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Skeletal Dysplasia in Two Indian Siblings under Individualised Homeopathic Care: CaseReports and Literature Review

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Abstract

van Buchem Disease (VBD) and sclerosteosis are two types of skeletal dysplasia that are extremely rare, and rarer still in the Indian context. They are mutations of the SOST gene that codes for sclerostin, an inhibitor of anabolism in bones. As a result, excessive bone deposition occurs, especially in the skull, leading to a spectrum of clinical symptoms. A detailed literature review shows lack of clarity regarding their presentation, management and prognosis. We present cases of two Tamil siblings born to consanguineously wed parents, diagnosed of skeletal dysplasia. While genetic testing was not done in their cases, VBD/sclerosteosis seem to be the most likely diagnosis. They were managed through out with classical homeopathy. The older sibling who was 18 years old at the time of first intake, had severe behavioural issues along with vision and hearing loss, had mild improvement in them but succumbed to complications of anaesthesia while being treated for an injury. The younger sister presented along with the older brother, when she was 11 years old, with minimal loss of vision in the left eye. Her condition stabilised under classical homeopathy and the MRI showed halt in progress of the disease, one year into the treatment. She has been followed up for over 9 years and is a thriving adult with minimal symptoms at present. The two cases of rare skeletal dysplasia (probably VBD/sclerosteosis) outline the salient features of this disease in an Indian context. While no causality may be attributed to classical homeopathy for the halting of the disease, there were clear

improvements in vision and hearing under this treatment in both the siblings. These observations need to be extended with scientific studies to make any conclusion about the treatment.

Keywords: van Buchem disease; Sclerosteosis; SOST protein; Case report; Classical homeopathy

Introduction

Skeletal dysplasia (ICD10 Q79.9) [1] is a heterogenous group of over 40 types of bone and cartilage disorders, known to occur in 1/5000 children [2]. They may lead to vision loss, hearing impairment and neurological symptoms. The effect of the disorder may be relatively mild, to lethal [2]. Of these, van Buchem Disease (VBD) and scleorsteosis are two of the autosomal recessive sclerosing bone dysplasias, relatively rare and with uncertain course. Both involve mutation in the SOST gene, which encodes for the protein sclerostin [3,4], and inhibits anabolism in bones. Therefore, the mutation causes excess bone mass. VBD (OCD10 M85.2; OMIM entry #239100) [1,5] is a very rare form with only around 30 reported cases so far, and mostly from Dutch ancestry. There are about a hundred reported cases of sclerosteosis (ICD10 M85.8, OMIM entry #269500) [1,5], which has a more severe clinical effect than VBD [6]. Few people with sclerosteosis survive into old age [7]. While both disorders are characterised, at the molecular level, by increased new bone deposition by osteoblasts, the difference is apparent clinically in the presence of syndactyly, craniotubular bone involvement and a shortened life span in the sclerosteosis patient [7,8]. Both disorders show characteristic high forehead with frontal bossing, wide nose bridge and protruding mandible. Radiologically, there is hyperostosis of calvaria, skull base and mandible. There may be narrowing of internal acoustic meatus, the foramina of the facial nerve, optic nerve, trigeminal nerve and the auditory nerve [7,9,10]. These may in turn lead to related clinical symptoms such as vision impairment, facial palsy, hearing loss, trigeminal neuralgia and anosmia [7]. Raised intracranial pressure may result from reduced intracranial volume and may even prove fatal, especially in sclerosteosis. Distinguishing VBD from sclerosteosis is difficult by phenotype observation alone. There is probably just the higher severity and syndactyly present in sclerosteosis [11,12]. While VBD has been mostly reported in the Netherlands, there have been some reports from Germany and Taiwan [13,14]. Sclerosteosis has been reported in Afrikaners, other parts of Africa, Europe, India, USA and South America. There has been a report of sclerosteosis occurrence in Tamil families in India with history of consanguineous marriages [14-19]. However, there are no reports of VBD from India, as far as the authors are aware.

VBD is classified into two types. Type1 where the bone deposition continues throughout life and a high level of alkaline phosphatase is found in blood. Type 2, known also as Worth disease shows cessation of the bone deposition by the 20th year and the alkaline phosphatase level in blood is normal during adult life [20]. Regarding management, it is usually symptomatic. Case reports on both VBD and sclerosteosis provide varied observations. While Hsu and colleagues report that surgery was not beneficial in their case, Datema et al. report that decompression surgery of the skull was helpful in reducing dysaesthesia and cognitive impairment [13]. As early as in 1988, there has been a report of mandible recontouring for cosmetic purpose in a case of VBD [21]. An earlier case report of siblings with VBD reports onset of symptoms in early adult life and benefit from decompression surgery and partial craniectomy. However, later in life, they still developed cerebellar deficit and paraparesis [22] Therefore, there is no clarity on long term benefit from the surgical approach. Here, we present cases of two siblings with skeletal dysplasia, with predominantly VBD features but without clarity on whether it was VBD or sclerosteosis, who were managed with

classical homeopathic therapy. The authors are not aware of similar report in literature, of skeletal dysplasia under homeopathic care.

Case Series

Case 1

Case presentation: On 4/12/2014, an18-year-old Tamil male presented with loss of vision and hearing to the homeopathic physician. He could not open his eyes and heard no sound at presentation. He also developed recurrent abscesses on face **(supplementary video 1)**.

History of presenting complaints: At the age of 8 years, the patient lost his vision, and his hearing was lost at the age of 15 years. The eyelids had closed up and he could not open them at all. He could not hear anything, and speech was slurred and incomprehensible.

Past medical history*:* He was born of a consanguineous marriage, through forceps delivery. He did not cry immediately after birth and had developed febrile convulsions two days post-partum. He had to be put on Gardinal for 15 days for this and there was no recurrence of the seizures.

The parents reported that patient had mild delay in his milestones and suffered gall stone colic at the age of 12 years. However, no objective assessments of these were available. Parents reported that the patient had three episodes of recurrent fever before the onset of worsening vision.

Family history: Patient's parents were both healthy, but they were first cousins. There were no other known major diseases in the family.

Diagnosis*:* A CT scan of the orbits in 2006 revealed diffuse calvarial thickening and he was diagnosed of polyosteotic fibrous dysplasia, skeletal dysplasia. An MRI of brain and cochlea in 2011 reported diffuse thickening of the calvarium and narrowing of bilateral internal auditory meatus and canals, along with thinning of the bilateral vestibulocochlear nerve bundles **(Figure 1)**.

Homeopathic consultation: The boy exhibited severe behavioural issues **(supplementary video 2)**. He was aggressive, struck people and threatened to kill his parents. He was ambitious, spoke of achieving many things in business and was inclined to pray excessively. The parents were especially concerned about his behavioural issues for which they hoped homeopathy might help.

Prescription: The pathology of the skeletal dysplasia (overgrowth of bone) was considered along with the mental/emotional pathology of excessive ambition and that he prayed a lot. The remedy indicated was Aurum metallicum **[23,24]**. Aurum metallicum 12C was given three times a day for one month.

Follow up and outcome*:* Aurum metallicum 12C resulted in slow improvement in hearing so the remedy was given with increase in potency (up to 24C) in the next 6 months. Later, other remedies were required. The follow up is provided in **Table 1.**

Table 1: Case 1 follow up.

Date	Symptoms		Prescription
08/12/14	Fever for 2 days, Temp – 102º F		Aurum metallicum 12C, five times a day for 2 days.
27/12/14	Fever for 12 days since previous follow up, resolved on its own, no fever now Talks to himself. Restlessness, walks around Eyelids slightly open (left better than right) Abscess on face (painful to touch) Patient speech clearer than last time; excessive and impulsive speech better. Hearing – no change		Aurum metallicum 12C, five times a day for 8 days. Followed by Aurum metallicum 14C, three times a day for 1 month followed by Aurum metallicum 16C, 18C and 20C for one month each, in succession.
12/05/15	Abscess appeared on face and discharged foul pus. Eruptions over chest. No fever in the meantime. Hearing much better. Both eyes open a little now Speech clearer and voice louder. Patient calls out to his mother which he did not do earlier. Excessive and impulsive speech is better Talking to himself increased. Sleeplessness day and night +++	**MRI Brain (01/05/2015) abnormal findings: Figure 4** Diffuse thickening of the bones of skull vault/ base with gross narrowing of internal auditory meatus and canal with compromised bony labyrinth. Suspicious atlanto-axial subluxation noted. Foramen magnum is small with a shallow posterior cranial fossa. Clinoidal process bulky; suggestions of compromised optic canals, right more than left; right orbital globe smaller – microphthalmia? Cranio lacunation noted	Aurum metallicum 22C, three times a day for 1 month
13/06/15	Sleeplessness increased. Breaks things and hits others when angry. Cries after breaking things. Goes out and rolls about on the road in rage. He asks about getting married		Aurum met 24C three times a day for 1 month

29/06/15	Abusive. Violent anger. Does not like the touch of cloth over his body. No sleep for 10 days	Hyoscyamus 10M, one dose
06/07/15	Fever - 102°F Patient is able to sleep after a month of sleeplessness. Behavior has mellowed down He expresses hatred towards parents	Nil
20/07/15	No episodes of fever. Patient was better after Hyoscyamus 10M, was calm and loving towards parents for 1 week after the last fever. Relapse for 1 week, shows anger only on parents, says he wants to kill them. Does not sleep for more than 10 minutes at a stretch. Has taken 2 sips of water and 500 ml of cold soda drink in 2 days.	Hyoscyamus 10M one dose, repeated one dose on 01/08/15
08/08/15	Dances in the night. Strikes and attacks people Speech has been clearer than before; Vision and hearing no further improvement	Tarentula Hispanica 200C, one dose; 1M one dose on 14/08/15 and on 16/08/15
29/10/15	Masturbates in front of people; desires to be naked. Dances all night. Attacks and strikes people without cause	Tarentula hispanica 1M, one dose repeated on 07/11/15
13/12/15	Attacking others has increased. Dancing reduced Wants to be alone. Shouting and crying from 2 to 4 pm every day. Undressing and masturbation persists. Bites people Urination and stool - does not wash or clean himself	Hyoscyamus 10M, one dose. Repeated on 07/01/16
16/01/16	Though the patient is abusive verbally, speech is clearer. Patient slept better Washes himself after stool. Obscene behaviour is considerably better Hearing seems better. No change in vision or speech. Appetite decreased, does not drink water.	Nil

11/02/16	Screaming, shouting, attacking, and striking others increased in the last 5 days. Desires to be naked in bed and masturbation no change Dancing no change Appetite decreased, losing weight. Sleeplessness increased in the last 5 days.	Hyoscyamus 10M followed by 50M one dose the next day.
28/02/16	Dancing no change. Sleeps naked in bed. Does not wash after going to toilet again. Undresses and dances.	Hyoscyamus CM, one dose.
13/03/16	Screaming, Shouting increased in the last 2 days. Dancing – no change Sleeps in the daytime. After the toilet washes by himself if persuaded. Was better for 10 days after medicine. Perspiration increased with eruption on back. Boil on left eyeball appeared 1 week ago. Abscess on right thigh in the last 4-5 days. Aggression is better.	Nil

While there was a slight improvement in the vision, hearing, and speech over the follow up period, the behavioural issues did not respond much. The last homeopathic follow up was on 13/03/16. The patient had an episode of rage, got very aggressive and hit his hand against the TV, causing cuts. He was rushed to the hospital to get stitches, but his violence couldn't be managed even with 3 people restraining him and he was put under anaesthesia. This led to complications and his death shortly after. The benefit from homeopathy was minimal but definite in this case, in the form of improvement in speech, vision and hearing.

Case 2

Case presentation*:* The younger sister of the patient described above was brought for homeopathic consultation on 04/12/2014, same day as her brother consulted the first time. She already exhibited impairment of vision on the left side and facial features of skeletal dysplasia – wide nasal bridge and bossing of forehead **(Supplementary Figure 2)** **(supplementary video 3)**.

History of presenting complaints*:* The girl was born normally, and her milestones were normal. The diagnosis was made in 2006 as a routine check-up because of her brother's condition.

However, the vision had started to deteriorate only recently and was associated with an episode of fever just before it began.

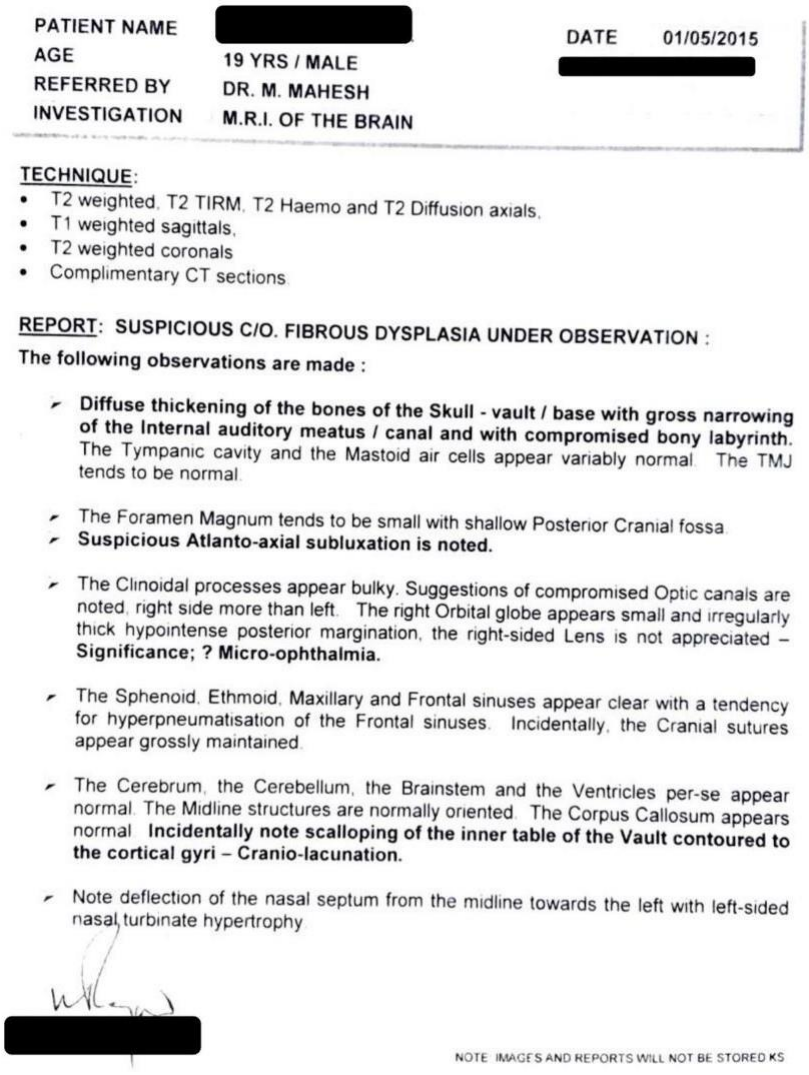
Past medical history*:* she had a state of low vitamin C a few years earlier and had suffered constipation with sheep-dung-like blackish stools as a baby. Her gums were mildly inflamed since many years.

Family History*:* Parents were healthy, but their marriage was consanguineous, and they were first cousins. Brother had been diagnosed with the same condition. She has two younger siblings(twins) who are apparently normal.

Diagnosis: She was diagnosed with skeletal dysplasia in 2006 by an MRI of brain (reports unavailable). She was 3 years old at that time. Another MRI on 25/02/2013 showed diffuse thickening of skull vault and narrowing of neural foramina and bilateral optic canals with Delano Type III optic canals. There was also mild thinning of the optic nerves **(Supplementary Figure 3)**. The most recent MRI Brain at the time of first intake reported as follows:

The patient is a known case of skeletal dysplasia with diffuse thickening of the skull vault and narrowing of neural foramina and bilateral optic canals. Delano type III optic canals. Compared to previous scan no change in size of optic canals and neural foramina.

Repeat MRI on 25/11/2014 **(Supplementary Figure 3)**, compared to previous scan showed worsening of the situation with increase in the mass effect due to diploic space widening of the bones adjacent to the optic canal. Dilatation of optic nerve sheaths was increased; The bones forming the walls of the optic canals appeared more sclerosed; Increase in the narrowing of bilateral internal auditory meatus was noted without significant increase in mass effect; Brain parenchyma appeared normal.



PATIENT NAME [redacted]
AGE 19 YRS / MALE
REFERRED BY DR. M. MAHESH
INVESTIGATION M.R.I. OF THE BRAIN
DATE 01/05/2015 [redacted]

TECHNIQUE:
- T2 weighted, T2 TIRM, T2 Haemo and T2 Diffusion axials.
- T1 weighted sagittals.
- T2 weighted coronals
- Complimentary CT sections.

REPORT: SUSPICIOUS C/O. FIBROUS DYSPLASIA UNDER OBSERVATION :

The following observations are made :

- **Diffuse thickening of the bones of the Skull - vault / base with gross narrowing of the Internal auditory meatus / canal and with compromised bony labyrinth.** The Tympanic cavity and the Mastoid air cells appear variably normal. The TMJ tends to be normal.
- The Foramen Magnum tends to be small with shallow Posterior Cranial fossa.
- **Suspicious Atlanto-axial subluxation is noted.**
- The Clinoidal processes appear bulky. Suggestions of compromised Optic canals are noted, right side more than left. The right Orbital globe appears small and irregularly thick hypointense posterior margination, the right-sided Lens is not appreciated – **Significance; ? Micro-ophthalmia.**
- The Sphenoid, Ethmoid, Maxillary and Frontal sinuses appear clear with a tendency for hyperpneumatisation of the Frontal sinuses. Incidentally, the Cranial sutures appear grossly maintained.
- The Cerebrum, the Cerebellum, the Brainstem and the Ventricles per-se appear normal. The Midline structures are normally oriented. The Corpus Callosum appears normal. **Incidentally note scalloping of the inner table of the Vault contoured to the cortical gyri – Cranio-lacunation.**
- Note deflection of the nasal septum from the midline towards the left with left-sided nasal turbinate hypertrophy.

[redacted]

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Figure 1: MRI of case 1 dated 1/5/2015.

Homeopathic consultation: a totality of her physical and mental suffering was taken into consideration. The basic pathology was that of sclerosis and overgrowth of bones. This was considered along with her psychological suffering of anxiety. She exhibited great anxiety about health and had fears regarding being in the dark, animals (dogs and cats), and of injections. She was an empath and got anxious if someone in the family was not well. Her physical generalities, as it is termed in homeopathic parlance, included increased thirst with craving for cold drinks and aversion/aggravation from eggs. These are important symptoms that indicate a specific remedy in homeopathy [23].

Prescription: Phosphorus 12C three times a day for 1 month. This was increased to 14C on 18/01/2015.

Follow Up and outcome*:* The patient has been followed up for over 9 years and the details are provided in **Table 2.**

Table 2: Case 2 follow up.

Date	Symptoms	Investigations	Prescription
27/12/2014	Blurring of vision in the left eye is slightly better. Height 4.6 ft Weight: 34.1 kg **(supplementary video 5)**		Phosphorous 12C, five times a day for 8 days, followed by 14C, three times a day for 1 month, followed by 16C, three times a day for 23 days
22/02/2015	Fever since last night. Ailments from getting wet. Patient wants warm drinks.		Lycopodium 200C, three times a day for 3 days followed by Phosphorous 16C, four times a day for 10 days followed by 18C, three times a day for 20 days followed by Phosphorous 20C, three times a day for 15 days followed by 20C, five times a day for 15 days
01/05/2015	Acute resolved with Lycopodium. Progressive improvement in vision of the left eye. Patient can recognize dark colors now. Itching in ears Weight: 35.6 kgs	**MRI Brain (supplementary Figure 4a and 4b)** Mild thickening of the skull vault noted with loss of diploic definitions. Internal auditory meatus/canal appears thin along withbony labyrinth. The optic canals appear satisfactorily normal, along with orbits and contents. Note deflection of the nasal septum towards the right with mild left inferior nasal turbinate hypertrophy.	Phosphorous 22C, three times a day for 15 days followed by 22C, five times a day for 15 days; followed by Phosphorous 24C, three times a day for 15 days followed by 24C, five times a day for 15 days

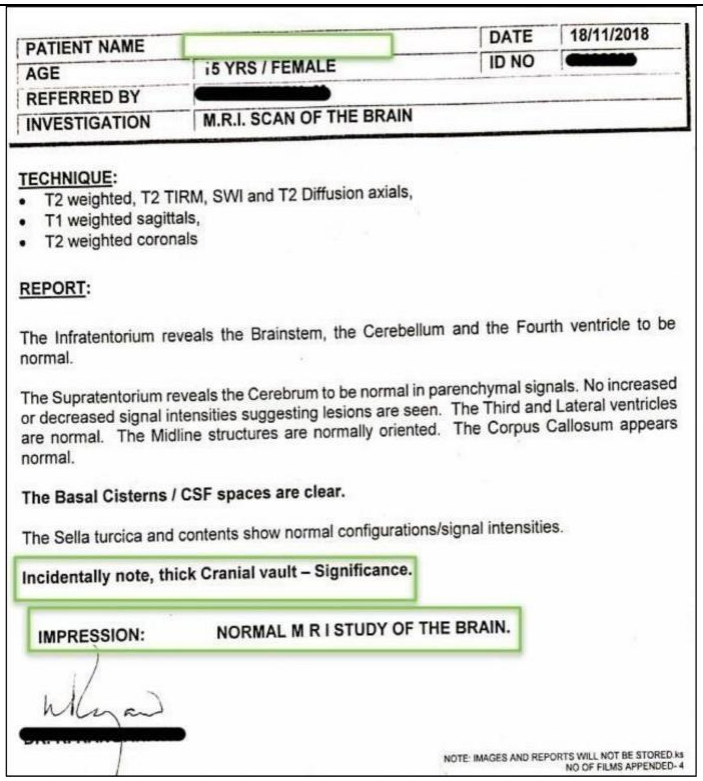
06/07/2015	Fever for 3 days. Fever, aggravated at midnight. Aphthae on tongue. Throat pain, relieved by warm drinks. Nausea during fever		Lycopodium 200C, three times a day for 3 days
20/07/2015	Acute resolved with Lycopodium. Patient has bilateral nasal obstruction with thick, green discharge		Phosphorous 26C, three times a day for the first 15 days followed by 28C for 15 days, 30C for 2 months followed by 32C for 1 month
30/09/2015		**HRCT study of temporal bones (supplementary Figure 5)**: Diffuse thickening of skull bones and facial bones noted. Well defined high density of ~200 – 300 HU with few areas of calcifications within noted in bilateral external auditory canals. Both the ears – middle and inner ear normal findings. Pneumatisation of both anterior clinoid processes and base of pterygoid plates surrounding the optic canals bilaterally	
04/01/2016	Fever (101°F) with headache.		No medication
11/02/2016	Acute resolved without any medication. Vision better than before. Right ear feels obstructed. Eruptions on thighs. Itching in genitalia		Phosphorous 34C, three times a day for 15 days followed by Phosphorous 36C, TID, 15 days followed by 36C, 5 times a day, 15 days followed by 38C for 15 days

22/04/2016	Bedwetting occurred in the last week. Appetite diminished. Ailments from fright (brother's death) Fear of death. Aversion to fruits No change in vision		Ignatia 200C, one dose 15 days followed by Phosphorous 40C for 1 month followed by 42C form 15 days and 44C for 15 days
24/06/2016		**MRI brain dated 24/05/2016 (supplementary Figure 6a and 6b):** Thickening of bony calvarium with inner table lacunations Prominent left sided posterior ethmoidal aircell encroaching onto the infero-medial optic canal – pnuemosinusdilatans	
17/07/2016	Patient attained menarche (06/07/2016). She is 13 years old now. Vision is improving		Phosphorous 44C, TID, 1 month
22/08/2016	Patient developed diarrhoea in the last week. Offensive, loose stools. No change in vision Anxiety about health. Fear of losing vision and hearing (+++) Fear of cats and dogs Craving for bananas		Tuberculinum bovinum 12C, 4 times a day for 1 month
03/01/2017	Fever with chills (102.4^{o}F) Ailments from fright Headache fever during relieved by pressure Nausea during fever		No medication

09/12/2017	Acute resolved without medication Vision is improving Ringing in ears – mild **(supplementary video 6)**		Tuberculinum bovinum 34C, three times a day 1 month
01/03/2018	Sadness Desires death Sadness better by praying Burning in urethra, urination after.		Aurum metallicum 200C, one dose followed by 12C, twice a day 1 month followed by 14C twice a day for 1 month followed by 16C for month
23/07/2018	Complaints are generally better Occasional vomiting and coldness of extremities Weight: 55 kgs		Aurum metallicum 18C, TID, 1 month followed by Aurum metallicum 30C, one dose (on 27/08/2018)
18/11/2018		**MRI brain (Figure 7):Thick cranial vault,otherwise normal study of brain**	
30/01/2019	Ringing in ears, reduced. Coldness of extremities persists. Constipation Appetite increased. Aversion to sweets Anticipatory anxiety++ Timidity in public		Ambra grisea 10M, one dose
19/01/2020		**MRI Brain (supplementary Figure 8a and 8b): No significant neuro-parenchymal abnormality detected**	

11/07/2021		**MRI Brain (supplementary Figure 9a and 9b):** Prominent paranasal air sinuses (more so the bilateral frontal sinuses) and mastoid air cells. Note made of thickened cranial vault. Bilateral optic nerves appear thinned and tortuous with prominent preoptic CSF space.	
14/02/2023	Dizziness and headache for a few days. Vision in the left eye – usually can see sunlight and shadows but this diminishes during headache. Sleepless at night, from dwelling on past disagreeable things. She is craving more salt of late		Natrum muriaticum 10M one dose
10/05/2023	Clinically patient has mild improvement in vision over the years. Auditory symptoms are better compared to before, but the tinnitus persists. Behaviour wise, she has overcome her fears and anxieties and feels joyous. Her menses and secondary sexual characters are normal. She is still under treatment with an effort towards further betterment of vision.		Wait

15/02/24	Generally stable. Headaches occasionally resolve on their own. Psychologically – happy and no sadness or anxiety like before.		Wait



PATIENT NAME [redacted] DATE 18/11/2018
AGE 15 YRS / FEMALE ID NO [redacted]
REFERRED BY [redacted]
INVESTIGATION M.R.I. SCAN OF THE BRAIN

TECHNIQUE:
- T2 weighted, T2 TIRM, SWI and T2 Diffusion axials,
- T1 weighted sagittals,
- T2 weighted coronals

REPORT:

The Infratentorium reveals the Brainstem, the Cerebellum and the Fourth ventricle to be normal.

The Supratentorium reveals the Cerebrum to be normal in parenchymal signals. No increased or decreased signal intensities suggesting lesions are seen. The Third and Lateral ventricles are normal. The Midline structures are normally oriented. The Corpus Callosum appears normal.

The Basal Cisterns / CSF spaces are clear.

The Sella turcica and contents show normal configurations/signal intensities.

Incidentally note, thick Cranial vault – Significance.

IMPRESSION: NORMAL M R I STUDY OF THE BRAIN.

[redacted]

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Figure 7: MRI of Case 2 dated 18/11/2018 – note normal study of the brain.

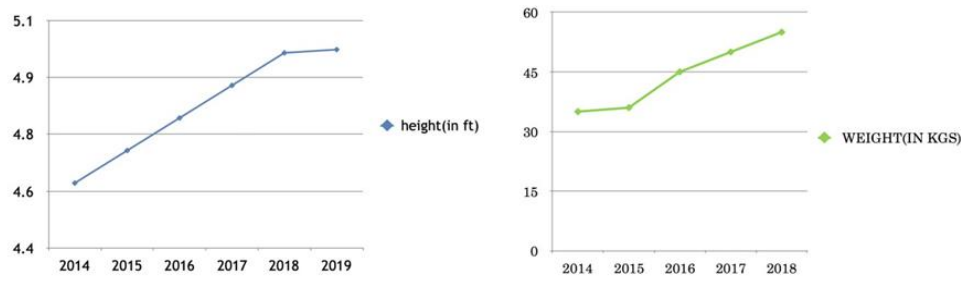
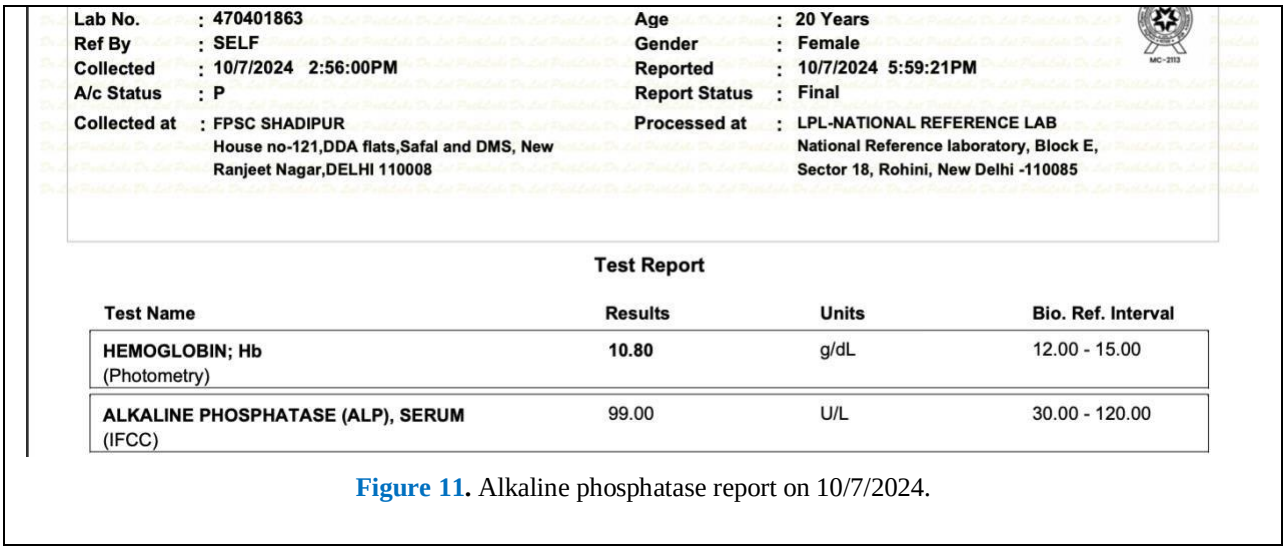


Figure 10: Height and weight of Case 2, over the years.



Lab No.	: 470401863	Age	: 20 Years
Ref By	: SELF	Gender	: Female
Collected	: 10/7/2024 2:56:00PM	Reported	: 10/7/2024 5:59:21PM
A/c Status	: P	Report Status	: Final
Collected at	: FPSC SHADIPUR House no-121,DDA flats,Safal and DMS, New Ranjeet Nagar,DELHI 110008	Processed at	: LPL-NATIONAL REFERENCE LAB National Reference laboratory, Block E, Sector 18, Rohini, New Delhi -110085

Test Report

Test Name	Results	Units	Bio. Ref. Interval
HEMOGLOBIN; Hb (Photometry)	**10.80**	g/dL	12.00 - 15.00
ALKALINE PHOSPHATASE (ALP), SERUM (IFCC)	99.00	U/L	30.00 - 120.00

Figure 11. Alkaline phosphatase report on 10/7/2024.

The main outcome in this case was halting of the disease from progressing further, as evidenced by the repeated MRIs. At the beginning, the disease was on a progressive course but within a year of starting treatment, the progress stopped. Clinically, there has been no worsening of her vision issues. The hearing did not worsen, and she is well enough to work as a radio jockey today. Her height and weight have followed a normal curve for her age and heredity (no stunting or gigantism) **(Figure 3)**. She attained menarche and had regular cycles without event. Her secondary sexual characters are normally developed. The wider nasal bridge, which was very pronounced in her first consultation has become less prominent over the years. The acute infections that she developed over these years initially required homeopathic treatment but those developing in recent years resolved on their own, indicating a stronger immune system. She had fright, depression, and grief during the course of treatment due to circumstances, creating new clinical symptoms. These were handled with homeopathic remedies as well. At the last follow up, the girl was relatively happy and healthy **(supplementary video 4)**. On insistence by the homeopathic physician, the patient underwent investigation for alkaline phosphatase, which turned out to be in the normal range, indicating the Worth disease diagnosis as most likely.

Discussion

In VBD and Sclerosteosis, the symptoms are secondary to thickening of bone. While they are rare, differentiating them from other sclerosing bone dysplasia is difficult and sometimes, more than one type may co-exist **[3,4]**. In the above two cases, genetic testing was not carried out, making it difficult to delegate a definite diagnosis. Clinically, however, it seems to have a milder course and not life threatening, and one of the siblings' alkaline phosphatase was normal, making VBD Type 2, a more likely diagnosis than sclerosteosis. The genetic inheritance is most likely of autosomal recessive type as both siblings were affected in apparently normal, consanguineously wed parents **[25]**. Previously, a detailed study of 15 VBD patients demonstrated that most exhibited facial paralysis as the first symptom, occurring at a median age of 2.5 years. While children exhibited no dysmorphism, the adults showed a large head and some degree of facial distortion. The stature was normal, and no

abnormalities were found in the digits, exostosis of external auditory meatus with fixation of ossicles was detected in one patient. In most cases, the radiology showed thickened calvarium and narrow internal auditory meatus. The effect on hearing and olfaction was minimal and no vision loss was seen in these patients. Lumbar puncture was performed in 3 of these patients to resolve the symptoms arising from increased intracranial pressure. One of these patients had a complete resolution after the procedure, the second had to be given acetazolamide for a few months to achieve resolution, while the third needed a ventricular – peritoneal drain and prednisone to help with the symptoms. In most cases, the symptoms stabilised in adulthood with no complications **[4]**. Another case series described the 13 Dutch patients affected by VBD, 12 of them from the same ancestry. They were 8 males and 5 females, diagnosed based on the radiological and phenotypic findings – hyperostosis of the calvarium and mandible. They all had facial abnormalities including frontal bossing, high forehead, and thick chin. There were some cranial nerve deficits, mainly hearing loss. The authors found that the radiological abnormalities became apparent by the second decade of life and progressed through life **[9]**. The loss of hearing was corroborated by another study, as a feature of sclerosteosis. 55% exhibited severe and 40% profound hearing loss. The investigators found that this was a result of progressive bone formation in the middle ear, internal auditory canal, and the round and oval windows of the cochlea. Conductive, sensory, and neural auditory pathways were compromised **[26]**. Sclerosteosis, in general, has displayed poor prognosis in terms of life expectancy and effect on cranial nerves, as analysed by a South African study. 63 patients of sclerosteosis were analysed for the course of disease over a 38-year period. 34 individuals died, mostly from the effect of calvarial overgrowth resulting in increased intra cranial pressure. The mean age of death was 33 years and there was no difference between males and females. This study also reiterated that facial palsy and deafness were seen in most cases (82%). The 29 who were alive at the time of the survey, were ≤20 years of age **[27].**

Recently, SOST gene mutations were observed in an Italian family, where it had not been found hitherto. This family exhibited severe craniofacial hyperostosis which caused cranial neuropathy in childhood. Chronic headache and obstructive sleep apnoea was observed in the adults. The genetic makeup made a difference to the severity of symptoms, where the homozygous patients had more severe hyperostosis and symptoms compared to the heterozygous **[28]**. Further, it was found that the radiological features of hyperostosis and the cranial nerve deficit becomes more prominent with age, in VBD, suggesting that the gene involved in VBD is actively involved in bone metabolism throughout life **[9]**. The only study that accounts for ophthalmological involvement, as seen in the cases above, describes the effect of intracranial pressure and hyperostosis in causing papilloedema, proptosis, divergent strabismus, and excessive lacrimation. There was no evidence of effect on the 2nd cranial nerve in most patients with sclerosteosis. However, the severe autosomal recessive form caused optic atrophy, microphthalmia, micro cornea, cataracts, and blindness. The autosomal dominant forms did not exhibit involvement of the eye **[12].** The difference in laboratory findings between VBD patients, asymptomatic carriers and healthy controls is shown in **Table 3**. The authors conclude that VBD patients

continue to produce small amounts of sclerostin, which accounts for the milder symptomatology compared to sclerosteosis, where sclerostin is undetectable in blood [4]. Another case of a 37-year-old woman was reported of VBD in association with syringohydromyelia, that probably developed from the thickening of the calvarium. In this case, along with the thickening, there was loss of medullary cavity, cervical canal stenosis, and bilateral herniation of cerebellar tonsils. A syringo-subarachnoid shunt was created in this case to relieve the symptoms [29]. VBD has been reported to present with an associated aneurysmal bone cyst as well [30].

Table 3: Laboratory parameters difference between van Buchem Disease patients, asymptomatic carriers and healthy controls (van Lierop 2013).

Parameter	VBD	Asymptomatic carriers	Healthy controls
Serum sclerostin	mean 8.0 pg/mL 95% CI 4.9-11.0 pg/mL	mean 28.7 pg/mL 95% CI 24.5-32.9 pg/mL p < 0.001	mean 40.0 pg/mL 95% CI 34.5-41.0 pg/mL p[sb12] < 0
Serum P1NP	mean 96.0 95% CI 54.6-137.4 ng/m	mean 47.8 95% CI 39.4-56.2 ng/mL p = 0.003	mean 37.8 95% CI 34.5-41.0 ng/mL p = 0.028
Bone mineral density	mean Z-score femoral neck: 8.7 ± 2.1 spine: 9.5 ± 1.9	mean Z-scores femoral neck: 0.9 ± 1.0 spine: 1.3 ± 1.5	NA

P1NP: procollagen type 1 amino-terminal propeptide; p<0.05 is considered significant.

A recent study in mice demonstrated the molecular mechanism behind the facial phenotype in VBD and sclerosteosis. Deletion of SOST gene resulted in significant overgrowth of the mandible. This was from thickening of the cortical bone and obliteration of vascular spaces. There is a disruption in the ratio of fibrous connective tissue and bone [31].

The effect of homeopathic therapy is impressive in these two cases in that it halted the disease from progressing further much earlier than expected. The second case showed stability, smoothening out of facial dysmorphism and resolution of psychological

affections as well. However, it is difficult to attribute causality in such rare diseases and we need to observe more cases to establish any effect of the homeopathic therapy.

Conclusion

Cases of two siblings with sclerosing bone dysplasia are reported here. There was no clarity in the diagnosis as they were not tested genetically. However, the most likely diagnosis seems to be Worth Disease/van Buchem Disease Type 2. While the established loss of vision and hearing could not be reversed, the children, under individualised homeopathic therapy for a long period, showed cessation in progress of disease much earlier than expected. The older sibling died from complications of anaestheisa during an injury treatment, but the younger sibling is stable and thriving as an adult. As it is a rare disease, causality cannot be attributed for the effect of homeopathy in these cases but we may continue to observe in future cases to establish the effect.

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Data availability: available on request to corresponding author

Supplementary material: available at DOI: 10.6084/m9.figshare.25650261.

Supplementary material (Videos): available at DOI: 10.6084/m9.figshare.25650261 Video 1: Case 1 patient at first intake, exhibiting facial features and abscesses.

Video 2: Case 1 exhibiting aggressive behaviour **Video 3:** Case 2 patient at first intake (4/12/2014). **Video 4**: Case 2 recent follow up (19/11/2018).

Video 5: Case 2 at 3 weeks after starting homeopathic treatment (27/12/2014) Video 6: Case 2 on 9/12/2017.

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