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Case Report

Misdiagnosis is a Notable Cause of a Patient's Lifetime Agony

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Abstract

Background: Clinical and radiological misconceptions lead towards clinical fallacy. Clinical fallacy is a major part of misconception and misdiagnosis and can easily occur leading to ineffective therapy and long-term suffering for patients.

Case Report: A 38-year-old Austrian female sought my opinion, after she spent almost 3 decades seeking convincing diagnosis for her lifetime agony. She has been a client of different medical disciplines in Austria since she was 13-year-old. Recently, Ehlers-Danlos syndrome-hypermobility type (EDS-ht) has been recognized. For more than 2 decades, she complained of unpleasant symptoms which include: blurring of vision, cervical pain, lack of concentration, and syncope. Psychosomatic disorder was the only diagnosis made through various medical disciplines. Long lists of unnecessary antipsychotics have been prescribed since her early life. The author started a process of comprehensive clinical and radiological documentation.

Results: Clinical examination showed, normal craniofacial contour with no dysmorphic features. Musculo-skeletal examination revealed ligamentous hyper laxity corresponds to 6 out of nine in accordance with Beighton scale. No evident skin stigmata, and no elasticity of the skin were noted. Lateral skull radiograph revealed the presence of ossified/calcified interclinoid ligament. Contrast-enhanced computed tomography angiography of the cervical and cerebral arteries showed the followings; bilateral kinking of the right and left internal carotid arteries. Interestingly, sharp angle of more than 90°more marked of the carotid arteries, compatible with grade I dolichoarteriopathies (DICAs).

Conclusion: Precise clinical and radiological phenotypic interpretations are the first step towards reaching etiology understanding. Medical malpractice is a notable cause of the patient´s persistent agony. Lateral skull radiograph showed the presence of ossified/calcified interclinoid ligament of the sella-turcica associated with hyperostosis of the skull base. The significance of diagnosing the ossified interclinoid ligament and hyperostosis of the skull base in that it might affect the surrounding neurovascular structures. This ossified bridge might influence the blood flow in the internal carotid artery or cause dysfunction of the muscles of the eyes owing to possible compression of the oculomotor nerve. Angiographic studies confirmed bilateral acute kinking of the internal carotid arteries.

Keywords: *Ehlers-Danlos Syndrome (Hypermobile Type); Musculoskeletal Agony; Tomographic Studies; Dolichoarteriopathy*

Introduction

Ehlers-Danlos syndrome/hypermobility type (EDS/ht), encompassing a broad spectrum of phenotypic manifestations and has been considered the most common type of EDS. But nevertheless, the least diagnosed, heritable connective tissue disorder [1]. Three ba-

sic pathogenetic mechanisms for EDS; first, deficient collagen-processing enzymes. Second, dominant-negative effects of mutant collagen α-chains, and third the haploinsufficiency mechanism [2]. Despite the noticeable achievements in molecular genetics, the recognition of the genetic etiology of EDS-ht still of the genetic cause(s) of hEDS have submitted undetermined results [3]. The Beighton scoring system, encompasses the most reliable evaluation for patients with generalized joint hypermobility [4]. Coiling/kinking/elongation of the internal carotid artery (ICA) is not a common imaging manifestation [5]. Dolichoarteriopathies of the internal carotid artery (DICAs), which extend to include the external carotid artery, can be present in three forms, tortuous, coiling and kinking. Kinking is the most common phenotypic abnormality. Kinking of the (ICA) manifests itself as a sharp angulation of the first portion of the internal carotid artery [6]. Metz., *et al*. divided kinking into three types/grades. Grade I abnormality signifies an acute angle of 90° - 60° between the two segments forming the kink-phenotype, grade II indicates an angle of 60° - 30° and grade III indicates an angle less than 30° [7]. No previous studies discussed the connection between Ehlers-Danlos syndrome/hypermobility type (EDS/ht) and DICAs. Though, studies focused on DICAs as a solitary phenotype and mostly as familial type displayed homozygosity for markers located at chromosome 20q13 [8].

Case Presentation

A 38-year-old Austrian woman came to my consultation seeking advice and opinion regarding her long-term musculo-skeletal agony since she was 13. Persistent generalized spinal and joint pain was her prime and constant complaint. At the age of 18, she gave birth to a premature male baby. After birth, her sufferings multiplied. Sudden episodes of dizziness were misdiagnosed as meningitis (lumbar puncture and extensive series of investigations were made to rule out the diagnosis). Then the treating doctors suspected leukemia, which was also eliminated. Anxiety, difficulties in concentration, alternating with bouts of syncope associated with intractable severe cervical pain which extends to include the entire spine and the lumbar region were experienced for almost more than two decades. Progression of her symptoms were noticed after the age of 34, when she started to experience temporary loss of vision accompanied with intolerable cervical pain. The neurologist and the orthopedic surgeon gave the diagnosis of cervical spondylosis coupled with a psychosomatic disorder. Meanwhile she was diagnosed by her gastroenterologist as having kinking of the bile duct accompanied with dilated pancreatic duct (stent was applied). Clinical examination showed normal craniofacial contour with no dysmorphic features. Musculo-skeletal examination revealed generalized ligamentous hyper laxity corresponding to 6 out of nine in accordance with Beighton scale associated with hypermobile joints. No evident skin stigmata, and no elasticity of the skin were noted. Apparent tenderness along the cervical area, more marked when she tries to turn her head. Her height was 170 cm with a body mass index of 17.9 kg/m^2. All her spinal movements were markedly reduced because of pain. Joint hypermobility included hips, shoulders, and elbow and wrist joints. She showed positive acromioclavicular compression tests in both shoulders. The FABER test was positive for both hips, albeit associated with pain. Her blood tests for hematology, biochemistry, ESR, hormonal, rheumatoid arthritis was normal. Calcium was 7.2 mEq/L (n.v 8.5 - 10.3 nEq/L), parathyroid hormone was 32.2 pg/ml (n.v 10.0 - 65 pg/ml), and 25-Hydroxyvitamin-D measurement with a DiaSorin radioimmunoassay was 9.1 ng/ml (n.v 9.0 - 37.6 ng/ml). Inflammatory markers were normal and HLA-B27 was negative. She underwent molecular genetic study via whole exome sequencing and no genetic mutations were noted in correlation with her phenotype.

Radiological and tomographic examination: Lateral skull radiograph showed the presence of ossified/calcified interclinoid ligament of the sella-turcica. We measured the length of the ossified ligament through the ossified bridge between the anterior and posterior clinoid ligament. The length of this ossified bridge was (4.7 mm and the width was 2.9 mm) (Figure 1). In this patient the ossified interclinoid ligament has the form of quite a thick bony trabecula, which unites the anterior and posterior clinoid processes. The interclinoid ligament bisects the wall of the cavernous sinus, dividing it into two triangles: the carotid trigone anteromedial and the oculomotor trigone posterolateral. Thus, ossification of this ligament may adversely influence the functions of the internal carotid artery and the oculomotor nerve. 3D reformatted sagittal CT scan confirmed the ossification of the interclinoid ligament (Figure 2). Thereby and in accordance with the unusual findings of the sella-turcica, we decided to further inspect the cervical and cerebral vasculature via Contrast- enhanced computed tomography angiography. The angiographic study confirmed bilateral kinking of the right and left internal carotid arteries (sharp

angle of more than 90°-red arrows); these findings are compatible with dolichoarteriopathy (DICAs grade I). These vascular changes are possibly in connection with redundant vascular elasticity and highly likely in correlation with a connective tissue disorder. Moderate kinking and coiling of the vertebral arteries have been noted (white arrows). According to these findings, coiling and kinking are a state of elongation and redundancy of the internal carotid arteries resulting in exaggerated curvature or in a circular configuration. The overall tomographic phenotype is compatible with the diagnosis of dolichoarteriopathy of the internal carotids (Figure 3).

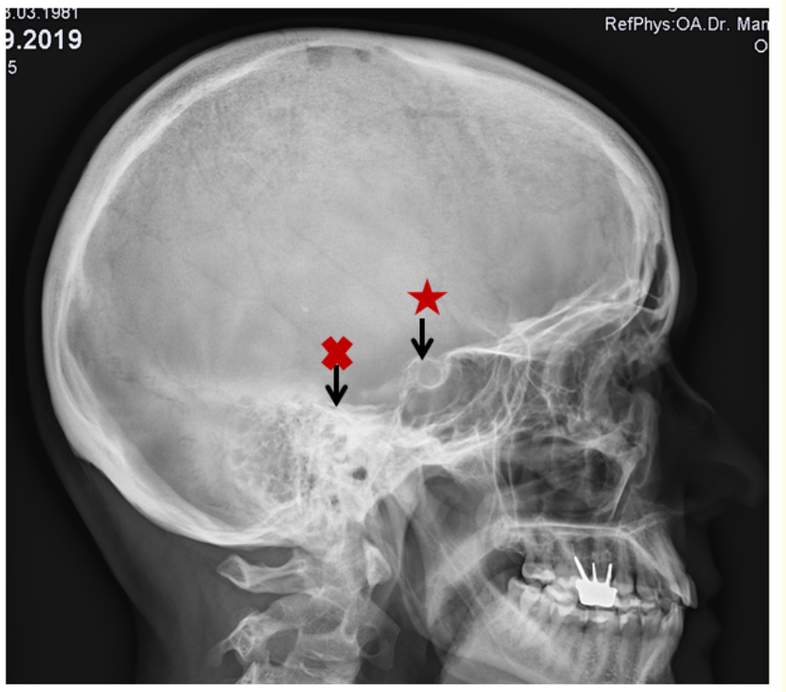

Figure 1: *Lateral skull radiograph showed bridging of sella caused by calcification of the interclinoid ligaments (red star). Hyperostosis of the skull base (red X). We measured the length of the ossified ligament through the ossified bridge between the anterior and posterior clinoid ligament. The length of this ossified bridge was (4.7 mm and the width was 2.9 mm).*

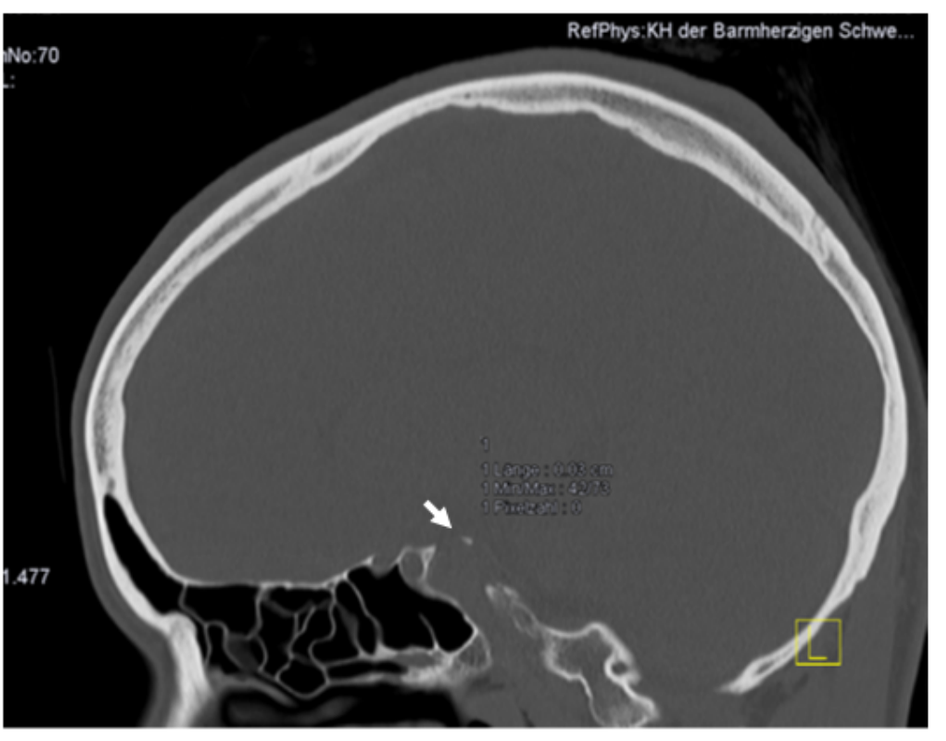

Figure 2: *3D reformatted sagittal CT scan confirmed the ossification of the interclinoid ligament (arrow).*

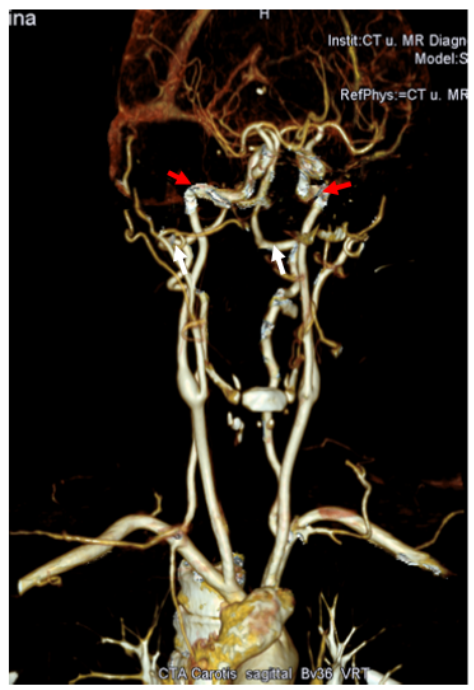

Figure 3: *Contrast- enhanced computed tomography angiography confirmed bilateral kinking of the right and left internal carotid arteries (sharp angle of more than 90°-red arrows), these findings are compatible with dolichoarteriopathy (DICAs grade I). These vascular changes are possibly in connection with redundant vascular elasticity and highly likely in correlation with a connective tissue disorder. Coiling (exhibiting the shape letter C) of the vertebral arteries have been noted (white arrows).*

Discussion

Some studies considered the ossification of the interclinoid ligaments as a physiological finding [9]. Du Boulay and Tricky, assumed that ligamentous ossification might result from normal ossification of the anterior and the posterior clinoid processes [10].

Archana., *et al*. described the ossification of the interclinoid ligament as being of significance especially when dealing with patients who are scheduled for surgical interventions because of vascular, neoplastic or traumatic lesions. They confirmed the direct correlation of lesions of the skull base with a broad spectrum of unpleasant clinical symptoms [11]. Ota., *et al*. studied the anatomical relationship between the ossified interclinoid ligament and the internal carotid artery through forming the caroticoclinoid ligament and shaping the vasculature and the cavernous sinus within a solid ring [12].

No previous study signifies the pathological relationship between the ossified interclinoid ligaments and dolichoarteriopathies (DICAs) in patients with Ehlers-Danlos syndrome/hypermobility type (EDS/ht).

The kinking type of DICAs, can lead to diminished cerebral blood perfusion. Therefore, the assessment of blood perfusion is mandatory, either via Computed Tomography (CT) perfusion, or Magnetic Resonance (MR) perfusion studies and also Single-photon emission

computed tomography (SPECT) analysis is an additional useful tool of examination [13]. The cerebral hemodynamic are altered in connection with the degree of bending of DICAs. In patients with a kinking angle of more than 60°, the blood flow decreases by more than 40%, and more than a 60% decrease of cerebral blood perfusion in patients with 30° kinking [14].

Pellegrino., *et al*. showed that female patients are more prone to develop kinking of the cerebral vasculature and the two sexes are equally susceptible to manifest the tortious type [15]. The reduced blood supply in patients with DICAs can lead to unpleasant symptoms of the brain and eyes simultaneously. DICAs can cause disturbed cerebral blood perfusion which might result in the development of a constellation of symptoms, such as dysfunction encephalopathy, vertigo, diplopia, transitory ischemic attacks and or infarction [16]. The ophthalmic artery is the first branch of the intracranial artery which plays a major role in the blood supply to the eyes. DICAs can result in altered blood perfusion to the eyes and consequently lead to ocular vascular insufficiency, resulting in visual impairments. The onset of visual disturbance can be subdivided into three types. Transient, acute, and or chronic types/patterns. These patterns can include various visual dysfunctions, such as painless temporary loss of vision in one or both eyes (amaurosis fugax), uveitis (which can be a serious manifestation, requiring prompt intervention). Other symptoms of ophthalmic artery dysfunction are retinal and ocular neuropathy [17].

There have been different surgical procedures to alleviate the pathological impact of DICAs. The aim is to correct and to a certain extent to overcome the kinking of the internal carotid artery. One of these procedures is performed through the shortening of the internal carotid artery, aiming to restore and maintain the blood flow in order to avoid cerebrovascular insufficiency. The intervention is carried out by end-to-end anastomosis with resection of the excessive/redundant internal carotid artery. Another procedure can be performed along the bases of carotid endarterectomy with or without resection of the excessive ICA, or *in situ* re-implantation of the ICA by grafting, shortening of the ICA by suturing and ICA dilatation by patch-grafting [18].

Conclusion

Failing to thoroughly understand the clinical and radiological phenotypic characterizations in patients with musculoskeletal disorders, is common. Diagnosis should be carried out with precision and wrong diagnosis can effectively lead to increased suffering for the patient. Clinical medicine and radiology are the base line tools and are the prime benefactors to the overall diagnostic complexes. Diagnoses can be overlooked because of limited clinical knowledge and lack of experience. The implementation of sophisticated radiological equipment can never replace the human potential in recognizing invisible anomalies. Medical imaging and its relevant interpretations are the basic necessities for any clinician. Clinicians' experience should rest on knowledge and training, which are mandatory to submit to vulnerable patients. A diagnostic error is a frequent practice, especially when an anomaly or a constellation of clinical features are omitted by the clinician at the time of primary clinical presentation. A misconception of vital clinical/radiological data might simply lead to total distortion of the diagnostic complex. We hope that clinicians and radiologists might improve their knowledge potential toward proper understanding of patient´s long term ailment. In our current case the ossified interclinoid ligament has the form of quite a thick bony trabecula, which unites the anterior and posterior clinoid processes. It showed therefore the pathological influence on the adjacent neurovascular structures, causing effectively unpleasant and long-term clinical symptoms. This ossified bridge adversely affected the blood flow along the internal carotid artery, causing dysfunction of the muscles of the eyes owing to possible compression of the oculomotor nerve. Angiographic studies confirmed bilateral acute kinking of the right and left internal carotid arteries (sharp angle of more than 90°- grade I). The vascular phenotype of this patient is in strong correlation with the redundant vascular elasticity as part of Ehlers-Danlos syndrome (hypermobile type).

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