Trigeminal nerve electrophysiological assessment in sickle cell anemia: correlation with disease severity and radiological findings
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Introduction
Sickle cell disease is the most common genetic disease of the blood [1]. It is most frequent in African, Arabian, Mediterranean, Middle Eastern, and Asian populations [2]. It is an autosomal recessive hemoglobinopathy that results from a single-point mutation in the $\beta$-globin gene. This mutation leads to the formation of the HbS molecule [3,4].

Upon deoxygenation, an abnormal HbS protein chain polymerizes reversibly into a gellatinous network of fibrous polymers. This polymerization stiffens the red blood cells' membrane and increases viscosity. The deformed red blood cells tend to adhere to the endothelium, worsening vascular occlusion, leading to ischemia and tissue infarction [3].

Sickle cell vaso-occlusive crisis (VOC) may cause painful trigeminal neuropathy because of nerve ischemia or infarction. The mandible is the most vulnerable area of the face because of the relatively low blood flow [5]. Moreover, it may result from compression of the inferior alveolar nerve (IAN), a branch of the mandibular division of the trigeminal nerve in the mandibular canal (MC), as a result of bone infarct or osteomyelitis of the mandible [6].

Purpose
The aim of our study was to assess, electrophysiologically, the possibility of associated subclinical trigeminal neuropathy in sickle cell anemia (SCA) patients and correlate the results with disease severity and findings of computerized tomography.

Materials and methods
Fifty patients with SCA were included; 20 of these patients had clinical unilateral trigeminal neuropathy (group II), whereas the others were asymptomatic (group I). Forty matched healthy individuals served as a control group. Trigeminal evoked potential (TEP) and inferior alveolar nerve (IAN) conduction studies were carried out for all patients and controls. Findings were correlated with the frequency of vaso-occlusive crisis, mental foramen (MF), and mandibular canal (MC) dimensions as measured by computerized tomography.

Results
There were highly significantly longer N13, 19, and 20 latencies and reduced N13-P19 amplitude in patient groups in comparison with the controls ($P<0.001$). There were delayed P19 latency, IAN latency, reduced IAN amplitude ($P<0.05$), and conduction velocity ($P<0.001$) in SCA patients with trigeminal neuropathy versus those without trigeminal neuropathy, and also in asymptomatic patients versus controls. The vaso-occlusive crisis frequency in group II was correlated positively with all TEP waves’ latencies and IAN latency and correlated negatively with IAN amplitude, conduction velocity, and N13/P19 amplitude. MF and MC dimensions were significantly reduced in group II in comparison with the controls ($P<0.05$). MF height and MC diameter were correlated negatively with ipsilateral P19 latency.

Conclusion
Subclinical trigeminal neuropathy may be associated with SCA. The trigeminal nerve could be affected along its peripheral or the central pathway. Central affection may occur as a result of lesions in its nuclei or at the somatosensory cortex. Electrophysiological assessment is recommended in SCA patients to diagnose trigeminal neuropathy and detect the level of its affection. This will provide new insights into its prevention and treatment.

Keywords:
inferior alveolar nerve, sickle cell anemia, trigeminal evoked potential, trigeminal neuropathy, vaso-occlusive crisis
Trigeminal neuropathy in sickle cell anemia (SCA) is underestimated. This may be explained as follows: first, the involvement may be subclinical and electrophysiologic examinations are not used routinely in patients without clinical symptoms. Second, in patients with central nervous system involvement, symptoms related to cranial neuropathy cannot be noticed because these symptoms are considered to be related to central nervous system involvement [6].

The mental nerve is a terminal sensory branch of IAN of the mandibular division of the trigeminal nerve [5]. Mental neuropathy may be considered a complication of SCA. It is a sensory neuropathy characterized by altered sensation, numbness, or continuous aching pain in the distribution of the mental nerve, lower lip, lower anterior gingiva, and chin [2].

Trigeminal evoked potential (TEP) and IAN conduction studies are considered the most valuable methods to assess the trigeminal complex centrally and peripherally, respectively [7].

Therefore, we aimed to assess the trigeminal nerve electrophysiologically in SCA patients with and without symptoms/signs suggestive of trigeminal neuropathy, and correlate the results with clinical disease severity, frequency of VOC within the last year, and computerized tomography (CT) findings of the mandible including mental foramen (MF) dimensions and MC diameter.

Materials and methods
Fifty patients with SCA, from among those presenting to the Hematology, and Physical Medicine, Rheumatology and Rehabilitation outpatient clinics of Ain Shams University Hospitals, were included. The diagnosis of SCA (HbSS) was made on the basis of clinical history and examination, and confirmed by hemoglobin electrophoresis.

These patients were subdivided into two groups:

Group I: 30 SCA patients, who were clinically free from any symptoms or signs of trigeminal neuropathy bilaterally.

Group II: 20 SCA patients, who had unilateral symptoms and/or signs of trigeminal neuropathy (facial pain, parathesia, decreased pain and light touch sensation at facial skin area, weakness of muscles of mastication, or absent jaw reflex).

We excluded patients who had other causes of trigeminal neuropathy such as diabetic neuropathy, CNS tumors, and multiple sclerosis as well as patients with other causes of numb chin syndrome such as a recent history of dental procedures at the lower mandible within the last year, a history of fracture mandible, and patients with a space-occupying lesion of the mandible. The control group included 40 healthy age-matched and sex-matched volunteers.

The study protocol was in accordance with the Helsinki declaration of human rights and was approved by the local ethics committee of Ain Shams Faculty of Medicine. Written informed consent was obtained from each patient and control.

All patients were subjected to the following:

(1) Full assessment of history, with a focus on the frequency of sickle cell VOC within the last year.
(2) Thorough physical and neurological examination, including a detailed trigeminal nerve examination.
(3) Electrophysiological studies were carried out to assess the trigeminal nerve (for all patients and controls) by the Schwarzer Topas electromyography system (WI 53562, USA), using silver cup surface recording electrodes and a bipolar surface electrode for stimulation.

Trigeminal evoked potential
Using the standard technique described by Stohr et al. [8], the long-latency TEP response (cortical events occurring >10 ms after the onset of the stimulus) was evoked by electrical stimulation of the mental nerve at the lower lip. Stimulus intensity was set two to three times of the sensory threshold, with an intensity range of 5–15mA. Rectangular pulses of 200 µs duration were delivered at a repetition rate of 3 Hz. The recording electrodes were placed at C5¢ and C6¢ according to the (10-20 international system). The reference electrode was placed at Fz on the posterior aspect of the forehead near the hairline in the midline. The ground electrode was fixed to the zygomatic process on the face ipsilateral to the stimulus side. TEP responses included components of polarity (N, for negative upward deflection; P, for positive downward deflection); peak latency of N13, P19, and N30 as measured in milliseconds; and peak-to-peak amplitude of N13/P19 as measured in microvolt.

Sensory nerve conduction of the inferior alveolar nerve
Sensory nerve conduction of the IAN was assessed using the technique described by Jaaskelainen et al. [9]. The IAN was recorded orthodromically using surface electrodes. The active recording surface electrodes were placed beneath the zygomatic arch in front of the temporomandibular joint about 3 cm anterior to the
tragus. The reference electrode was placed on the skin overlying the zygomatic arch. The ground electrode was wrapped around the upper arm.

A bipolar surface-stimulating electrode with the cathode placed on the mental nerve at its exit from the MF was used. The position of the foramen was estimated by the location of the premolar and by palpation. Electrical stimuli (square-wave pulses with a duration of 0.2 ms) with an intensity three to five times the sensory threshold, ranging from 6 up to 15 mA, were applied. Sensory IAN onset latency, amplitude, and conduction velocity (CV) were measured in millisecond, microvolt, and m/s, respectively.

**Radiological assessment**

CT scans of the mandibles were obtained for SCA patients with trigeminal neuropathy and controls using the CT Pro-Speed VX device (Indiana, USA) according to Bar–Ziv and Salsaky [10]. The MF was identified as the entire opening on the lateral surface of the mandible at the terminus of the mental canal on axial and cross-sectional CT scans. The height and width of the MF were measured in millimeters. The MC was identified on CT scans as a narrow radiolucent region bordered by a radio-opaque line in the spongiosa of the mandibular body. The inner diameter of the MC was detected in the cross-sectional plane at the middle of its horizontal portion between first and second molar teeth.

**Statistical analysis**

IBM SPSS statistical software package (V. 19.0, 2010; IBM Corp., New York, USA) was used for data analysis. Data were expressed as mean ± SD for quantitative measures. Comparison between two independent groups of numerical parametric data was performed using Student’s t-test. A post-hoc test was carried out to compare between the means of the individual groups. Pearson correlation coefficient ($r$) was used to study the possible association between two variables. The probability of error was considered significant at 0.05 and highly significant at 0.001.

**Results**

This study included 50 SCA patients who were divided into two groups: group I included 30 patients (13 men and 17 women) and group II included 20 patients (nine men and 11 women) according to the absence or presence of clinical manifestations of trigeminal neuropathy, respectively.

The patients’ age ranged from 20 to 55 years, with a mean of $37.43 ± 11.05$ in group I, and from 23 to 56 years, with a mean of $36.8 ± 9.91$ in group II. Forty healthy individuals (16 men and 24 women), ranging in age from 20 to 57 years, with a mean of $36.6 ± 11.53$ years, served as controls. Group I, group II, and controls were age and sex matched ($P > 0.05$).

Sickle cell VOC was significantly more frequent within the last year in group II versus group I: range of two to eight times/year, with a mean of $5.25 ± 1.62$, versus range of one to six times/year, with a mean of $3.63 ± 1.47$, respectively ($P = 0.001$).

For the TEP test, there were highly significantly longer N13, 19, and 20 latencies and reduced N13-P19 amplitude in both group I and II in comparison with the controls ($P<0.001$), whereas only P19 latency was significantly longer in SCA patients with trigeminal neuropathy: group II (range $19.7–28.8$ ms, mean $24.36 ± 2.5$ ms) versus SCA patients without trigeminal neuropathy, group I (range $18.4–27.2$ ms, mean $22.21 ± 2.32$ ms) ($P<0.05$) (Table 1 and Fig. 1).

In group II, patients with SCA with trigeminal neuropathy had significantly longer IAN latency (with a mean of $2.90 ± 0.92$ ms), reduced amplitude (with a mean of $8.54 ± 3.78$ µV) ($P<0.05$), and highly significantly reduced CV of IAN (with a mean of $43.85 ± 9.02$ m/s) ($P<0.001$) than group I; SCA without trigeminal neuropathy (with a mean of IAN latency, amplitude, and CV: $2.34 ± 0.5$ ms, $11.3 ± 3.89$ µV, and $53.45 ± 5.63$ m/s, respectively). In addition, there was a significantly prolonged IAN latency, reduced amplitude ($P<0.05$), and highly significantly reduced CV of IAN ($P<0.001$) in group I versus controls (Table 2 and Fig. 2).

**Table 1 Parameters of trigeminal evoked potentials in groups I and II, and controls**

| TEP parameters | Group I ($n=30$) | Group II ($n=20$) | Controls($n=40$) |
|----------------|-----------------|-----------------|-----------------|
|                | Range           | Mean ± SD       | Range           | Mean ± SD       | Range           | Mean ± SD       |
| N13 latency (ms) | 12.3–16.8       | 14.38 ± 1.3     | 11.9–18.6       | 15.36 ± 1.9     | 11.5–13.9       | 12.77 ± 0.76    |
| P19 latency (ms) | 18.4–27.2       | 22.21 ± 2.32    | 19.7–28.8       | 24.36 ± 2.5     | 18.5–19.9       | 19.18 ± 0.44    |
| N30 latency (ms) | 27.6–36.8       | 33.35 ± 2.27    | 29.4–38.5       | 34.8 ± 2.73     | 29.1–31.3       | 29.99 ± 0.72    |
| N13-P19 amplitude (µv) | 1.01–3.37 | 1.87 ± 0.74     | 0.96–3.24       | 1.5 ± 0.69      | 1.86–3.68       | 3.02 ± 0.57     |

TEP, trigeminal evoked potential.
The dimensions of the MF and the MC, as assessed by CT, showed significantly narrower MF (reduced MF height and width) and reduced MC diameter in group II in comparison with the controls; the mean MF height, width, and MC diameter in mm were 2.8 ± 0.91, 2.67 ± 0.99, and 3.72 ± 1.49, respectively, in group II versus 4.02 ± 0.89, 3.53 ± 0.82, and 4.61 ± 1.17, respectively, in the controls (P<0.05) (Table 3).

In group II, patients’ age showed a statistically significant negative correlation with the CV of IAN (r = -0.452, P = 0.046), whereas it showed no significant correlation with either IAN latency, amplitude, or all TEP parameters (P > 0.05). There was no significant correlation between patients’ age in group I with any of the electrophysiological parameters of TEP and IAN (P > 0.05). Patients’ sex in both group I and II showed a statistically nonsignificant correlation with all parameters of TEP and IAN conduction studies (P > 0.05).

VOC in group II was correlated positively with all TEP waves’ latencies, N13, P19, and N30 (r = 0.58, P = 0.002, r = 0.55, P = 0.002 and r = 0.48, P = 0.007, respectively) and correlated negatively with IAN amplitude (r = -0.43, P = 0.02), whereas it showed a highly significant negative correlation with N13/ P19 amplitude (r = -0.67, P = 0.001) and IAN CV (r = -0.73, P = 0.001) and a highly positive correlation with IAN latency (r = 0.56, P = 0.001). For the TEP and IAN parameters in group I, there was no significant correlation with the frequency of VOC (P > 0.05).

MF height was correlated negatively with ipsilateral P19 latency (r = -0.484, P = 0.031) and ipsilateral IAN latency (r = -0.547, P = 0.013) and correlated positively with ipsilateral IAN amplitude (r = 0.450, P = 0.04) (Figs 3 and 4). In addition, MC diameter was correlated negatively with ipsilateral P19 latency (r = -0.578, P = 0.008).
Discussion

VOC in SCA can predispose to trigeminal neuropathy. Ischemic neuropathy in SCA may be a result of vaso occlusion in nutrient blood vessels of the trigeminal nerve [11]. Orofacial involvement in SCA patients is estimated to be present in 79% [12]. In this study, all patients in group II had unilateral trigeminal neuropathy; this was in agreement with other researchers who reported that trigeminal neuropathy symptoms are usually unilateral in patients with SCA [2,5,13].

We observed more frequent VOC in the last year in SCA patients with symptoms of trigeminal neuropathy than in those without trigeminal neuropathy. However, Okayucu et al. [6] showed that there was no significant difference between the frequency of VOC crisis in SCA patients with and without peripheral neuropathy (P = 0.3), but they did not study SCA with and without cranial neuropathy as in our study.

We found delayed P13, P19, and P20 latencies and reduced N13/P19 amplitude in both SCA with and without trigeminal neuropathy than controls. However, Sundaram et al. [14] reported TEP delayed latencies on the affected side in unilateral symptomatic trigeminal neuralgia in comparison with the unaffected side. Also, other studies reported increased P19 latency and reduced N13/ P19 amplitude on the involved side than the normal side in patients with idiopathic unilateral trigeminal neuralgia [15,16]. The delay in TEP latencies is expected as a result of loss of myelin and decreased CV through the region of damage in the trigeminal nerve lesion [17]. We reported that only P19 latency is delayed in SCA with trigeminal neuralgia than without trigeminal neuralgia. This was explained by many researchers [18–21], who reported that the most reliable and accurate TEP wave is P19 latency, as well as Otsuka et al. [22], who concluded that P19 was the most stable TEP wave response and easy to recognize.

The function of trigeminal afferent fibers can be assessed accurately with direct orthodromic recording of the sensory nerve action potentials (SNAP) of IAN [23]. SNAPs of the IAN are used as a diagnostic test for neuropathic trigeminal disorders [24]. In terms of IAN findings, our results were confirmed by Jaaskelainen [23] and Thygesen et al. [24], who reported that IAN latency is a valuable parameter in the assessment of mental neuropathy in SCA patients and it is the most sensitive tool for the diagnosis of unilateral IAN lesions as the latency difference between sides within a given patient is very small.

IAN amplitude and CV were significantly lower in both SCA with and without trigeminal neuralgia than controls, and were significantly lower in SCA patients with trigeminal neuralgia than those without trigeminal neuralgia. This could be attributed to the fact that the amplitude of SNAP is an indicator of the amount of axonal damage of IAN and a nerve conduction study for myelinated fibers is more sensitive to compressing than lacerating peripheral nerve lesions [19]. Compression of IAN resulting from mandibular lesions in SCA can damage the nerve and may result in its degeneration, either partially or completely. It may occur acutely or may evolve over time because of progressive irritation or compression [25].

CT scans are more accurate for the measurement of MF and MC diameters than conventional radiographs [26–28]. It is the most suitable tool for
the assessment of anatomical landmarks of mandibular structures, especially in SCA patients, as SCA causes radio imaging observable differences in the jaw structure, especially in the mandible [29]. The CT scan measurement of MF height, width, and MC diameter in our controls was in agreement with many studies that assessed MF and MC in normal healthy individuals using CT images [26,27,30,31].

In our study, reduced MF height, width, and MC diameter were observed in SCA patients with trigeminal neuralgia compared with healthy individuals. This can be attributed to the effect of SCA on MF and MC, where chronic inflammation, bone infarcts, or bone sclerosis may reduce MF and MC dimensions in patients with SCA. This was in agreement with Neves et al. [27], who attributed this to the fact that during generalized sickle cell crises, vaso-occlusive involvement of the mandible can occur, resulting in mandibular pain or mental neuropathy.

Our study found a negative correlation between patients’ age and only IAN CV. This is in agreement with Cruccu et al. [32], who reported the same correlation in patients with trigeminal neuralgia. However, Mendes et al. [33] found a nonsignificant correlation between patients’ age and IAN latencies, amplitudes, and CV in SCA patients. In our study, patients’ sex was not correlated significantly with all parameters of the TEP and IAN sensory nerve conduction study; this was in agreement with the result of Jaaskelainen et al. [9].

In SCA patients with trigeminal neuropathy in this study, there was a significant correlation between the frequency of VOC and all parameters of TEP and IAN conduction studies. This is in agreement with Ghassan et al. [34], who reported that cases of mental neuropathy in SCA patients were associated with increased frequency of VOC.

We can suggest from the negative correlation between P19 latency and either MF height or MC diameter that the main etiology of a trigeminal nerve lesion in SCA may be caused by compression within MF and MC, in addition to its involvement in the generalized neuropathic process. The mental nerve, the peripheral sensory branch of IAN of the trigeminal nerve, is commonly involved in SCA ischemic neuropathy. Mental neuropathy affection can be attributed to local anatomical factors as IAN is confined to the narrow MC. Also, it is exposed to injury because of mandibular bone infarction during the VOC in SCA patients [6]. In addition, the trigeminal nerve could be affected along its central pathway as a result of lesions in its nuclei or at the somatosensory cortex in SCA.

The diagnosis of motor and sensory dysfunction in the trigeminal complex by clinical assessment may be difficult. Hence, motor dysfunction is only identifiable in severe lesions. In addition, there is no objective means for the assessment of sensation in the face; in addition, jaw reflex is not usually accompanied by a visible movement of the chin. Therefore, electrophysiological study, which is an objective, noninvasive, and useful technique used to study trigeminal functions, remains a convenient diagnostic and research tool to document clinically evident lesions or uncover subclinical abnormalities [7]. To the best of our knowledge, very few studies have assessed trigeminal neuropathic lesions in SCA using nerve conduction studies of IAN and TEP for further larger studies.

In conclusion, trigeminal neuropathy is present in a considerable percentage of patients with SCA, either subclinical or symptomatic. TEP and IAN sensory action potentials are the most reliable tests to assess trigeminal nerve nuclei, somatosensory cortex, and its sensory afferents, respectively. Moreover, MF and MC dimensions as measured by CT scan are reliable parameters to evaluate the anatomical factor involved in trigeminal neuropathy. Thus, electrophysiological study of the trigeminal nerve is recommended as a routine examination to diagnose early trigeminal neuropathy in SCA patients. This will increase the identification of this complication and ultimately provide new insights into its prevention and treatment.

Acknowledgements
Conflicts of interest

There are no conflicts of interest.

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Trigeminal nerve assessment in SCA Gadallah et al. 79

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