Headache and Sleep-Related Breathing Disorders Among Patients With Sclerosteosis and Disease Carriers: The First Family in Italy

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Short report

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Abstract

Background

Headache and sleep-related breathing disorders among patients with sclerosteosis and disease carriers has been little studied. We investigated the neurological and neuroimaging features of patients and gene carriers of a large Italian family with sclerosteosis.

Main body

In this Italian family with sclerosteosis, genetic tests detected the homozygous mutation p.Gln24X (c.70C>T) of the SOST gene in the proband, and a heterozygous mutation between 9 siblings. Severe hyperostosis of the skull caused chronic headache secondary to intracranial hypertension due to venous hypertension and obstructive sleep apnea syndrome in adult homozygotes. There was transosseous intracranial-extracranial occipital venous drainage which indicated a compensatory mechanism for intracranial venous hypertension, one of the causative factors of increased CSF pressure in sclerosteosis. While mild hyperostosis of the skull was associated with headache and snoring in heterozygotes.

Conclusions

Headache and sleep-related breathing disorders are the most common clinical manifestations among patients with sclerosteosis and disease carriers. Cerebral venous hypertension leading to intracranial hypertension and facial deformities are the causative factors of headache and sleep-related breathing disorders. These data suggest that venous stenting to accommodate cerebral venous drainage could be useful in the treatment of intracranial hypertension, and correction of facial deformities to relieve obstructive sleep apnea may play a role in the treatment of patients with sclerosteosis. The data highlight that it is reasonable to extend neurological evaluation and radiological study to gene carriers.

Background

Sclerosteosis is a rare cause of hyperostosis of the skull, manifested in particular by facial dysmorphism, enlargement of the jaw and frontal bossing [1]. It is transmitted as an autosomal recessive trait, and is caused by the mutation of the loss of function of the SOST gene in the chromosome 17q12-q21 [2]. Due to the limited number of affected individuals by sclerosteosis described mainly from South Africa, the neurological features of patients have been little studied and the presence of clinical manifestations of the disease among carriers remains still uncertain [3]. We report the clinical features and neuroimaging results in patients and gene carriers of an Italian family with sclerosteosis.

Methods

Participants
The Calabrian family of Southern Italy included living subjects of 3 different generations. All participants made a careful general and neurological evaluation. The neuroimaging study included computed tomography (CT) of the head, brain magnetic resonance imaging (MRI), and cerebral MRI venography. CSF pressure was assessed through 1-hour CSF monitoring by spinal needle, as described elsewhere [4]. Polysomnography was used to diagnose obstructive sleep apnea syndrome (OSAS).

**DNA analysis**

DNA was tested for SOST gene mutations in all participants. Genomic DNA was extracted from peripheral blood using standard methods. The primers alongside all 2 exons and the intron-exon boundaries of SOST were designed using the Primer 3 website (http://bioinfo.ut.ee/primer3-0.4.0/). The purified PCR products were analyzed on 3500 Genetic Analyzer.

**Results**

The family consisted of 13 subjects, 9 males and 4 females. Pedigree analysis revealed autosomal recessive inheritance. Molecular screening of SOST gene detected a nonsense homozygous mutation p.Gln24X (c.70C>T) in the proband, and a heterozygous mutation in 9 siblings (Figure 1).

**Patients**

Clinical characteristics of patients and disease carriers are summarized in Table 1. The proband, a middle age male, complained of chronic refractory headaches associated with transient visual disturbances, tinnitus, dizziness, snoring and daytime sleepiness from the age of 20. At the age of 5 he suffered from bilateral facial nerve paralysis. Neurosensory hearing loss and left eye blindness occurred a few years later. The clinical evaluation indicated a height of 1.70 m and a weight of 97.1 kg with a body mass index of 33.6 kg/m$^2$. It also showed bilateral exophthalmos, marked enlargement of the mandible and a frontal bossing. Routine serum analysis, electrolytes, hormonal evaluation were all normal.

Another middle age male had facial deformities and complained of similar disorders. He reported unilateral hearing loss and bilateral paralysis of the facial nerve since childhood. From the age of 20 he complained of severe chronic headache and night snoring.

CT images of the skull obtained with high-spatial-resolution bone algorithm revealed thickening of the calvarium, skull base and mandible, and narrowing of the optic canals, internal auditory meatus, facial nerve canals, and vascular foramina. The mastoid cells were not aerated (Figure 2 C). Hyperostosis of the orbital walls reduced intraorbital volume and led to a slight proptosis. Brain MRI displayed depletion of subarachnoid spaces, empty sella turcica, flattening of posterior aspect of the globes, distension of the optic nerve sheaths, and cerebellar tonsillar descent below the level of the foramen magnum. Cerebral MRI venography showed a global engorgement of the suboccipital plexus with evidence of superficial temporal and retromandibular temporal veins, absence of right transverse sinus and left transverse sinus flow gap, suggesting an intracranial venous hypertension; 3D Volume Rendering of MR venography
exhibited the presence of transosseous occipital venous collateral indicating an intracranial-extracranial cerebral venous drainage. (Figure 2 B and D).

One-hour lumbar CSF pressure monitoring through spinal needle revealed an elevated CSF pressure (opening pressure 370 mmH$_2$O, mean pressure 264 mmH$_2$O) indicating an intracranial hypertension (IH). At the end of the short pressure monitoring a CSF subtraction of about 20 ml was carried out which produced a normalization of the closing pressure. Polysomnographic testing confirmed an obstructive pattern of sleep apnea (apnea-hypopnea index of 15). The patient began therapy with acetazolamide 1000 mg/day, and ventilatory therapy with the Continuous Positive Airway Pressure Device (CPAP), which produced an improvement of symptoms.

**Disease carriers**

Facial alterations such as enlarged jaw and frontal bossing were present in 6 of 9 disease carriers, and were more pronounced in adults. In addition, two had a radial deviation of the phalanges of the last two fingers. Seven individuals complained of severe episodic or chronic headaches. Five out of nine also had night snoring from early childhood. Headache and snoring had become more severe in adulthood.

CT scans of the skull in the bone window of 2 symptomatic heterozygotes showed a slight thickening of the calvarium mainly in the occipital region with a prominence of the external occipital protuberance in the adult individual, while the child had normal CT results (Figure 3 B and C).

Table 1. Neurologic features of patients with sclerosteosis and disease carriers.
| Subjects | Genetic status | Age at Onset and first clinical manifestation | Clinical features | Progression | Findings |
|----------|----------------|-----------------------------------------------|-------------------|-------------|----------|
| F/ 66    | Heterozygous   | 20 years                                     | Enlarged mandible, radial deviation of phalanges, chronic headache, snoring | stable       | Snoring  |
| M/ 67    | Heterozygous   | 30 years                                     | Enlarged mandible, frontal bossing, episodic headache, snoring | stable       | Snoring  |
| M/ 43    | Refused genetic test | 4 years | Bilateral exophthalmos, enlarged mandible, frontal bossing, unilateral hearing loss, bilateral facial nerve palsy, chronic headache with postural variations, tinnitus, transient visual disturbances, vertigo, snoring | Multiple cranial nerve palsy onset in the first 2 decades, chronic headache and snoring since the III decade, stable since the IV decade | Snoring  |
| M/ 40    | Heterozygous   | 30 years                                     | Enlarged mandible, frontal bossing, chronic headache | stable       | Unknown  |
| F/ 41    | Heterozygous   | NA                                           | Enlarged mandible, radial deviation of phalanges | stable       | Unknown  |
| M/ 39    | Homozygous     | 5 years                                       | Bilateral exophthalmos, enlarged mandible, frontal bossing, unilateral blindness, unilateral sensorineural hearing loss, bilateral facial nerve palsy, chronic headache with postural variations, tinnitus, transient visual disturbances, vertigo, snoring | Multiple cranial nerve palsy onset in the first 2 decades, chronic headache and snoring progressive worsening up to time of observation, stable since the age of 37 | Intracranial hypertension, OSAS, cerebral venous hypertension |
| M/ 28    | Heterozygous   | 12 years                                     | Enlarged mandible, chronic headache, snoring | Worsening of headache | Snoring  |
| F/ 31    | Wild-type      | NA                                           | Normal appearance | NA          | NA       |
|    |    |    | of the skull |    |    |
|----|----|----|-------------|----|----|
| M/ 5 | Wild-type | NA | Normal appearance of the skull | NA | NA |
| M/ 15 | Heterozygous | 8 years | Episodic headache | stable | Unknown |
| M/ 6 | Heterozygous | 5 years | Enlarged mandible, episodic headache, snoring | Worsening of snoring | Snoring |
| F/ 4 months | Heterozygous | NA | Normal appearance of the skull | NA | NA |
| M/ 5 | Heterozygous | 5 years | Enlarged mandible, episodic headache, snoring | Worsening of snoring | Snoring |

NA: not applicable

**Discussion**

Headache and sleep-related breathing disorders were the most common clinical manifestations among patients with sclerosteosis and disease carriers. Skull hyperostosis was the cause of intracranial hypertension (IH) and of facial deformities which in turn caused headache and sleep-related breathing disorders in patients and carriers of sclerosteosis. These data suggest that venous stenting to accommodate venous outflow, and correction of facial deformities to relieve obstructive sleep apnea may play a role in the treatment of headache secondary to IH in patients with sclerosteosis.

Nocturnal headache and chronic morning headache aggravated by postural changes and Valsalva-like maneuvers were common among patients and disease carriers of this Italian family with sclerosteosis. The onset of nocturnal attacks of pulsating pain and persistent headache in the morning, exacerbated by postural changes and coughing, can be explained by the presence of abnormal CSF pulsations occurring during sleep and the posture changes in patients with intracranial hypertension [5]. One possible basis for increased intracranial pressure in patients with sclerosteosis is a reduction of the intracranial diameter due to overgrowth of the calvarium and of skull base [6]. However, IH cannot be entirely attributed to reduction of the intracranial diameter. A possible contributory factor to IH may be the presence of intracranial venous hypertension due to venous outflow disturbances caused by vascular foramen narrowing. Consistent with this hypothesis, we detected transosseous intracranial extracranial venous drainage which indicated a compensatory mechanism for intracranial venous hypertension which in turn resulted in increased intracranial pressure in the patient with sclerosteosis. This fact suggests that improved cerebral venous drainage using venous stenting [7] could be useful in the treatment of intracranial hypertension in patients with sclerosteosis.
The presence of sleep-related breathing disorders has never been reported in patients with sclerosteosis. To explain this finding, we hypothesize that excessive growth of skull bones alters the structure of the upper airway causing obstructive sleep apnea in patients with sclerosteosis. The role of craniomandibular anatomical abnormalities in the development of obstructive sleep apnea is well recognized [8]. Increased inspiratory effort against the closed airways during obstructive sleep apnea causes hypercapnia and hypoxia, which in turn induce changes in brain perfusion pressure and increased intracranial pressure [9]. In accordance with this pathogenetic mechanism, the association between breath-related sleep disorders and chronic headache has been observed in OSAS patients [10, 11]. Similar mechanism could be the cause of nocturnal snoring and chronic headache in heterozygotes with mild skull hyperostosis. Overall, these data suggest that correction of facial deformities to relieve airway obstruction could play a role in the treatment of sleep-related breathing disorders in patients with sclerosteosis.

Although it is recognized [3] that heterozygotes have no manifestations of disease 6 gene carriers had headaches and mild cranial hyperostosis in this family. In fact, characteristic facial dysmorphic aspects were detected in heterozygotes, with more marked alterations in adult individuals. In addition, we also found the presence of mild abnormalities of the limbs in adult disease carriers. Consistent with these results, a previous study [12] reported a significant reduction in sclerostin activity in heterozygotes, which caused an increase in bone density compared to healthy controls. The latter data indicate a gene-dose effect of the SOST mutation on circulating sclerostin. The presence of disease manifestations in heterozygous individuals in this Italian family provides evidence that sclerostin, which has been reported to be transmitted as an autosomal recessive trait [2], may instead be a co-dominant autosomal condition. Overall, the results suggest that it is reasonable to extend neurological evaluation and radiological study to disease carriers.

In this Italian family we found a homozygous and heterozygous mutation without sense p.Gln24X (c.70C>T) in exon 1 of the SOST gene. This mutation without sense which, according to the predictions of Mutation TasterServer (http://www.mutationtaster.org), exerts a deleterious effect and leads to the premature cessation of the protein. The same mutation has been previously reported in an African family [2]. The identification of the same mutation in this family from southern Italy, considering the geographical proximity that facilitates migration from that continent to southern Italy, suggests the potential founding effect.

**Conclusion**

Severe hyperostosis of the skull manifests with chronic headache secondary to intracranial hypertension due to intracranial venous hypertension and OSAS in affected adults by sclerosteosis. Mild hyperostosis of the skull manifests with headache and snoring in gene carriers. Our study expands the clinical spectrum of hyperostosis of the skull due to sclerosteosis.

**Abbreviations**
Declarations

Acknowledgements: not applicable

Contributors: Study concept and design: FB; LR, FB, collected, analyzed and interpreted data; LR, MG, CB, GA, GD FB drafted the manuscript; FB revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Consent for publication: Written informed consent was obtained from all adult participants and parents of the children included in the study.

Competing interests: The authors declared they have no competing interests.

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**Figures**

**Figure 1**

Simplified pedigree of the family and genetic findings. The family consisted in 3 generations, which included subjects in homozygous state and heterozygous state (A). DNA sequence of SOST gene of the proband compared to a normal control displayed c.70C>T nonsense mutation results in a stop codon (p.Gln24X) (B).
Figure 2

MR venography of the intracranial venous outflow in a patient with sclerosteosis. 3D Reconstruction of the scalp with evidence of transosseous occipital venous collateral indicating an intracranial-extracranial venous drainage (A and B). Cranial CT image showing a transosseous occipital venous collateral (arrows) (C). 3D Volume Rendering of cerebral MR venography displayed a global engorgement of the suboccipital plexus and disturbances of intracranial venous outflow indicating venous hypertension (D).
Figure 3

Head CT scan of patient with sclerosteosis and of two symptomatic heterozygous carriers (father and son). Head CT study: (A) severe hyperostosis of the skull in a patient with sclerosteosis; (B) mild thickening of the calvarium mainly in occipital region with exuberant occipital prominence in heterozygous father; (C) normal CT findings of heterozygous son.