F = female; M = male; SNAP = sensory nerve action potential; LLN = lower limit of normal.

Table 2: Demographic, etiological, diagnostic score and BR data for all patients

					Right stimulation			Left stimulation			
Patient	**Age**	**Sex**	**Etiology**	**Diagnostic criteria score**	**R1**	**iR2**	**cR2**	**R1**	**iR2**	**cR2**	**Blink reflex**
1	69	M	Gluten/celiac	12.7	11.4	32	35.6	11	35	36	Normal
2	41	F	Gluten/celiac	6.8	10.6	30	29.9	10.7	31.8	30	Normal
3	61	M	Gluten/celiac	9.9	10.8	50	50.8	9.8	NR	NR	Delayed iR2/cR2 on right, absent iR2/cR2 on left
4	20	M	Friedreich's	11	10.3	36	40.6	10.7	34.4	35	Normal
5	24	M	Friedreich's	11	9.1	42	39.4	9.7	40.2	43	Delayed iR2 on right
6	20	F	Friedreich's	11	9.4	39	42	9.7	38.2	43	Normal
7	76	F	Idiopathic	10.7	13	30	33.5	12.6	26.1	26	Normal
8	67	F	Idiopathic	12.7	9.8	34	30.8	10.5	35.4	34	Normal
9	73	F	Idiopathic	11	9.1	33	30.8	9.5	36.4	33	Normal
10	73	F	Idiopathic	4.8	10.8	42	41.2	10.4	40.4	43	Delayed iR2 on right
11	54	M	Idiopathic	12.7	10.2	37	36.6	11.2	37.4	36	Normal
12	65	F	Idiopathic	11	11.6	39	40.4	10.6	37.5	42	Normal
13	72	F	Idiopathic	9.6	14	36	37.5	14.1	31.8	31	Delayed R1 bilaterally
14	79	M	Paraneoplastic	9	12	37	38	10.1	42.8	45	Relative delay of R1 on right, delayed iR2/cR2 on left
15	76	M	Paraneoplastic	9	11	42	41	10.9	40.4	39	Delayed iR2 on right
16	71	M	Paraneoplastic	5.9	10.8	33	34	10.8	36.1	34	Normal
17	77	M	Paraneoplastic	12.7	10.2	32	31.3	9.2	37.9	30	Relative delay of iR2 on left
18	68	F	Paraneoplastic	11	NR	31	33.2	NR	29.5	31	Absent R1 bilaterally
19	60	F	Sjögren's	9.9	10.5	36	34.6	10.9	33.2	34	Normal
20	65	F	Sjögren's	11	10.2	32	31.6	10.9	34.2	32	Normal
21	51	F	Sjögren's	12.7	11.6	36	36	12	37.4	35	Normal
22	71	F	Sjögren's	7.9	9	32	34.6	9.4	34.1	35	Normal
23	73	F	Sjögren's	11	10.4	38	38.8	10.5	39.1	40	Normal
24	65	F	Sjögren's	6.8	9.6	33	33.5	9.8	36.8	36	Normal
25	67	M	Sjögren's	12.7	8.6	47	48.9	9.2	39.3	39	Delayed iR2/cR2 on right
26	75	M	Sjögren's	7.9	11	33	32.4	11.7	33.2	32	Normal

Figures in red indicate values outside of normal range. R1 and R2 latency values are in milliseconds. Maximum latency is 13 ms for R1, 41 ms for IR2, and 44 ms for cR2. The maximum side-to-side difference in latency is 1.8 ms for R1 and 5.7 ms and 9.4 ms for ipsilateral and contralateral R2, respectively. BR = blink reflex; cR2 = contralateral R2; iR2 = ipsilateral R2; F = female; male = male.

Our finding of R2 abnormality with preservation of the R1 latency in patients with Friedreich's ataxia is similar to findings from a previous study examining BR and auditory evoked potentials in this group of patients.[19] Intriguingly, an autopsy of a patient with Friedreich's ataxia demonstrated loss of secondary sensory neurons in the trigeminal nuclei,[20] an observation that would manifest on the BR as prolongation/absence of the R2 component. We are not aware of any neuropathological studies looking at the Gasserian ganglion in cases of confirmed SG.

An important observation in our study is the finding of abnormal BR responses in paraneoplastic cases. It has previously been reported that the BR is normal in SG seen in association with malignancy[11]; however, we found abnormalities in four of five patients. Although such patient numbers are small, this is in clear contrast to the previous report in which no BR abnormalities were reported in 17 cases of paraneoplastic SG. Although some of the patients with a paraneoplastic SG had only mild R2 abnormalities that one might argue are of equivocal significance, two patients had abnormalities of the R1, which is a robust marker of pathology. The disparity between our findings and those of previous studies could relate to the patchy nature of such disease.

In conclusion, we report BR abnormalities in 34.6% of our SG cohort. The most common abnormality was prolongation of the R2 component, although R1 abnormalities were seen in one-third of those with an abnormal BR. The most likely cause of the BR abnormality is pathology at the level of the Gasserian ganglion, although involvement of the central polysynaptic pathways could also potentially cause abnormalities of the R2 response. Finally, BR abnormalities can be seen in SG related to paraneoplasia.

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Disclosures

TA, ASEB, JJPA, MH, and DGR do not have anything to disclose.

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