



Morbid Constellation of Osseous and Vascular Abnormalities in a Female Patient with Congenital Central Hypoventilation/Overgrowth Syndrome

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Abstract

Background: Congenital Central Hypoventilation Syndrome (CCHS), is a condition characterized by ventilatory impairment that results in arterial hypoxemia. Studies revealed that the vast majority of patients with CCHS are free from any associated pulmonary, cardiac or brainstem pathologies.

Material and Methods: F.R is a 20 -year-old- Austrian-girl presented in my consultation seeking advice for her unpleasant clinical history. In her early life, seizures were the first serious clinical presentation. Followed later on with hypertension, bouts of respiratory dysfunction and impairment of consciousness. In 2019 she underwent surgical intervention to remove a 2 cm hamartoma (posterior upper aspect of the right thigh). Few years later, another hamartoma on the ventral side of the tongue has been identified as well. Early on, she received the diagnosis of Mediterranean fever syndrome and the geneticist encountered homozygosity to the MEFV M694V mutation as the reason behind the constellation of the current unpleasant symptomatology. Later on a presumptive diagnosis of Ehlers-Danlos syndrome-hypermobile type has been suggested in other Medical Institutions. We proceeded with our documentation via clinical and radiological phenotypic characterizations.

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Results: Clinical examination showed growth above the 97th percentile (overgrowth) with no specific facial dysmorphic features. She manifested generalized ligamentous hyper laxity. Her ligamentous hyperlaxity was compatible with 6 points out of 9 in correlation with Beighton scoring test. On the bases of skeletal survey; lateral skull radiograph showed features of mastoid and temporal bone characterized with extensive-pneumatization. Axial CT scan shows bilateral hyper-pneumatization of the temporal bones, demonstrating expansion of arial spaces with loss of the bony trabeculae and thinning of the mastoid bone. Mastoid cells appear to be in communication with a large intracranial epidural air cavity in the temporal and parietal regions. Reformatted CT scan of temporal bone, through coronal and axial images, at the level of the cavum tympani and the mastoid, showed a defect in the right tegmen appeared as cloudy/ opaque lesions around the cavum and the surrounding air cells. Contrast- enhanced computed CT angiography of the cervical and cerebral vasculature showed unusual malalignment and spiral twisting along several vascular segments resulted in the mal-development of basilar artery stenosis without atherosclerosis. The current patient manifested overgrowth syndromic entity with a constellation of osseous and vascular abnormalities resulted in a clinical course of congenital central hypoventilation syndrome.

Conclusion: The etiology behind the extension of pneumatization has most likely occurred because of defective ossification of the occipito-mastoid synchondrosis . The reason behind the extension of pneumatization into the occipital and parietal bone is probably due to incomplete closure of the occipito-mastoid synchondrosis, lambdoid and sagittal sutures, which usually close in early adulthood and later, even at the age of thirties. In our patient, we postulate that the history of multiple hamartomas and abnormal vascular phenotype in conjunction with extensive hyper-pneumatization of the skull were the main etiology behind her unpleasant course of her devastating ailment regardless the genetic results. Our impression is neither Mediterranean fever syndrome nor Ehlers-Danlos syndrome seem compatible with her current constellation of osseous and vascular abnormalities. The overall clinical and imaging findings are highly likely in connection with either one of the different types of overgrowth syndromes or might be a novel syndromic association. We believe that congenital central hypoventilation is a symptom complex rather than a diagnostic entity.

Keywords

Congenital Central Hypoventilation Syndrome; Mediterranean Fever Syndrome; Angiography; Computerized Tomography

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Introduction

Congenital Central Hypoventilation Syndrome (CCHS), which is also known under the term of “Ondine’s curse”. Several theories and assumptions have been arisen to define and to connect (CCHS) to a reason [1]. CCHS might appears at any age from birth to adulthood. Patients manifest marked reduction in the alveolar capacity of ventilation and central apnoeas, highly likely during sleep. The aforementioned abnormalities are due to impaired physiological ventilator in responses to hypercapnia and low level of oxygen. Some reports showed that CCHS can be isolated or occurs in connection with other dysautonomia-related conditions such as Hirschsprung disease or neural crest tumours [2].

Pneumoceles are usually attain large volume which might be enough to produce mass effect on the nearby structures like external acoustic canal or may extend to involve the adjacent bones and joints. These usually need special surgical plan, the type of which account upon the location and the affected bones. Though purely unnoticed localized pneumocele like some published cases, lead to the formation of a remarkable retro-auricular mastoid swelling without any other symptoms, is quite rare and require proper clinical and imaging documentations [4-6]. Molecular studies in some patients with CCHS showed, mutations of the paired like homeobox 2b gene (PHOX-2B) [3,6]. Vascular anomalies and tortuosity in the vertebral-basilar artery has been described. Spiral twisting and tortuosity can result in poor blood perfusion to the brain, causing effectively the development of transient ischemic attack [7-9]. On the light of the aforementioned combination of osseous and vascular anomalies, we feel reluctant to accept the hypothesis that Mediterranean fever syndrome and the homozygosity to the MEFV M694V mutation as the reason behind the constellation of the current unpleasant symptomatology. Similarly, the conception that most patients with CCHS might show mutations of the paired like homeobox gene (PHOX-2B) is unacceptable. For two reasons, firstly, we believe that CCHS is a symptom complex. Secondly, most of the studies gave the term CCHS as a syndrome. In practice, a syndrome means a combination of clinical and radiological abnormalities. This study signifies the pros and cons that escorted journey of agony of this girl, which has been started at the age of 3 years-present and get worse day after day.

Clinical Presentation

Few years ago she received the diagnosis of Mediterranean fever syndrome and she found to be homozygous to the MEFV M694V mutation. Later on, the treating medical team changed the diagnosis and Ehlers-Danlos syndrome-hypermobility type has been suggested. At the age of 3 ½ years, there was a post fall urinary retention with hydronephrosis and a conspicuously large bladder with a capacity of 500 ml. At the age of 13 year, she experienced increased impulsivity, without typical depression. Depression manifested itself in sudden, unpredictable suicide attempts and a history of dissociative disorder. She has been always seemed to be

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"contained", with sudden unexplainable clouding of consciousness with observed pauses in intermittent breathing. Strong sedatives were administered for the first time in combination with psychotropic drugs. Her ligamentous hyper laxity was compatible with 6 points out of 9 in correlation with Beighton scoring test. She had a history of hypertension and reduced cardio-respiratory fitness. No specific skin stigmata, except a large dimple over her right arm. She manifested hamartoma over the left ventral surface of her tongue. All sorts of laboratory tests showed almost normal results. Skeletal survey has been performed; lateral skull radiograph showed features of mastoid and temporal bone extensive-pneumatization and calcification of the inter-clinoid ligament (Fig. 1). Axial CT scan shows bilateral hyper-pneumatization of the temporal bones demonstrating expansion of aerial spaces with loss of the bony trabeculae and thinning of the mastoid bone. Mastoid cells appear to be in communication with a large intracranial epidural air cavity in the temporal and parietal regions clearly delimited by an altered skull with multiple air spaces and septa in the diploe. Reformatted CT scan of the temporal bone at the level of the cavum tympani and the mastoid, showed a in the right tegmen (arrow) and opacification of the cavum and nearby air cells (Fig. 2). Axial reformatted cerebral CT scan showed, the close temporal relations, the final origin of the trans- tegmental herniation (arrow) of the inferior temporal gyrus into the petrous bone can be attributed to a forced coughing suppression effort that usually accompanies a sudden rise of intracranial pressure in the sense of a Valsalva maneuver (Fig. 3). Contrast- enhanced computed tomography angiography of the cervical and cerebral arteries showed the followings: Unusual curving and spiral twisting in multiple segments of the vertebral arteries causing effectively the development of basilar artery tortuosity and stenosis without atherosclerosis (Fig. 4).



Figure 1: Lateral skull radiograph showed a net like appearance suggestive of hyper-pneumatization of the temporal bone. Shows large expansible honeycomb appearance covers

the mastoid and extends posteriorly to involve other parts of the temporal bone and the lambdoid sutures respectively. Note features of sclerosis of the occipito-mastoid suture (red arrow). Note a large expansile honeycomb appearance covers the mastoid and extends posteriorly to involve other parts of the temporal bone. White arrow showed calcification and thickening of the interclinoid ligament which creates the form of quite a thick bony trabecula along the sella turcica, 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. Thereby calcification of this ligament may adversely influence the functions of the internal carotid artery and the oculomotor nerve respectively.



Figure 2: Axial CT scan shows hyper-pneumatization of the temporal, occipital and parietal bones associated with suspected soft tissue emphysema. Hyper-pneumatization looks as a space occupying lesion with expansion of the aerial spaces. A temporal bone High Resolution Computerized Tomography (HRCT) scan revealed a hyperpneumatization of the right temporal bone with expansion of aerated spaces extending through the mastoid tip and causing a large intracranial epidural air cavity.



Figure 3: Axial reformat CT scan showed, the close temporal relations, the final origin of the trans- tegral herniation (arrow) of the inferior temporal gyrus into the petrous bone can be attributed to a forced coughing suppression effort that usually accompanies a sudden rise of intracranial pressure in the sense of a Valsalva maneuver. In this sense, our classification of the fistula as a “spontaneous” one appears to be justified.

Axial CT scan shows hyper-pneumatization of the right temporal bone demonstrating expansion of aerial spaces, loss of bony trabeculae and thinning of the mastoid bone. Mastoid cells appear to be in communication with a large intracranial epidural air cavity in the temporal and parietal regions clearly delimited by an altered skull with multiple air spaces and septa in the diploe.

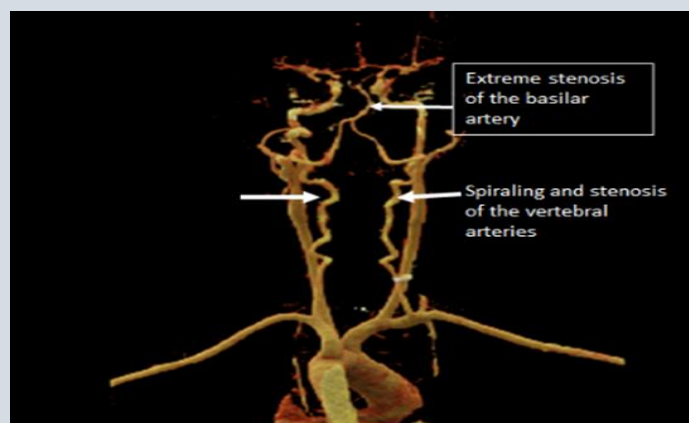


Figure 4: Contrast- enhanced computed tomography angiography of the cervical and cerebral arteries showed the followings: Unusual curving and spiral twisting in multiple segments of the vertebral arteries causing effectively the development of basilar artery tortuosity and stenosis without atherosclerosis. The overall current vascular phenotype can leads to hypertension; syncope and stoke.

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Discussion

Trang, et al., published a study encompassed of 34 consecutive patients with CCHS (from the age of 4 years-16 years and six months respectively). They studied different aspects, included the socio-demographic data, genetic data and medical history. In addition to the CCHS-related assessments, neurocognitive evaluation was performed as has been advised by the systematic care of patients with CCHS [6]. Authors totally omitted the necessity to perform clinical and radiological phenotypic characterizations. These are the baseline tools for proper management. Throwing all patients in one basket can cause tremendous harm to the whole documentary procedures. Clinical documentation should accounts and considers the diversity in the clinical individualistic.

The etiology behind the extension of pneumatization has most likely occurred because of defective ossification occipito-mastoid synchondrosis. The cause of the extension of pneumatization into the occipital and parietal bone is probably stemmed from incomplete closure of the occipito-mastoid synchondrosis, which usually close in early adulthood and later, even in the 30s. Asymptomatic patients should be aware of possible complications and in this case, operative therapy is often indicated. Collections of air such as seen in this patient has been described by other medical institutions occurred as a result of injury and more possibly, infection. Such speculations are totally rejected.

Temporal bone pneumatization is considered a normal variant in adults. The condition can affect the mastoid, squamo-mastoid and petrous apex portions of the temporal bone and is seen in varying degrees of severity in healthy individuals [1,2]. However, pneumatization of the occipital bone is rare and has been only sparsely reported. In one case described in the literature, occipital bone pneumatization was an incidental finding on a CT scan obtained to evaluate the cause of the patient's headaches. Furthermore, the mal-alignment and the distorted anatomy of the cervical and cerebral vasculature along multiple segments of the vertebral and the basilar arteries were the paramount etiology behind the drastic clinical history. Highly likely, added burden to the progressive deterioration of patient's clinical status and possibly contributed adversely to the episodes of hypertension, syncope and possibly might lead to stroke. Vascular anomalies and tortuosity in the vertebra-basilar artery has been described [3]. Spiral twisting and tortuosity can result in poor blood perfusion to the brain, causing effectively the development of transient ischemic attack [4]. Spiral twisting and tortuosity of the vertebral arteries can be encountered in old age patients, who are mostly presented with hypertension. Previous studies postulated the connection between vertebra-basilar artery tortuosity and connective tissue disorders [7-9]. In elderly patients, hypertension, diabetes and lipid metabolism disorders can promote atherosclerosis and degeneration of blood vessels, thereby aggravating vertebra-basilar artery spiral twisting in which progressive defective vascular elasticity and degeneration, are highly likely to develop [9,10]. Pellegrino, et al., described that female patients are highly susceptible to develop kinking of the cerebral vasculature, but never

the less, the two sexes might manifest the tortious type [11]. The impaired blood supply in patients with tortious vasculature can lead to unpleasant symptoms of the brain and eyes simultaneously [12]. In our current young patient, we postulate that the history of multiple hamartomas and abnormal vascular phenotype of the vertebral arteries in correlation with extensive hyper-pneumatization of the skull were the main etiology behind her unpleasant course.

Conclusion

When different medical disciplines are unable to think clearly or ignore the phenotypic specifications in patients with musculoskeletal disorders, the outcome won't be favorable. Diagnosis should be based on proper reading of the clinical signs backed up through precise interpretation of the images. Detailed clinical examinations should run side by side with profound scrutiny of multi-system analysis via radiological and imaging anatomy. It's highly likely that the constellation of abnormalities in this female patient are ranging between multiple hamartoma, hyper-pneumatization of the temporal bone and tortious vertebral arteries, in other words, a constellation of a genetically programmed disorder. According to these findings, congenital anatomical abnormalities of the cervical and cerebral vasculature in association with calcification of the inter-clinoid ligaments, it could possibly negatively amplified the surrounding neurovascular structures, instigating the appalling current clinical status. Congenital vascular abnormalities of the cervical and the cerebral vasculature may lead to pathophysiological condition that give away/conduce to enhance the CCHS. The overall imaging phenotype could explain the course of the natural history of unpleasant symptoms. Because of the nearby temporal relations, the final origin of the trans-tegmental lesion of the inferior temporal gyrus into the petrous bone can be attributed to a forced coughing suppression effort that usually accompanies a sudden rise of intracranial pressure in the sense of a Valsalva maneuver. We wish to stress that the constellation of the aforementioned vascular and osseous abnormalities might be compatible to different types of overgrowth syndromes such as Bannayan-Riley-Ruvalcaba, Cowden or Kosaki overgrowth syndrome. The latter might overlap with Cowden syndrome. Patients in both syndromic entities can develop hamartomas and other non-cancerous lesions associated with congenital vascular anomalies.

Conflict of Interest

The authors verify that there is no conflict of interest.

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