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## Case report

# Neurofibromatosis type 2 (NF 2) or schwannomatosis? – Case report study and diagnostic criteria

Maciej Radek<sup>a</sup>, Bartłomiej Tomasiak<sup>a</sup>, Maciej Wojdyn<sup>a</sup>,  
Dorota Snopkowska-Wiaderna<sup>b</sup>, Maciej Błaszczyk<sup>a,\*</sup>, Andrzej Radek<sup>a</sup>

<sup>a</sup>Department of Neurosurgery and Peripheral Nerve Surgery, Medical University of Łódź, University Hospital WAM-CSW, Łódź, Poland

<sup>b</sup>Department of Clinical Pathomorphology and Cytopathology, Medical University of Łódź, University Hospital WAM-CSW, Łódź, Poland

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## ABSTRACT

**Introduction:** Neurofibromatosis type 2 (NF2) and schwannomatosis are entities that may, due to the similarity of clinical symptoms, cause diagnostic difficulties. Incidence rate of both diseases is similar and estimated between 1:25,000 and 1:40,000. The genes associated with the development of the aforementioned disorders are located on chromosome 22 and lay in proximity. Schwannomatosis is characterized by an incomplete penetrance and the risk of its transmission to the offspring is significantly lower than in the case of NF 2. Schwannomatosis clinical characteristic is similar to the NF2, however vestibular schwannomas are not present. Therefore the imaging studies evaluated by an experienced radiologist play a key role in the diagnostic process.

**Case report:** Forty two-year-old female hospitalized three times because of the tumors of the spinal canal was admitted to the Department of Neurosurgery and Peripheral Nerve Surgery in 2008 because of the cervical pain syndrome with concomitant headache. She was diagnosed with a schwannomatosis, recently distinguished, the third form of neurofibromatosis. MRI imaging revealed craniocervical junction tumor. Suboccipital craniectomy with concomitant C1–C2 laminectomy was done in order to remove the lesion. After the surgery the patient did not present any deficits in neurological examination and was discharged from hospital in good general condition.

**Conclusions:** The patient was diagnosed with schwannomatosis, recently established neurofibromatosis entity which may resemble NF2 clinically. In patients after the age of 30, in whom we observe multiple schwannomas without the concomitant hearing impairment, the diagnosis of schwannomatosis is very likely.

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\* Corresponding author at: University Hospital WAM-CSW, Department of Neurosurgery and Peripheral Nerve Surgery, Żeromskiego 113, 91-647 Łódź, Poland. Tel.: +48 42 639 35 51.

E-mail address: [maciej.blaszczyk88@gmail.com](mailto:maciej.blaszczyk88@gmail.com) (M. Błaszczyk).

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## 1. Introduction

Schwannomas are one of the most common peripheral nerve sheath neoplasms. These typically benign tumors occur spontaneously in a vast majority of cases, yet may also arise in patients with type 2 neurofibromatosis (NF2) or another entity called schwannomatosis.

NF2 is a relatively rare, dominantly inherited syndrome with the incidence rate estimated to be between 1/25,000 and 1/40,000 [1,2]. The identification of the NF2 gene, which is localized on chromosome 22 (22q12) have led us to a better understanding of this disease. NF2 is a tumor suppressor gene and its product, merlin, shows similarity to certain cytoskeletal proteins. Merlin functions are still not fully described, although it can bind to actin or a transmembrane CD44 receptor, which is involved in cell interaction with extracellular matrix [3]. There are multiple diagnostic criteria for NF2 e.g. the Manchester Criteria, the National Institutes of Health Criteria, and the Children's Tumor Foundation Criteria [2,4-6]. However, all of them indicate that bilateral vestibular schwannomas are the hallmark of this condition. Worth mentioning, the presence of vestibular schwannoma excludes the diagnosis of schwannomatosis.

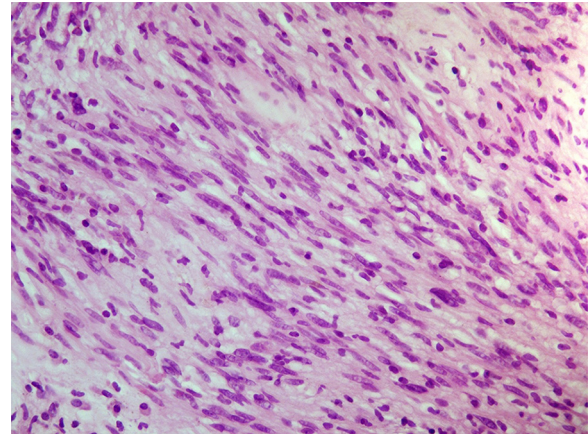
Schwannomatosis is a relatively new condition which has been established over the last few decades. It can be diagnosed when multiple schwannomas, without cranial nerve VIII involvement, occur. Thus, experienced radiologist plays a crucial role in diagnosing schwannomatosis and differentiating it from NF2. Little is known about the genetic background of this condition. A family history is present only in 15-25% of cases [7]. Although somatic mutations of NF2 in the tumor tissue are quite common in schwannomatosis, NF2 role in the pathogenesis of this condition has been ruled out by several authors [8,9]. However other studies revealed germline mosaicism of the SMARCB1 gene (also called INI-1), which is localized on chromosome 22 near the NF2 gene [10,11]. Due to the strong resemblance to the NF2 it is hard to estimate the prevalence of schwannomatosis but probably it is similar [12]. We present an interesting case report, showing that the differential diagnosis is not easy and could be a major clinical challenge.

## 2. Case report

A 42-year-old patient was admitted to the Department of Neurosurgery and Peripheral Nerve Surgery in 2008 because of craniocervical junction tumor. She had the history of three hospitalizations due to the tumors within the spinal canal. The family history was negative, patient denied the occurrence of similar symptoms in relatives. The first symptoms, which were the pain in the thoracic spine followed by spastic paresis of the lower extremities, occurred in 1994 (the patient was 28-year-old) after the childbirth. During the neurological consultation the initial diagnosis of multiple sclerosis (MS) was made. However subsequent thoracic MRI indicated the tumor at the Th12/L1 level. The laminectomy was performed and during this procedure the intrameningeal and extraspinal tumor was resected. Histopathological examination has

shown that it was a schwannoma (Fig. 1). After the operation the patient did not present any deficits in neurological examination.

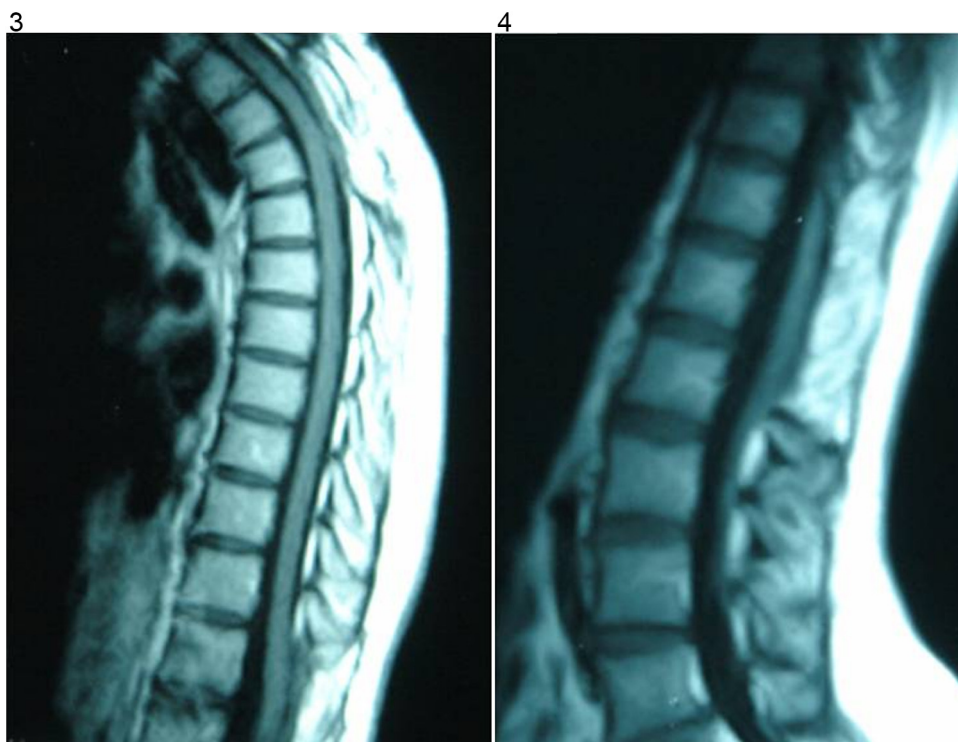
A year later a control thoracic and lumbar MRI was performed. No changes in the operated region were found although the study revealed a new, asymptomatic tumor at the Th12-L1 level (Fig. 2). We decided to perform Th12-L1 laminectomy, during which another schwannoma was resected. A mild dysesthesia on the outer side of the thigh on the right side was found during the post-surgery neurological examination. The follow-up MRI examination in 1996 did not reveal any changes (Figs. 3 and 4).



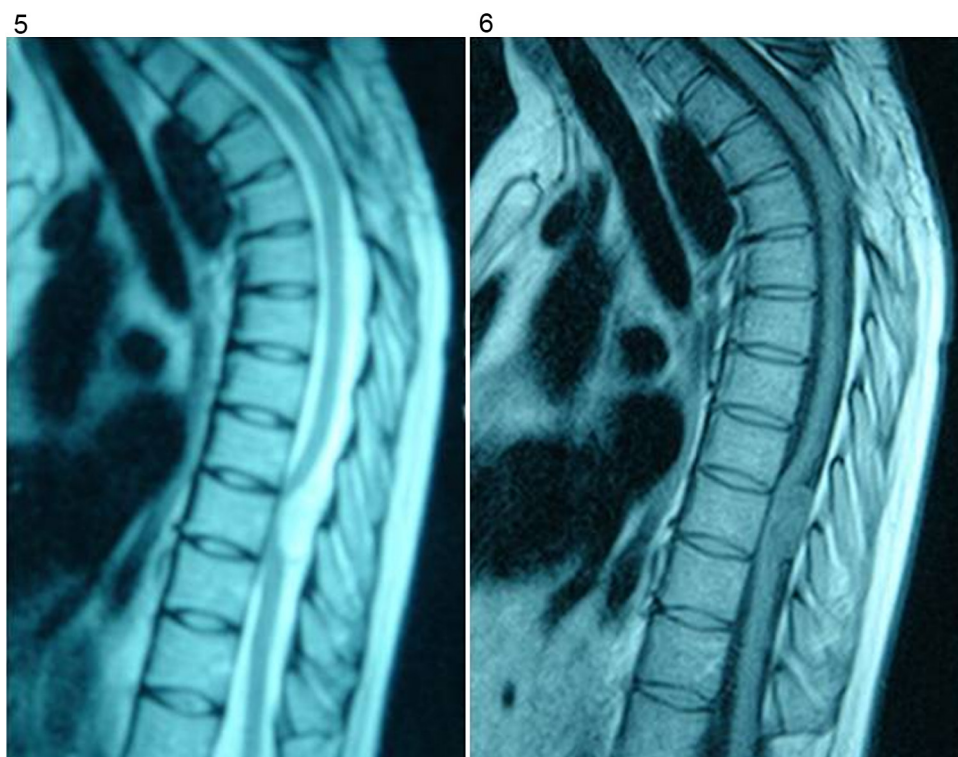
**Fig. 1 – Fascicular arrangement of elongated uniform cells with small pleomorphism (H + E) (400×).**



**Fig. 2 – Thoracic and lumbar spine MRI shows hyperintense lesion at Th12-L1 level (checkup – 1995).**



**Figs. 3 and 4 – Thoracic and lumbar spine MRI shows no pathologic changes (checkup – 1996).**



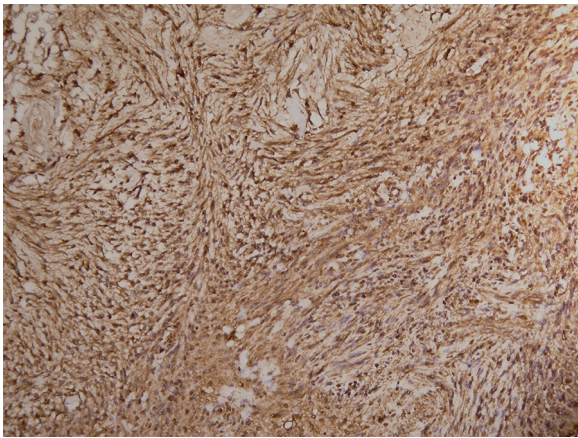
**Figs. 5 and 6 – Thoracic and lumbar spine MRI shows hyperintense lesion at Th8-Th9 level (imaging study 2006).**

The patient presented no symptoms until 2006 when she was admitted to our Department with thoracic pain syndrome and paraparesis. MRI examination found a Th8-Th9 tumor and concomitant lesions at Th10-Th11 and Th11-Th12 levels.

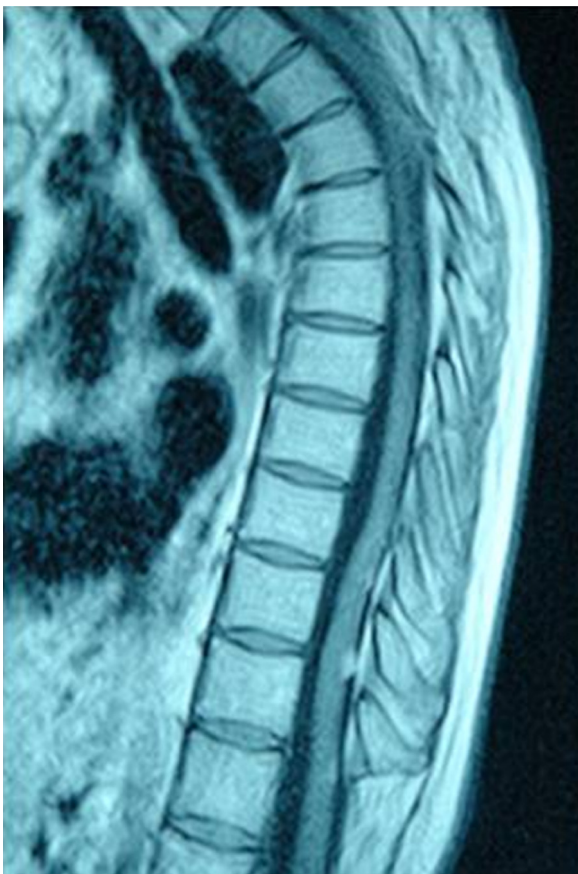
There was no local recurrence at the site of previous surgery (Figs. 5 and 6). In smaller tumors we decide to introduce watchful waiting strategy because they did not compress the spinal cord. Thus Th8-Th9 hemilaminectomy was performed.

During this procedure the intramenigeal and extraspinal tumor was resected. Further histopathological examination confirmed that it was a schwannoma. The immunohistochemical reaction for S-100 was positive (Fig. 7). After the surgery the patient did not present any deficits in neurological examination. The follow-up MRI examination in 2007 did not reveal any changes (Fig. 8).

In 2008 the patient was admitted again to our Department. She presented cervical pain syndrome with concomitant



**Fig. 7 – Positive immunohistochemistry for S100 protein (200×).**



**Fig. 8 – Thoracic and lumbar spine MRI shows no progression of pathologic changes (checkup – 2007).**

headache without deficits in neurological examination. MRI examination revealed craniocervical junction tumor (Figs. 9–12). We decided to perform C1-C2 laminectomy and left side suboccipital craniectomy. The tumor was completely resected during this procedure. After the surgery the patient did not present any deficits in neurological examination. Histopathological examination once again showed that the tumor was a schwannoma.

In 2009 another follow-up MRI was done and did not find any pathological lesions (Figs. 13 and 14). The patient is under the care of our clinic to the present day.

### 3. Discussion

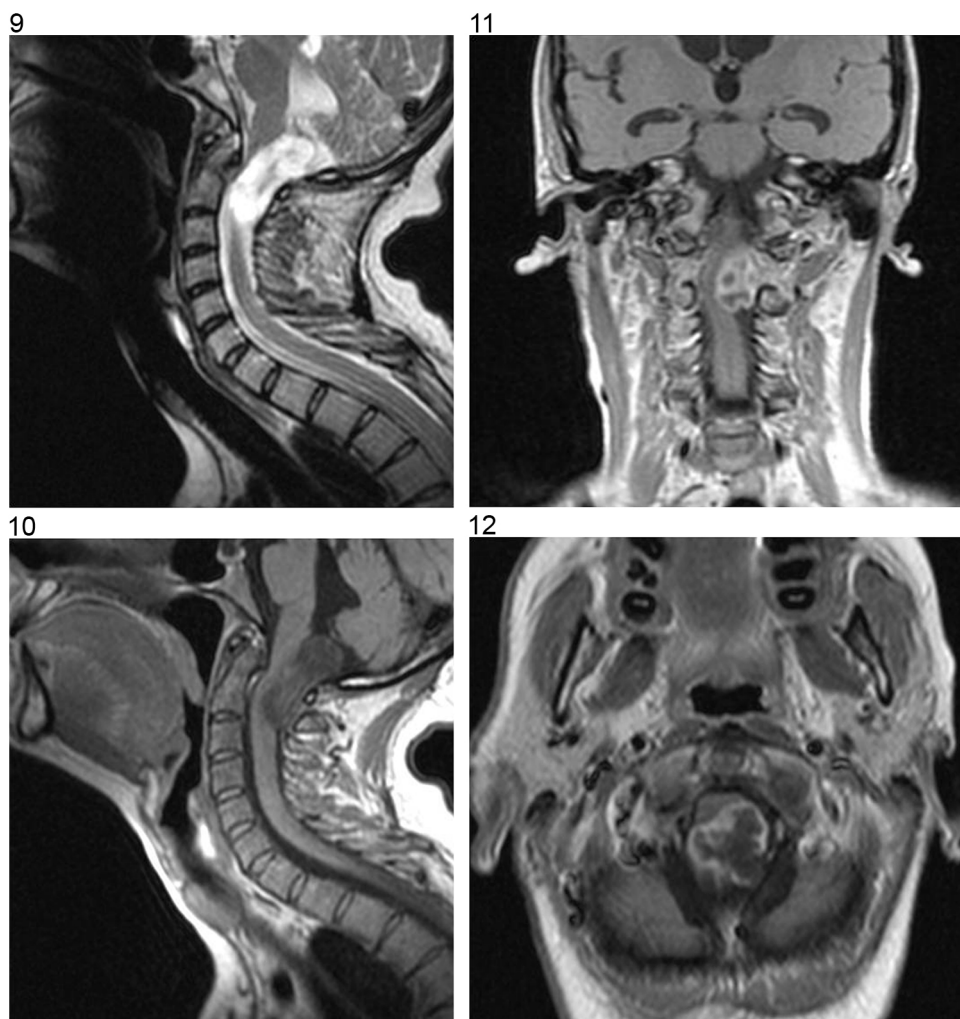
In the reported case we presented the patient with numerous, slow-growing central nervous system tumors. Histopathological examination for each lesion revealed schwannoma etiology therefore one can assumed that the patient suffered from NF2. However the tumors of the cranial nerve VIII did not appear in our patient. The age of the patient is not helpful in terms of final diagnosis, because first symptoms of both disorders may develop in the late twenties. Taking into consideration abovementioned description a differential diagnosis between NF2 and schwannomatosis should be carried out. It should be kept in mind that in 95% of NF2 cases the first symptom of a disease is hearing impairment caused by bilateral vestibular schwannomas [13]. During the last few decades' first reports describing patients who developed multiple schwannomas not related to NF1 or NF2 appeared in the literature. First mentions of such cases may be found in the studies from the eighties and [14,15]. Since then, the term “schwannomatosis” started to exist as a distinct neurofibromatosis entity [16].

Some researchers considered that schwannomatosis is an „incomplete” form or a subcategory of NF2 [17]. According to others, it is a separate entity – it has been proven that genetic background of schwannomatosis differs from that of the NF2 [9]. In most cases of schwannomatosis the tumors occurring in this entity have no distinctive morphologic features in comparison to sporadic schwannomas. The only discrete difference is the mosaic expression of BAF47 (INI-1), i.e. the patchy nuclear immunohistochemical reaction for this protein in schwannomatosis contrary to uniform positivity in sporadic schwannomas. In our case this examination was inconclusive [18].

Since then, new diagnostic criteria, which included schwannomatosis biology, have been introduced [7]. They are divided into molecular and clinical part which are presented below.

#### 3.1. Molecular diagnosis

1. Two or more schwannomas or meningiomas and genetic studies of at least two tumors showing loss of heterozygosity at chromosome 22 and NF2 mutations. The presence of a common SMARCB1 mutation defines SMARCB1-associated schwannomatosis.
2. One schwannoma or meningioma and a germline pathogenic SMARCB1 mutation.



**Figs. 9–12 – Cervical spine MRI shows hyperintense lesion at craniocervical junction level (imaging study 2008)**

### 3.2. Clinical diagnosis

1. Two or more non-intradermal schwannomas (at least one with pathological confirmation) and the absence of vestibular schwannoma on thin-sliced MRI.
2. One schwannoma or meningioma and affected first-degree relative.
3. Possible diagnosis when two or more non-intradermal schwannomas (without pathological confirmation) and chronic pain associated with tumors exist.

According to abovementioned criteria, the exclusion criteria are as follows: germline pathogenic *NF2* mutation, fulfilled criteria for *NF2*, first-degree relative with *NF2* and schwannomas in radiation field only.

In the presented case subsequent lesions had similar histogenesis which indicates the genetic background. That might suggest *NF2* although vestibular schwannomas were not present.

When *NF2* is suspected the physician should keep in mind the possibility of schwannomatosis. The clinical course of both of the diseases might be similar and confusing [19]. Helpful

features to distinguish cases of schwannomatosis from cases of *NF2* include the absence of ocular pathology, ependymomas and vestibular schwannomas by the age of 30.

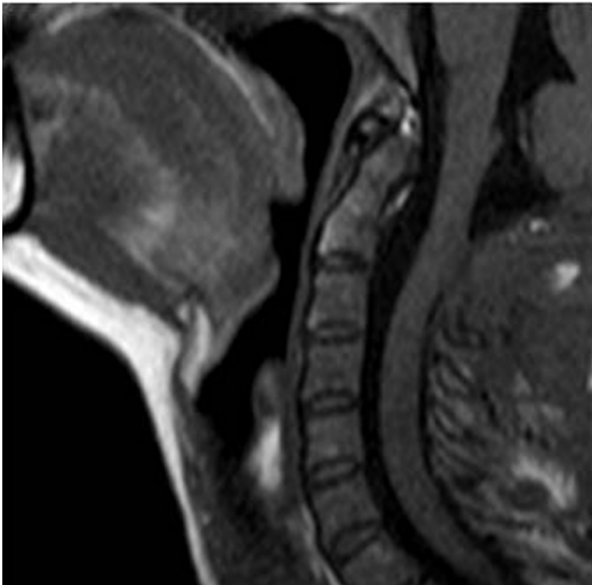
Schwannomatosis is a rare disorder which might cause diagnostic difficulties due to its similarity to *NF2*. We believe that abovementioned case report is a great example of such difficulties because the first lesions appeared in the late third decade of life, had similar histogenesis while family history was negative. The diagnosis of schwannomatosis was stated after the series of MRI's which did not reveal vestibular schwannomas. By this example we also want to emphasize that in this group of disease tumors can occur in every part of human body. When the tumor causes any symptoms it is an indication for surgery but in case of small, asymptomatic lesions we can decide to control them regularly by MRI and so has been done in the reported case.

Patients with schwannomatosis constitute only a small subgroup of patients with schwannomas. According to different studies the proportion varies from 3 to 5% [18]. The vast majority of patients with schwannomatosis is middle-aged and usually undergo many operations during their adult life and therefore can be described as a “high-risk” group [12].

13



14



**Figs. 13 and 14 – Cervical spine MRI shows no pathologic changes (checkup – 2009).**

Genetic tests might improve the diagnostic process in those patients but the results do not affect the decisions taken by the surgeon because the most crucial issue is thorough diagnostic imaging.

#### 4. Conclusions

1. In case of multiple schwannomas with concomitant absence of vestibular schwannomas and hearing impairment the diagnosis of schwannomatosis should be taken into consideration.
2. In doubtful cases neuroimaging (MRI) and audiological testing are helpful to distinguish schwannomatosis from NF2.

3. Despite presented similarities NF-2 and schwannomatosis are two distinct entities both genetically and clinically.

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#### Conflict of interest

None declared.

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#### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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