

VAN BUCHEM'S SYNDROME

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1. Core Definition

Van Buchem's Syndrome (VBS), formally known as Hyperostosis Corticalis Generalisata, is an exceedingly rare genetic disorder characterized by progressive and generalized thickening and hardening of the bones, a condition termed **hyperostosis** and **sclerosis**. This syndrome is classified as a sclerosing bone dysplasia. The primary pathology involves excessive bone deposition throughout the skeleton, which significantly impacts the skull, face, mandible, clavicles, and the shafts of long bones. Unlike some other forms of generalized skeletal overgrowth, VBS is specifically an **autosomal aberration**, typically inherited in an autosomal recessive pattern, signifying that an individual must inherit two copies of the defective gene, one from each parent, to manifest the condition. The severity of the syndrome often relates directly to the mechanical consequences of this unchecked bone growth, particularly the encroachment upon critical neurological structures.

The crucial functional definition of VBS centers on the resulting compromise of nervous system function, often observed when the expanding bone compresses cranial nerves as they exit the skull base or pass through narrowed foramina. This compression frequently leads to the syndrome's most debilitating symptoms, including **facial paralysis**, progressive **sight loss** (optic nerve compression), and profound **hearing loss**. The auditory impairment is often compounded by **Otosclerosis**, the abnormal growth of bone in the middle ear, further interfering with sound conduction. Clinical indicators generally begin to appear near the age of **pubescence**, though the underlying skeletal changes may commence earlier, necessitating early diagnosis and management to mitigate irreversible neurological damage.

2. Etymology and Historical Development (The Discoverer)

Van Buchem's Syndrome is aptly named for its founder, the Dutch physician **Francis Steven Pete Van Buchem** (1907-1997). Van Buchem, a distinguished internist and professor of medicine at the University of Groningen, first described this novel clinical entity in the mid-twentieth century. His initial comprehensive descriptions detailed the characteristic radiological and clinical findings of generalized cortical hyperostosis affecting multiple members of specific families, distinguishing this condition from milder or related forms of bone dysplasia. The original case studies provided the medical community with the foundational understanding of the syndrome's unique blend of skeletal pathology and neurological consequences.

The significance of Van Buchem's work lies in the meticulous classification of a disorder previously

undifferentiated within the broad category of skeletal hyperostoses. His research provided the clinical framework that allowed subsequent geneticists and molecular biologists to pinpoint the precise molecular cause. By documenting the familial clustering and the specific pattern of bone thickening--particularly the involvement of the skull, face, and trunk--Van Buchem established the syndrome as a distinct, genetically determined disease, separating it from diseases acquired later in life or those resulting from metabolic imbalances.

3. Pathophysiology and Genetic Basis

The fundamental pathophysiology of VBS is rooted in a disruption of the body's delicate mechanism for regulating bone density and turnover. VBS is caused by specific mutations in the **SOST gene**, located on chromosome 17q12-q21. The SOST gene provides instructions for making a protein called **sclerostin**, which is primarily produced by osteocytes (mature bone cells) and acts as a potent negative regulator of bone formation. Sclerostin functions by inhibiting the **Wnt signaling pathway**, a central cascade responsible for stimulating osteoblast activity (bone-building cells).

In the case of VBS, the SOST gene typically carries a large deletion or a null mutation, resulting in a complete absence or severe deficiency of functional sclerostin protein. Without the natural braking mechanism provided by sclerostin, osteoblasts become excessively active, leading to relentless, uncontrolled bone formation (hyperostosis). This constant deposition of new, thick cortical bone explains the widespread bone thickening observed throughout the skeleton, which is the hallmark radiological feature of the syndrome. The excessive bone growth is not simply cosmetic; it is fundamentally structural, leading to the clinical complications detailed below.

It is critical to distinguish VBS (autosomal recessive inheritance, complete sclerostin deficiency) from its phenotypically similar, but genetically distinct, counterpart, Sclerosteosis (autosomal recessive, often caused by mutations in the LRP5 gene or SOST mutations resulting in some residual function). While both disorders involve excessive bone growth, the severity, onset, and specific patterns of skeletal involvement can differ, underscoring the importance of molecular confirmation via genetic testing for accurate diagnosis.

4. Clinical Manifestations (Key Characteristics)

The clinical presentation of Van Buchem's Syndrome is dominated by the consequences of skeletal overgrowth, which typically becomes evident during late childhood or early adolescence, aligning with the observed onset near the age of **pubescence**. The most striking characteristic is the general thickening of the bones, particularly the skull and face. This involves an enlargement of the mandible (macrognathia), leading to a prominent jawline and often causing difficulty with dental alignment and mastication. The facial bones become progressively thickened, sometimes resulting

in a characteristic coarse facial appearance.

Neurological complications represent the most serious aspect of the syndrome. As the skull base thickens, the small canals and openings (foramina) through which cranial nerves pass become dangerously narrow, leading to compression neuropathies. Compression of the optic nerve (Cranial Nerve II) is common, often resulting in progressive vision loss and potentially blindness if not addressed. Similarly, compression of the facial nerve (Cranial Nerve VII) causes unilateral or bilateral **facial paralysis**, impairing facial expression and muscle function. Furthermore, the auditory nerve (Cranial Nerve VIII) and the associated structures within the temporal bone are compressed, leading to severe sensorineural hearing loss, frequently accompanied by the conductive hearing loss caused by **Otosclerosis**.

Beyond the craniofacial region, the trunk and limb bones are also affected. The diaphyseal cortex of the long bones (such as the femur and tibia) thickens significantly, often appearing abnormally dense on radiographs. This hyperostosis, while increasing bone mass, paradoxically does not guarantee bone strength; these bones can still be prone to pathological fractures, particularly following trauma, due to the compromised quality of the rapidly deposited bone matrix and remodeling defects.

5. Diagnosis and Differential Diagnosis

Diagnosis of Van Buchem's Syndrome relies on a combination of clinical presentation, radiographic findings, and molecular genetic confirmation. Radiographic studies are essential, typically revealing generalized **hyperostosis corticalis**, defined by dense, thickened cortical bone throughout the skeleton. Key radiological features include marked thickening of the calvaria (skullcap) and skull base, obliteration of the paranasal sinuses, prominent mandibular enlargement, and diffuse sclerosis of the long bone diaphyses. Bone density scans (DXA) typically confirm extremely high bone mineral density, often exceeding the measurement capabilities of standard equipment.

Differential diagnosis is crucial, as several other sclerosing bone dysplasias present with similar features. The primary condition to exclude is **Sclerosteosis**, which is also an autosomal recessive condition involving the **SOST** gene locus but typically presents with greater severity, including syndactyly (fusion of fingers or toes), which is generally absent in VBS. Other conditions that must be ruled out include Camurati-Engelmann disease, Osteopetrosis (marble bone disease), and Paget's disease of bone, especially in adult-onset cases. Genetic testing confirming null mutations or large deletions in the **SOST** gene provides the definitive diagnostic confirmation, distinguishing VBS from these other disorders.

6. Treatment and Management

Currently, there is no curative treatment for the underlying genetic defect causing Van Buchem's Syndrome; therefore, management is focused entirely on addressing the clinical complications arising from the progressive skeletal overgrowth. The cornerstone of management involves careful monitoring of the cranial nerves to detect early signs of compression.

Surgical decompression is often necessary to preserve neurological function. If vision or hearing loss progresses rapidly due to bony encroachment, neurosurgical intervention may be required to relieve pressure on the optic, facial, or auditory nerves. These surgeries are technically challenging due to the extreme hardness and density of the sclerotic bone. Regular audiology assessments and ophthalmological examinations are mandatory to track the progression of sensory deficits. Furthermore, orthopedic management may be required for fractures or for addressing deformities related to the bone overgrowth in the limbs and joints.

Looking forward, therapeutic research is increasingly focused on targeted pharmacological interventions. Given that VBS results from a deficiency of the sclerostin protein, research into agents that can regulate osteoblast activity or potentially replace sclerostin function is ongoing. Furthermore, the development of treatments for the related condition, osteoporosis, involving anti-sclerostin antibodies, has provided profound insights into the Wnt signaling pathway, potentially paving the way for future gene therapies or targeted molecular treatments for VBS itself.

7. Significance and Impact

The study of Van Buchem's Syndrome has had a significance in medical science far exceeding its low prevalence. Due to the clear genetic mechanism--a functional knockout of the sclerostin protein--VBS serves as a critical model for understanding the physiological role of **sclerostin** and the **Wnt signaling pathway** in human bone metabolism. Insights derived from VBS patients have been foundational in developing novel pharmacological agents, such as monoclonal antibodies against sclerostin (e.g., Romosozumab), which are now successfully used to treat severe postmenopausal osteoporosis by promoting bone formation.

Thus, VBS has transitioned from being merely a rare, debilitating disorder to a key piece of evidence proving the central regulatory role of the SOST gene in determining skeletal mass and architecture. The legacy of Van Buchem's initial description extends into modern endocrinology and osteology, providing essential validation for therapeutic strategies aimed at modulating the fundamental processes of bone formation and resorption for broader public health concerns.

Further Reading

[Wikipedia: Van Buchem disease \(Hyperostosis corticalis generalisata\)](#)

[Online Mendelian Inheritance in Man \(OMIM\): Hyperostosis Corticalis Generalisata](#)

[National Institutes of Health \(NIH\) Genetics Home Reference: SOST Gene](#)

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