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RESEARCH ARTICLE

Progressive Migraine in Patients with Ehlers-Danlos Syndrome (Hypermobility Type)

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Abstract

Objective: Frequent and intolerable bouts of migraine originating from the neck and radiated to the head creating a constellation of symptom-complex. Ranging from vision problems and cognitive impairment to episodes of syncope and possibly stroke.

Materials and Methods: Three female patients (aged 20, 25, and 33 years old, respectively). Tall stature (above 97 th percentile), long and thin limbs overwhelmed through generalized ligamentous hyperlaxity, were the paramount clinical features. A history of frequent migraine attacks and early onset joint pain since late childhood, were the reasons behind frequent hospitalization. Clinical and radiological phenotypic characterization have been organized as well as tomographic studies to further understand the etiology behind.

Results: All patients manifested the clinical phenotype compatible with the diagnosis of Ehlers- Danlos syndrome –hypermobile type (EDS-ht). Molecular genetics showed no *COL3A1* mutation, though family gathering information was strongly suggestive of (EDS-ht). We encountered variable cranial, vertebral and vascular abnormalities. The first patient´s 3D reformatted CT scan of the cranio-cervical junction showed sub-clinical basilar invagination (bulging of the odontoid into the brain stem of 17-mm above Chamberlain´s line). The contrast- enhanced computed tomography angiography of the cervical and cerebral arteries for the second patient, revealed anomalies of cervical vasculature (kinking/tortuosity and stenosis in several segments of the right and left common carotid arteries associated with stenosis in the lower third of the left common carotid artery and the left subclavian artery). Lateral skull radiograph of the third patient showed elements of osteoarthritis and derangement of the temporomandibular joint (TMJ). We confirmed our findings via 3D reformatted CT scan, which showed narrowing of the joint space in connection with dysplastic disc of the (TMJ)

Conclusion: Patients with a complex multisystem disorder, serious situations are to be expected. It is mandatory to determine the etiology. Pitfalls and speculations in diagnosis are extremely hazardous element, though they are commonly practiced through many medical disciplines. The profound clinical analysis and family history are fundamental tools tin solving the complicated clinical status of chronic illnesses. Congenital vascular and bony abnormalities may cause progressive headaches and might lead to severe neurological deficits.

Introduction

The etiology of primary headache disorders is varied and correlates with a wide spectrum of pathologies. Migraine is not an uncommon disorder affecting approximately 18% of the female population and 6% of the male population [1]. Migraine manifests itself with persistent or episodic severe headache associated with vegetative symptoms. A remarkable number of these patients might experience temporary neurological symptoms mostly involving the visual system prior to or during the migraine attack, known as migraine aura [2]. Migraine has been considered as a functional deficit of the brain, and might be strongly connected to the vascular system [3].

Ehlers-Danlos- syndrome hypermobility type (EDS-HT), manifesting a phenotypic spectrum with the joint hypermobility, is likely the most common, though it is rarely detected in medical disciplines. EDS-HT is a hereditary connective tissue disorder defined by the association of generalized joint hyperlaxity/ instability, early onset joint pain, with minimal skin changes and positive family history [4].

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Headache, and progressive neurological deficits are well known complications in a number of heritable connective tissue disorders such as Ehlers-Danlos Syndrome. The clinical features and presentations are attributable to generalized and severe ligamentous hyper-laxity. Atlanto-axial instability is a major part of the clinical picture and has been referred to ligamentous laxity and instability of atlantoaxial joints [5]. Abnormal developmental anomaly of the cranio-vertebral junction can cause a morbid neurological deficits [6]. Migraine is strongly correlated to congenital malformation of the cervical vasculature [7].

The temporomandibular joint dysfunction in connection with ligamentous hyper-laxity encompasses unpleasant symptoms such as migraine, limitations in joint mobility and clicking/ unusual sounds during the chewing process. Congenital hyper-laxity of the temporomandibular joint (TMJ) adversely affects the anatomical integrity and leads to dysfunction of the head and neck [8].

Material and Methods

Ethical approval:

The patients enrolled in this study provided informed signed consent for their involvement in this research, which were designated in accordance with the Helsinki declaration and approved by the institutional review ethical community of the Mongi Slim University Hospital, Institute of Human Genetics Tunis (ref. 25/21).

Developmental History: The severe ligamentous hyperlaxity with poor muscular development was confused by the pediatricians as congenital myogenic disease. Their subsequent course of development showed delayed walking up to 18 months albeit with difficulties. Climbing the stairs was another difficult task to perform. Abnormal gait, and to a certain extent, clumsiness associated with poor fine motor development were characteristic features in all patients.

Natural History: One patient was born prematurely because of premature rupture of the membranes. Neither abnormal wound healing nor scar tissues have been recorded. No history of any unusual gastro-intestinal pathological events. Easy fatigability associated with early onset joint pain, particularly over the weight bearing zones were evident in their early childhood. Two female patients revealed a family history of fatal stroke in connection with ruptured cerebral aneurysm. One relative died because of ruptured aneurysm of the internal carotid artery and another relative died because of berry aneurysm of the posterior communicating artery. Family history of aneurysms have been considered to further investigate our patient via the contrast- enhanced computed tomography angiography of the cervical and cerebral vasculature.

Clinical phenotype: All patients manifested tall stature, and long thin limbs, excessively hypermobile joints, with less marked skin elasticity. All were compatible with (EDS-ht). Bilateral passive dorsiflexion of the little finger beyond 90°. Thumbs showed bilateral passive dorsiflexion to the flexor aspect of the forearm. Bilateral hyper-extension of the elbows of 15° was a noticeable feature. Forward flexion of trunk with knees full extended showed palms and hands can rest flat on the floor. Hyperextension of the knees beyond 10° has been confirmed as well. Examination of the skin did not show any signs of hyper-elasticity. The generalized ligamentous hyper-laxity was compatible with 9 points out of 9 in correlation with Beighton scoring test. Easy fatigability was of progressive nature and was a major obstacle in joining sport lessons at the school. Early osteoarthritis was a chronic complaint in all patients. Neck pain and headache have been diagnosed primarily as being a combination of tension-type headache and migraine. Though, the marked hyper-mobile cervical spine and temporomandibular joint dysplasia (TMJ) have been considered as additional factors for migraine.

Radiological examination: Lateral skull radiograph in one patient showed elements of temporomandibular osteoarthritis. Lateral cervical spine in one patient gave the impression of an overlapping and ill-defined anatomical cranio-vertebral junction. 3D reformatted sagittal CT scan was organized. For one female patient, and in accordance with her family history of two incidents of rupture aneurysm, we arranged contrast-enhanced computed tomography angiography of the cervical and cerebral vasculature. The 3D reconstruction CT scan for one patient showed Wormian bones along the lambdoid sutures

Results

Molecular Genetics:

EDS-HT belongs to a heterogenous group of connective tissue disorders known as Ehlers–Danlos syndromes (EDS) that are caused by defective collagen synthesis [9,10]. EDS can be classified into 13 subtypes including the classic ((Type I/II), hypermobility (Type III), vascular (Type IV), kyphoscoliotic (Type VI), Arthrochalasia (type VII A and B), Dermatosparaxis (type VIIc), Kyphoscoliotic (type VIII), Brittle Cornea syndrome (type IX), Spondylodysplastic (type X), Musculocontractural (type XI), Myopathic (type XII), and Periodontal (type XIII), depending on the developed symptoms [9,11]. EDS can be inherited in an autosomal dominant or recessive manner. Most of these types are caused by mutations in more than 28 genes that encode collagens and other proteins [11]. The EDS-HT is the most common and the least severe subtype of EDS (3). However the underlying cause is still unknown, it has been found to be inherited in an autosomal dominant fashion [11].

Patient 1:

A 20-year-old girl with migraine as her paramount complaint since late childhood. Sagittal Craniocervical 3D reformatted CT scan (Fig. 1) showed: Tip of the odontoid is more cephalad

and protrudes into the foramen magnum (bulging of odontoid is more than 17 mm above Chamberlain´s line), highly likely resulted in partial anterior compression of the vertebro-basilar artery. This sort of compression falls within the group of compression syndromes of the vertebral artery that occur at the craniocervical junction. This compression leads to dynamic vertebral artery occlusion where the vessel courses around the atlas and the axis-the so-called V3 segment (figure 1). This in turn leads to insufficient collateral flow to the posterior fossa. [Figure1]

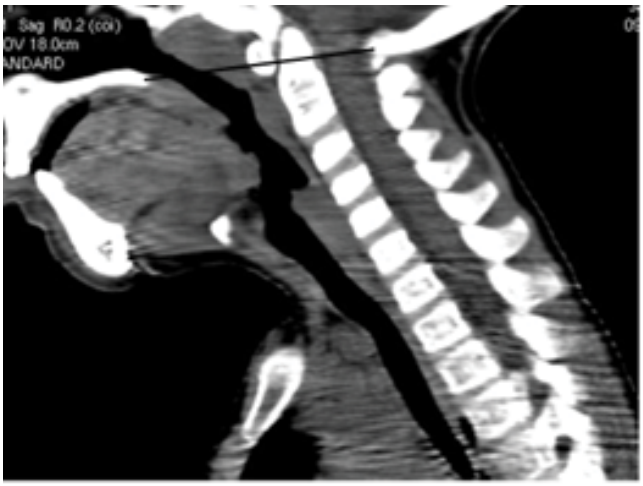

Figure1. 3D reformatted CT scan showed: Tip of the odontoid is more cephalad and protrudes into the foramen magnum (bulging of odontoid is more than 17 mm above Chamberlain´s line)

Patient 2: A-25-year-old-female patient, 3 D contrast-enhanced computed tomography angiography of the cerebral arteries showed kinking and tortuosity along several segments of the right and left common carotid arteries. Maximal magnitude of stenosis and kinking along the lower third of the left common carotid artery and kinking of the left subclavian artery (**a**). Stenosis is apparent along the right and left internal carotid arteries. Similarly degenerative pathology involving the vertebra-basilar arteries of maximal intensity over the left part (**a**). 3D reconstruction CT scan of the cranial bones showed Wormian bones (arrow) along the lambdoid sutures associated with bulging of the occiput (b) [Figure 2(a,b)]

Patient 3: A-33-year-old-female patient, her late childhood migraine is attributable to the temporomandibular osteoarthritis. Temporomandibular joint evaluation via manual palpation during vertical opening and closing movements revealed reciprocal clicking (i.e the click at mandibular opening seems louder than the click at closing). The sounds of clicking are highly likely due to slippage of the condyle over the posterior

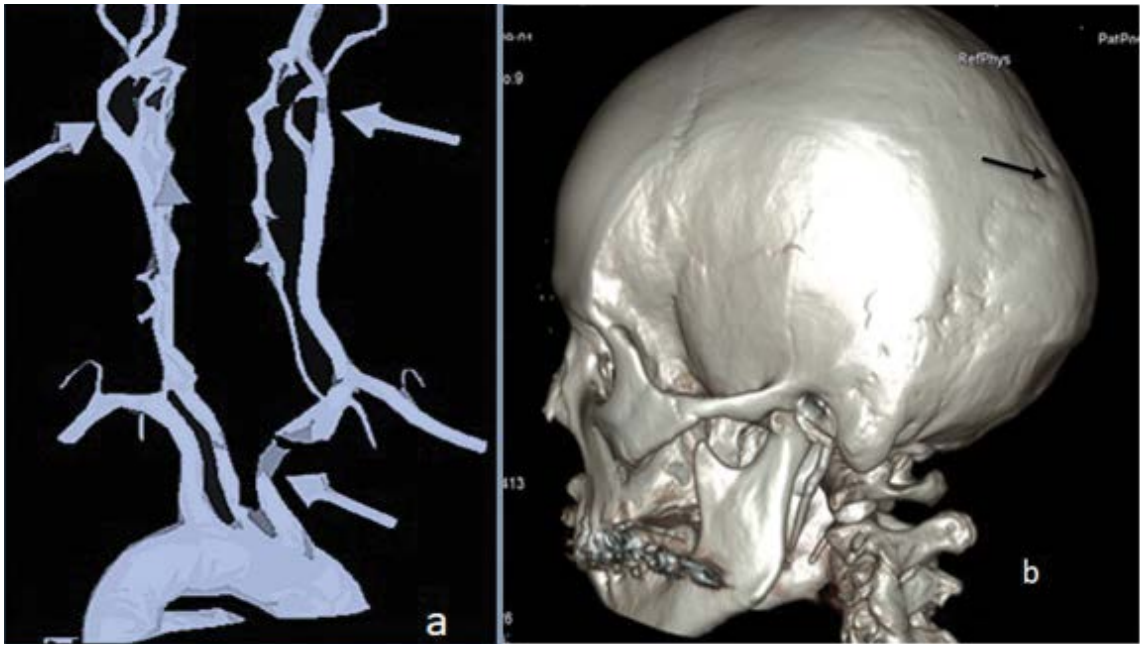

Figure 2 a,b. 3 D contrast- enhanced computed tomography angiography of the cerebral arteries showed kinking and tortuosity along several segments of the right and left common carotid arteries. Maximal magnitude of stenosis and kinking along the lower third of the left common carotid artery and kinking of the left subclavian artery (arrows). Stenosis is apparent along the right and left internal carotid arteries. Similarly degenerative pathology involving the vertebra-basilar arteries of maximal intensity over the left part (arrow) (a). 3D reconstruction CT scan of the cranial bones showed Wormian bones (arrow) along the lambdoid sutures associated with bulging of the occiput (b). Wormian bones are irregularly shaped bones formed from independent ossification centres found along cranial sutures (mainly along the lambdoid sutures), note the bulging occiput. Wormian bones can be encountered in (76) syndromic entities (London Medical Database).

edge of medially dislocated disc. She had experienced episodes of acute lock of the mandible. Lateral skull radiograph showed element of temporomandibular osteoarthritis/derangement **(3a)**. 3D reformatted CT scan showed dysplastic disc of the temporo-mandibular joint (TMJ), especially when blocked between the articular eminence and the condyle (arrow) **(3b).** The correlation of generalized ligamentous hyper laxity and the joint hypermobility caused immense dysfunction of the cranio-mandibular joints. [Figure 3(a,b)]

Discussion

Headache is the most common clinical presentation, more than 66% of the global population have such a complaint [12]. Around 18% of migraines could be attributable to craniocervical (neck) pathologies [13,14].

The Beighton Score (BS) is a set of maneuvers encompassing a nine-point scoring system, used as the standard method of assessment for generalized Joint Hypermobility. It was originally developed and applied to screen large African population to detect generalized hyperlax ligaments [15,16].

Basilar invagination (BI) is an abnormal bulging of the odontoid into the foramen magnum. It is not uncommon to see BI in association with a long list of syndromic entities (particularly in patients with heritable connective tissue disorders. Chamberlain described a radiological feature of the cranio-cervical in connection with chronic clinical presentations such as headache. The prime complaint of patients with subclinical BI is posterior headache or neck pain. The sequence of neurological deterioration/deficits are correlated to the degree of impingement of the brain stem [6,17].

Al Kaissi et al, described basilar invagination in association with different syndromic entities. 3D reformatted and reconstruction CT scan have illustrated a variety of BI/ impression in connection with; remnant of the persistence of dentocentral synchondrosis, atlanto-axial instability, severe generalized ligamentous hyperlaxity, progressive softening of the skull bones as in osteogenesis imperfetca type IV B, or in connection with persistent torticollis/ cervical scoliosis as seen in MURCS and VATER syndromes [18–22].

Schwedt and colleagues described almost 2/3 of patients with pretreatment headaches had substantial minimization of headache following treatment of unruptured aneurysm [23].

It is mandatory to perform profound studies to analyze the reason behind head and neck pain in connection with anomalies of the cervical vasculature (carotid and vertebral). The nature of the pain and its location varies from one patient to another and in many instances resembles migraine [7].

Studies have shown that the cranio-cervical vasculature area is a highly pain-sensitive structures capable, under unusual conditions, of giving rise to headache. In addition, they showed that branches of the external carotid arteries were directly connected with migraine headache and also for the sort of headache that is concomitant with arterial hypertension [24].

Migraine with or without aura has been described by Bendik et al as three times greater among a group of 28 women with EDS-HT in comparison with 232 controls with a cumulative frequency of 75 percent [25].

The temporomandibular joint, TMJ, and its correlated muscles are closely related to the functions of the head and neck. Congenital hyperlaxity of the TMJ adversely affect the anatomical integrity of the head and neck. The physiological functioning of the TM joint is typically like any other articulation. Osteoarthritis, dysplasia and possibly dislocation

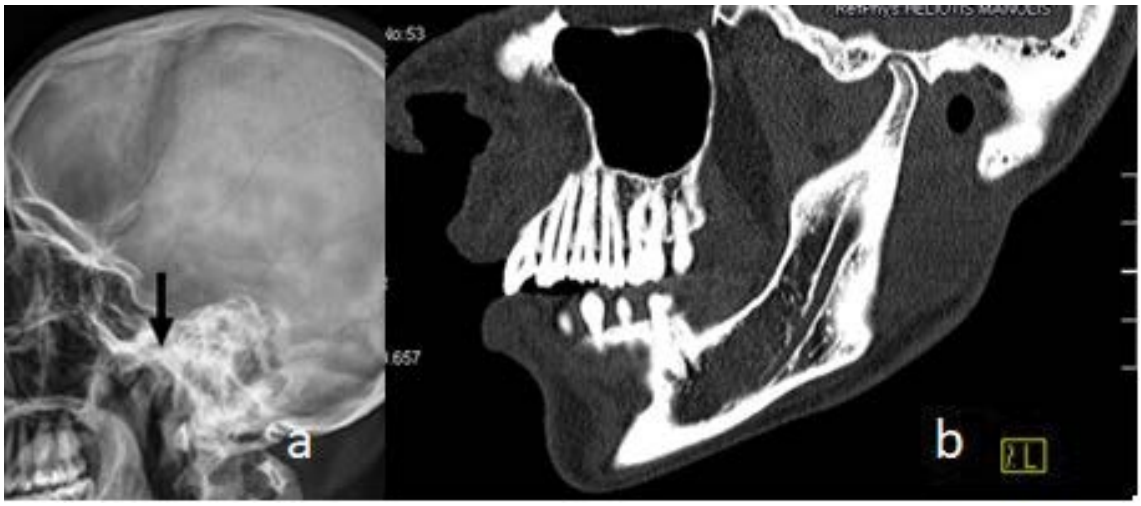

Figure 3 a,b. Lateral skull radiograph showed element of temporomandibular osteoarthritis/derangement (a) (arrow). 3D reformatted CT scan showed dysplastic and progressive narrowing of the disc of the temporo-mandibular joint (TMJ), especially when blocked between the articular eminence and the condyle-arrow (b).

of the TMJ can occur in patients with (EDS-HT). The head and neck in EDS patients, when confronted with excessive full dynamic movements (i.e., as in full extension or flexion), can easily lead to pathological damage of the TMJ. Migraine is not an uncommon paramount symptomatology in patients with temporomandibular disorders. Migraine /chronic migraine and tension-type migraine are strongly correlated to TMJ disorders [26].

Conclusion

The clinical phenotype is the first and foremost key factor in determining the precise direction of management in patients with chronic ailments. Clinicians need more awareness regarding different individualistic phenotypes. The phenotype is the baseline tool in the approach for a comprehensive etiology understanding. The patients described in this paper started consuming large amounts of different sorts of analgesia and tranquilizers in an attempt to alleviate the agony of their headache. The unpleasant outcome of prescribing medications without realizing the hidden pathology is a troublesome strategy. Clinicians' lack of knowledge can have detrimental outcomes for patient health. Extreme and generalized ligamentous hyperlaxity has a precise and effectual damage to the atlanto-axial ligaments effectively causing the development of atlanto-axial instability and adversely damaging other joints. Severe and generalized ligamentous hyperlaxity plays a major role in tailoring the vascular structures. Kinking/ tortious and or stenotic cervical vasculature must be considered in any comprehensive clinical documentations for patients with progressive migraine overwhelmed with severe hyper-lax ligaments. The cranio-vertebral segments are complex anatomical structures encompassing the vital bony (TMJ), the neuro elements, and the vascular elements. These anatomical structures need accurate assessment. These anatomical structures govern the normalcy of balance, stabilization, and biomechanics. Their major role is to protect the neurovascular anatomy with respect to range of mobility and motion. The usage of cranio-vertebral tomographic studies enables different medical specialties a better understanding of the confusing and overlapping anatomy of the skull-vertebral and vascular complex. Therefore, it is empirical for physicians and orthopedic surgeons to possess the capability for detecting the etiology, understanding of long-term health dilemmas as in progressive migraine. Finally, we wish to stress that the 3D reformatted and reconstruction CT scan and Contrast-enhanced computed tomographic angiography are useful investigative modality. The final target is the precise evaluation of the bony/vascular malformation complex especially in patients with long-term ailments such as migraine. Thereby, subclinical BI, TMJ dysplasia and vascular abnormalities can be considered as part of the long list of syndromic and familial types of progressive migraine.

Ethical approval: The patients enrolled in this study provided informed signed consent for their involvement in this research, which were designated in accordance with the Helsinki declaration and approved by the institutional review ethical community of the Mongi Slim University Hospital, Institute of Human Genetics Tunis (ref. 25/21).

Authors Contributions

AAK, FBC, FG (Clinical and Radiographic documentation, and writing the MS). LBJ, MS, SSR & SGK contributed in patient's and parents investigations. All authors approved the final version.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil

Conflicts of interest

There are no conflicts of interest.

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