CLINICAL ANATOMY AND EMBRYOLOGY OF VAN BUCHEM DISEASE AND SCLEROSTEOSIS: A REVIEW OF THE LITERATURE

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Review

ABSTRACT

BACKGROUND: Van Buchem Disease (VBD) is a rare condition present in parts of the Netherlands in which consanguineous marriage was common and causes sclerosing bone dysplasia. Its significantly worse equivalent, Sclerosteosis, is present in Afrikaners from Dutch descent and can be found mainly in South Africa. Both diseases, characterized by excessive formation of bone, have appalling consequences caused by the entrapment of nerves and blood vessels that pass through the foramina of the skull base.
OBJECTIVE: The aim of this study is to present an overview of the pathophysiology of VBD and to review the complicated embryology of the skull base and the four most involved cranial nerves: the trigeminal, facial, vestibulocochlear and vagal nerve.
METHODS: An extensive literature search on VBD and Sclerosteosis was conducted using various databases, including PubMed, Medline, EMBASE and the Cochrane Library. To create insights in the anatomy of the orofacial region, a mini-review was conducted.
RESULTS: VBD is recognized by neurological symptoms caused by compression of different cranial nerves (V, VII, VIII and X), high bone mineral density, craniofacial anomalies and increased intracranial pressure all caused by excessive growth of bone, so-called osteosclerosis. Sclerosteosis can be recognized by the aforementioned symptoms accompanied by syndactyly or other digital malformations. Both disorders are caused by a lacking regulatory element of the SOST-gene resulting in a deficit in the production of slerostin-protein.
CONCLUSION: VBD shows to be a disease with a fascinating pathophysiology. The symptoms from compression of the cranial nerves are a great vehicle to review the intricate embryology of the cranial base.

WHAT'S KNOWN: Rare bone deformation disorders, such as Van Buchem Disease (VBD), can provide insights in bone cell processes that may be involved in common diseases such as osteoporosis. Complex symptomatology in VBD can be explained using anatomical and embryological knowledge.

WHAT'S NEW: A comprehensive overview, ranging from embryological development and anatomical relations of involved structures to clinical features, is presented.

KEYWORDS: anatomy, cranial nerve, osteosclerosis, SOST-gene, Van Buchem Disease

Introduction

Urk used to be a small isle in the Zuiderzee, isolated from the rest of The Netherlands. For this reason, centuries have passed in which consanguineous marriages were frequent. The genome of this population contains different defects and the chance of genetic disorders has increased over the years. One of the typical disorders that only exist on Urk is Van Buchem Disease (VBD). VBD is a sclerosing bone dysplasia, first described in 1955 by Van Buchem and colleagues as hyperostosis corticalis generalisata familiaris [1]. In 1968, Fosmoe et al. introduced the eponym Van Buchem Disease for the first time [2]. When suffering from VBD, patients can endure a wide range of neurological symptoms including deafness, blindness and a form of peripheral facial paralysis (Bell's palsy) [3]. Sclerosteosis, a significantly worse type of VBD, has been mainly diagnosed among Afrikaners of Dutch descent, mainly habitants of South Africa [4].

Skeletal manifestations of VBD and Sclerosteosis are the result of endosteal hyperostosis and are characterized by progressive generalized osteosclerosis. The clinical result is enlargement of the jaw and facial bones leading to facial distortion, increased intracranial pressure and entrapment of cranial nerves, mainly CN V, VII, VIII and X. This phenotype is more severe in patients diagnosed with Sclerosteosis, compared to patients with VBD [5].

In this paper an overview of the pathophysiology of VBD and a review of the complicated embryology and anatomy of the skull base and CN V, VII, VIII and X is presented.

Material and Methods

A literature search on VBD and Sclerosteosis was conducted using PubMed, Medline, EMBASE and the Cochrane Library. The search strategy contained the following key words: Van Buchem Disease; Sclerosteosis; Osteochondrodysplasias; Sclerosing bone dysplasia. To enrich the results, Medical Subject Headings were incorporated within the search. Additional articles were included by cross-referencing.

With regard to the anatomy and embryology of the base of the skull or the cranial nerves in the oro-cervico-facial region, a mini-review was performed using various databases, including PubMed, Medline, EMBASE and the Cochrane Library and textbooks such as anatomical atlases.

Results

Embryological development of the base of the skull

The cranial base forms an important skeletal structure that provides protection and support of the brain [6]. Proper development of the base of the skull is paramount in the unimpeded passage of nerves and blood vessels through the skull base foramina. The development of the cranial base is regulated by several genes, including the Indian hedgehog-, Sonic hedgehog- (Shh-), Matrix metallopeptidase 9-genes and genes from the Dickkopf family [7-11].

The aforementioned genes and their appurtenant pathways among others, contribute to endochondral ossification of the skull base, which is a highly precise orchestration of cellular and molecular events [12-14]. Early in human development, the cranial base appears to be a sheet of undifferentiated mesenchymal cells. Endochondral bone formation starts with the formation of a cartilage template from condensed mesenchymal cells within this sheet. Chondrocytes in the center of the cartilage template undergo hypertrophic changes and subsequently undergo apoptosis. The vacant spaces within the cartilage template, called the primary ossification centers, undergo invasion of osteoblasts.

Both the cranial base and the long bones undergo this proces of endochondral ossification. However, in comparison to the chondrogenesis of the axial skeleton, the skull base develops cartilage in a later stadium. The postponed chondrogenesis of the skull base seems to be due to its insensitivity to Shh signaling [11]. The mesenchymal sheet forms the chondrocranium after condensation, chondrification and fusion of numerous individual cartilages [15].

The cranial base contains multiple growth centers to drive cranial and upper facial development. The growth centers of the prechondral, hypophyseal and parachondral cartilaginous plates form the central region of the cranial base [16]. These plates shape an uninterrupted cartillaginous structure spanning from the foramen magnum to the interorbital region. As development advances, ossification centers outline the ethmoidalFb; prespheoid; basisphenoid; and occipital bones [12,16]. Because development of cartilage through mesenchymal condensation occurs after the formation of organs, nerves and blood vessels, foramina develop on their specific locations [17].

Anatomy of the trigeminal nerve (CN V)

The trigeminal nerve forms the sensory supply of the orofacial region and provides motor innervation of the mastication muscles. From the peripheral orofacial region, multiple branches of the trigeminal nerve can be recognized. All these branches can be categorized into the three main branches of the trigeminal nerve that course towards the trigeminal ganglion: n. V1, V2 and V3, the ophthalmic, maxillary and mandibular nerve, respectively. The ophthalmic nerve has three peripheral branches, the lacrimal, frontal and nasociliar nerve. It courses through the superior orbital fissure after which it sprouts of the meningeal recurrent nerve. The sensory root of the pterygopalatine ganglion and the zygomatic and infraorbital nerves are the terminal nerves of the maxillary nerve. The zygomatic and the infraorbital nerve exit the orbital cavity via the inferior orbital fissure. The aforementioned three maxillary nerves fuse within the pterygopalatine fossa after they passed through the foramen rotundum. The mandibular nerve consist of four terminal branches: the lingual-, inferior alveolar-, auriculotemporal- and masticator nerves. The mandibular nerve emerges from the lateral part from the trigeminal ganglion, exits the cranial cavity through the foramen ovale and immediately passes between the tensor veli palatine muscle (medial border) and the lateral pterygoid muscle (lateral border). After exiting the skull, the meningeal branch and the medial pterygoid nerve are given off. The nerve then divides into two parts: a small anterior and large posterior trunk. The anterior division innvervates the mastication muscles, whereas the buccal nerve provides sensory to the cheek. From the posterior division three main sensory branches sprout, the auriculotemporal, lingual and inferior alveolar nerves. Furthermore, the motor fibers of the mandibular nerve supply the mylohyoid muscle and the anterior belly of the digastric muscle [18-23].

From the trigeminal ganglion, a motor and sensory rootlet course towards the lateral part of the pons where they enter the brainstem. The trigeminal tract runs in a dorsomedial direction, penetrates the middle cerebellar peduncle and then spreads over the central trigeminal nuclei 1) the mesencephalic nucleus; 2) the principal sensory nucleus; 3) the motor nucleus and; 4) the spinal trigeminal nucleus [24]. The mesencephalic nucleus is responsible for adjusting the bite by conveying proprioceptive fibers from the masticatory muscles, teeth, periodontium, hard palate and the temporomandibular joint. It also plays a prominent role in the function of the extraocular muscles [25]. The principal sensory nucleus is arranged in a dorsoventral organization; the mandibular division terminates most dorsal, the maxillary division intermediate and the ophthalmic division ventral. The principal sensory nucleus conduct both vital and gnostic sensory information of the orfacial region. The fibers of this principal sensory nucleus are both crossed and uncrossed and end in the ventral posteromedial nucleus of the thalamus. The trigeminothalamic tract is formed by the crossed fibers that originate from the ventral part of the principal sensory nucleus which ascend together with the controlateral medial lemniscus. The uncrossed fibers, originating from the dorsomedial part of the nucleus, ascend near the periaquaductal gray. The motor nucleus is located more medial from the principal sensory nucleus. Axons of the mesencephalic nucleus form a reflex arc in the modulation of the force of the bite together with the motor nucleus. The spinal trigeminal nucleus transmits pain and temperature. It extends from the midpons to the level of C2-C4 of the spinal cord and is located anterolateral to the fourth ventricle. It consists of three parts: an oral, interpolar and caudal part. The oral part receives sensory information of structures inside the nose and mouth. The interpolar part is related to the skin of the orofacial region whereas the caudal part represents the sensory information of the forehead, cheek and jaw [24].

Anatomy of the facial nerve (CN VII)

The course of the facial nerve can be subdivided into the intracranial segment, the segment in the facial canal and the extracranial segment where it pierces the parotid gland. In the cerebellopontine angle, in the caudal part of the tegmentum of the pons, the motor part of the facial nerve originates between the oliva and pons. Together with the vestibulocochlear nerve, the facial nerve runs through the internal acoustic pore. The facial nerve then courses through the petrous part of the temporal bone (pyramid) via the internal auditory meatus and canal into the facial canal. In this canal the nerve gives off the nerve to the stapedius. The motor part of the facial nerve runs through the stylomastoid foramen, posterior to the temporal styloid process, and forms an intraparotid plexus. Its peripheral motor branches, the temporal, zygomatic, buccal, marginal mandibular and cervical branch, can be found at the anterior edge of the parotid gland. Small communicating branches between other nerves and intercommunicating branches are discussed by others previously21. The facial nerve, however, does also contain visceromotor and parasympathic fibres. The parasympathic fibres, responsible for the correct action of the salvitory glands, run in the chorda tympani nerve. This nerve also provides taste in the anterior two-thirds of the tongue. When the fibers exit the glands and tongue they converge and run along

the lingual nerve (n. V3). This peripheral part runs towards the chorda tympani nerve and joins the facial nerve deep in the pyramid [21, 26-29].

Anatomy of the vestibulocochlear nerve (CN VIII)

The eighth cranial nerve consists of two different parts: a cochlear and vestibular part. The cochlear nerve originates as the organ of Corti (spiral organ) on the basal membrane of the cochlear membrane and sensors the orientation of the head in relation to the body. The axons of the cochlear nerve in the spiral organ are grouped together on the cochlea. The neuronal fibres of the peripheral neurons are connected to the cilia cells on the spiral lamina. The vestibular nerve arises from the junction of the superior and inferior vestibular nerves in the vestibular ganglion and has a sensor function in the balance and . Together with the cochlear nerve it runs through the temporal bone in the internal auditory canal and enters the cranial fossa through the internal acoustic pore [25-27]. The cochlear nerve lies posterolaterally to the vestibular nerve and together with the facial nerve it fills up the internal auditory canal [27]. The vestibulocochlear nerve crosses the cerebellopontine angle in the sagittal plane and enters the brainstem near the flocculus of the cerebellum in the cerebellopontine angle. The ampullary fibres join the superior (Bechterew nucleus), lateral (Deiters nucleus), medial (triangular) and inferior nuclei, which together form the four vestibular nuclei and can be found in the brainstems' rhomboid fossa. The saccular fibres terminate in the inferior vestibular nucleus and the utricle fibres end in the inferior and medial nuclei [30,31].

Anatomy of the vagal nerve (CN X)

The nucleus of the vagus nerve is shared with the glossopharyngeal nerve because they share sensory and motor function. Together with the accessory nerve and the glossopharyngeus nerve, the vagus nerve courses through the jugular foramen [25]. After exiting the skull, the vagus nerve has an extensive course through the human body, which is not considered to be within the scope of this review.

Pathogenesis of VBD and sclerosteosis

In order to understand the several clinical features of VBD, it is essential to comprehend that the compression of the cranial nerves, caused by the excessive formation of bone, is the common origin of the different symptoms. VBD as well as Sclerosteosis is caused by the lack of a regulatory element of the SOST gene (17q12-21), which encodes for sclerostin,

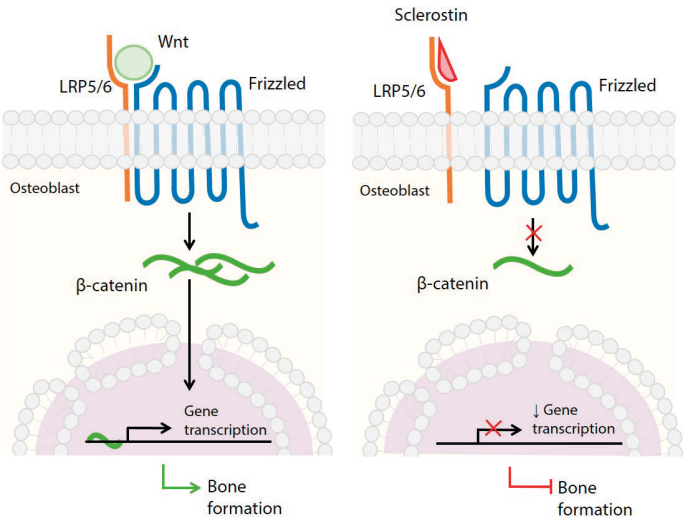

Figure 2: *Schematic model of antagonized canonical Wnt signaling. Canonical Wnt signaling involves formation of complexes of Wnts with Frizzled receptors and LRP5/6 co-receptors, resulting in the accumulation of β-catenin in the cytoplasm and translocation into the nucleus. The antagonist sclerostin inhibits canonical Wnt signaling by binding to probably the first β-propeller of LRP5/6. Whether sclerostin requires a cofactor like Kremen for Dkk1 to exert its antagonistic effect remains to be established.*

an osteocyte-derived protein that inhibits the formation of bone. In VBD a 52 kilobytes deletion can be found, 35kb downstream of the SOST-gene [32,33]. In Sclerosteosis, multiple SOST mutations have been reported thus far: three distinct stop mutations in families of Afrikaner, Brazilian, and mixed descent (northern European/Native American/African American) [34,35], a splicing mutation in an individual of African heritage from Senegal, and a missense mutation in siblings of Turkish stock [36].

SOST mRNA is expressed in many tissues during the embryonic development. Most postnatal tissues on the other hand, do not show these amounts of the sclerostin-protein. Terminally differentiated cells embed-

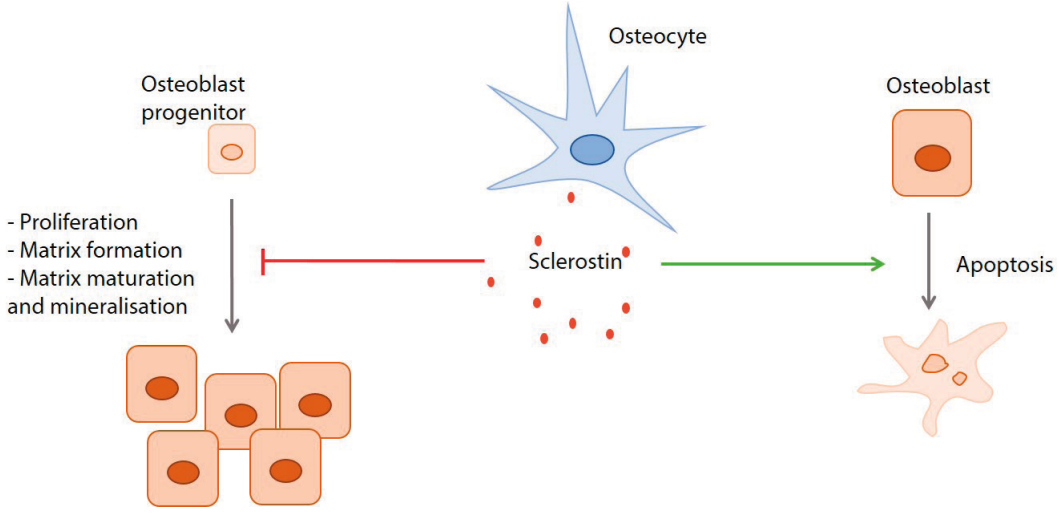

Figure 1: *Schematic model of the regulation of sclerostin on osteoblast development and survival. Sclerostin produced and secreted by osteocytes inhibits the formation of bone by inhibiting osteoblast proliferation and early and late differentiation and stimulating osteoblast apoptosis.*

ded within a mineralized matrix like osteocytes, mineralized hyperthrofic chondrocytes and cementocytes do express the SOST-mRNA in the postnatal situation. Osteoclasts, osteoblasts and bone lining cells on the other hand cannot produce sclerostin after birth [37]. The function of sclerostin mainly consists of an inhibitory effect on formation of bone for it decreases the life span of the osteoblasts by stimulating their apoptosis [38]. In knockout mice, formation of bone seemed to be increased. The skeleton of these mice showed a significant increase in radio density, bone mineral density and cortical and trabecular bone volume, bone formation and bone strength [39]. Molecular studies discuss the molecular pathway of sclerostin (Figure 1) as a member of the so-called DAN (differential screening-selected gene aberrant in neuroblastoma) family of glycoproteins. These glycoproteins can be subdivided into two different categories, the BMP-antagonists and Wnt-antagonists respectively. LRP5, a cofactor in canonical Wnt signalling, seems to be of great importance in the formation of bone. Sclerostin has been shown to bind LRP5 and the closely related co-receptor LRP6 to antagonize Wnt-signaling, which shows that sclerostin is a member of the Wnt-antagonists. Stimulation of the G-receptors via the Wnt-pathway causes β-catenin, an intracellular signalling molecule, to accumulate and translocate into the nucleus of the cell where it initiates transcription of target genes and increases bone formation. However, as sclerostin is a Wnt-antagnost, stimulation of the G-receptors by sclerostin causes proteosomal degradation of β-catenin, resulting in bone resorption and decreased bone formation. In order to understand the pathogenesis of VBD, it is necessary to understand when sclerostin is not available. When sclerostin is not available, β-catenin will not undergo proteosomal degradation by formation of an intracellular complex of proteins, which indicates that the "off-switch" of bone formation is not present. A part of this cascade is depicted in Figure 2 [37].

Clinical appearances of VBD and sclerosteosis

Clinical features of VBD include craniofacial abnormalities such as a high forehead, frontal bossing and a widened and thickened chin, as is depicted in Figure 3. Interestingly, VBD may be differentiated from other forms of widespread bony sclerosis such as osteopetrosis (Albers-Schonberg's disease), myelosclerosis and progressive diaphyseal dysplasia (Camurati Engelmann disease) because it causes cortical bone thickening along the shafts of long bones, clavicles, ribs and to a major degree of the skull bones and mandible. The pelvis and metaphyses show less marked changes however [40,41]. Radiological findings were increased thickness and hyperostosis of the calvaria, base of the skull and the mandible. Also, thickening of the cortex of the metacarpal bones and the phalanges is

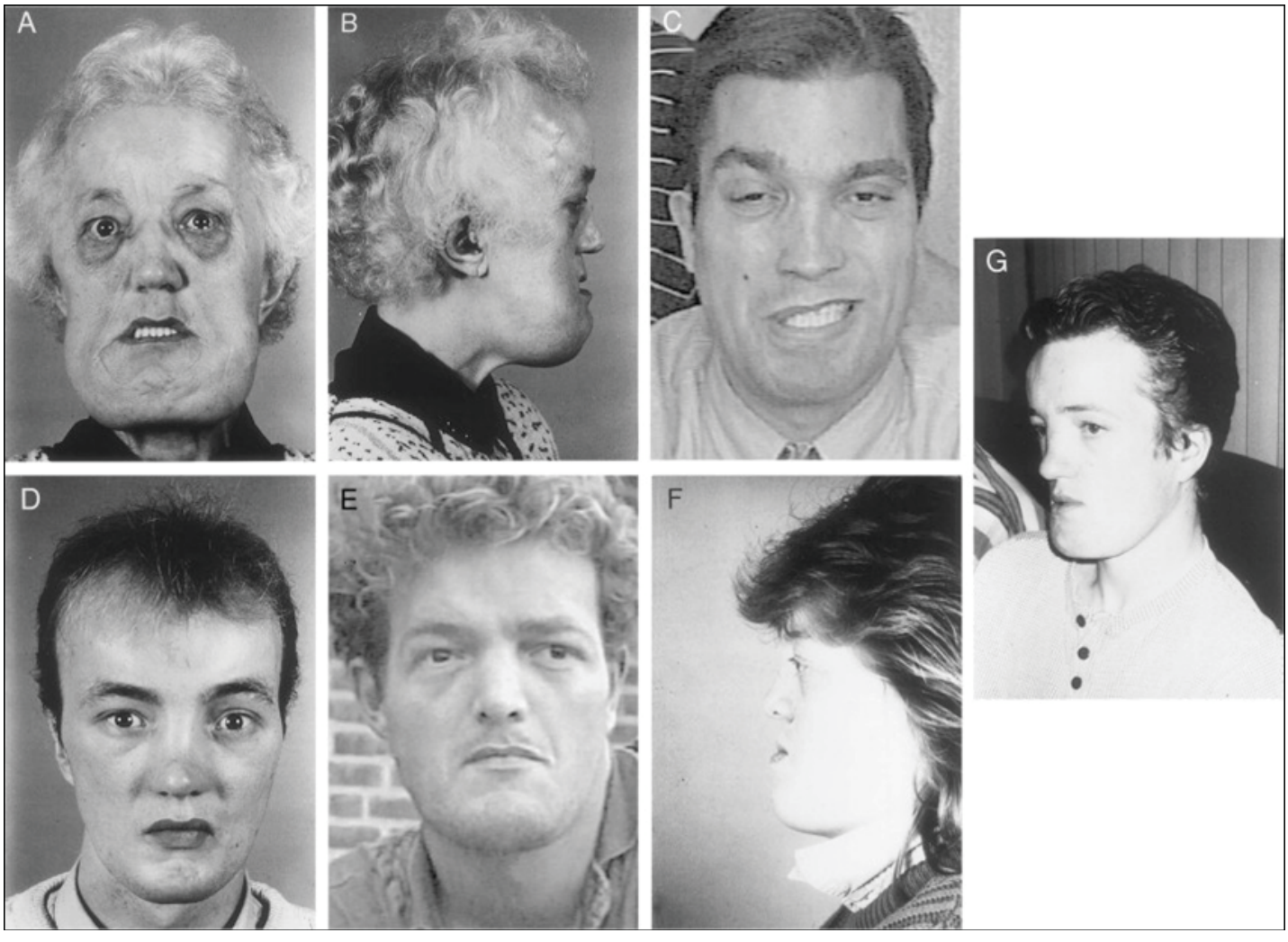

Figure 3: *Reproduced from Van Hul et al. [5]. Clinical pictures of seven patients showing characteristic features of van Buchem disease. Frontal (A) and lateral (B) views of patient 3. This patient, at age 65 years, was the oldest patient studied. C–G, Pictures of the five new van Buchem patients (patients 1, 2, and 9–11, respectively). All patients showed the characteristic features of protruding chin, high forehead, and facial nerve paralysis, as illustrated in panel C.*

seen, albeit the epiphyses are typically spared. Different neurological problems such as a Bell's palsy, sensorineural-, conductive- and mixed hearing loss are mentioned [2,3,40]. The neurological symtoms and craniofacial abnormalities seem to start at the adolescent age and become more prominent throughout life. Exceptional paediatric cases have been described as well [42]. Surgical treatment for both decompression of cranial nerves and re-contouring of the mandible has been reported with satisfactory results, although treatment must be repeated multiple times [43]. Currently, antibodies against cathepsin K and SOST and ClCN7 inhibitors are being developed by several pharmaceutical companies [44].

Clinical features of Sclerosteosis are alike of those of VBD. Again gross sclerosis and hyperostosis of the skull can be observed, including facies-mandibular overgrowth and asymmetry. Characteristic for Sclerosteosis is proptosis, typical hyperosteosis of the pelvis, syndactyly and other digital malformations. Facial palsy, deafness, blindness and increased intracranial pressure are common complications [45].

Discussion

Although VBD is an extremely rare disorder, much is known about its pathofysiological pathways and genetic backgrounds. This discrepancy in uncommonness of the disease and the amount of knowledge seems striking but can be easily explained by the fact that VBD is one of many sclerosing bone disorders. The plurality of sclerosing bone disorders makes this a diagnostic challenge. Main disorders that can induce high bone mass in adults can be categorized as 1) acquired; 2) iatrogenic; and 3) genetic. The acquired disorders consist of sclerosing metastasis (i.e. neoplasms from prostate or breast), myeloma, myelofibrosis, secondary hyperparathyroidism or secondary to hepatic infection (i.e. hepatitis C). The iatrogenic disorders can be caused by a surplus of bisphosponates or fluor. A wide variety of genetic disorders exist. Genetic disorders that cause endosteal hyperostosis include VBD, Worth Syndrome and Sclerosteosis [44,46]. These rare hereditary sclerosing bone disorders have shed light on multiple physiological pathways of bone cell metabolisms. The newly discovered genes and the pathways that come forth from this are new targets for pharmacological treatment not only of extremely rare disorders, but also of more common disorders such as postmenopausal osteoporosis. For example, the aforementioned antibodies against cathepsin K and SOST and ClCN7 inhibitors that were developed by several pharmaceutical companies [44]. Still, many factors of VBD and Sclerosteosis remain largely elusive. For example, as paediatric cases are exceptional, it remains unclear why the foramina start to be subject to excessive bone formation later in life, rather than in childhood age. Further research on these topics can provide insight in the activity of bone cell metabolisms through life, enriching the knowledge about mechanisms involved in bone formation disorders.

Immense embryological questions, however, remain unanswered. For example, what prevents the foramina from being obstructed by new bone formation? To gain insights in the embryology of nerves and bony landmarks, classical embryological studies must be critically reviewed. However, studies that investigate the neuroanatomy and -embryology by staining and microscopic research of the cranial nerves and related neuronal migration remain of great importance. For example, a more recent published report discussed neural migration of the cranial nerves in the embryological development and provided new insights in the morphological features of cranial nerves [47].

Another project that sheds new light on embryological questions, is the 3D-project performed at the AMC in Amsterdam, which provides 3D-models of different embryological structures [48,49]. These new articles and projects herald the start of a new era in embryological research.

Conclusion

VBD and Sclerosteosis have proven to be diseases with a fascinating pathophysiological pathways that can provide many insights in normal bone cell metabolisms. These insights may contribute in better understanding and treating other, more common bone diseases such as osteoporosis. Furthermore, the symptoms of compression of the cranial nerves are a great vehicle to review the intricate embryological development of the cranial base and the cranial nerves.

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