Comprehensive Clinical Report: Patient's Experience with Hajdu-Cheney Syndrome

Report Title: LONGITUDINAL CLINICAL PROFILE AND PROGNOSTIC ASSESSMENT OF HAJDU-CHENEY SYNDROME IN A 44-YEAR-OLD MALE PATIENT

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Purpose: To provide a detailed, chronological summary of my medical history, symptoms, diagnostic findings, and unique presentation related to Hajdu-Cheney Syndrome (HCS) for rheumatological or multidisciplinary review. This report synthesizes all shared information, including historical details, symptom progression, treatments, and imaging analysis. It includes a summarized section on typical HCS experiences and biochemistry, leading to newer medicines beyond bisphosphonates, as well as a speculative prognosis for the patient's future course. A summary of case studies from the last 7 years (2018-2025) is provided for contextual reference

Patient Demographics:

- Age: 44 years
- Sex: Male
- Height: 5'10" (reduced from 5'11" due to vertebral compression)
- Weight: 95 lbs (BMI approximately 13.6, indicative of severe undernutrition)
- Date of Birth: November 4, 1980

Diagnostic Overview:

The patient has a clinically confirmed diagnosis of Hajdu-Cheney Syndrome, made at age 3-4 (circa 1983-1985). HCS is characterized by progressive osteolysis and osteoporosis typically due to NOTCH2 gene mutations though I have not tested positive for known mutations, leading to skeletal fragility, deformities, and multisystem complications. The patient's course demonstrates early onset acro-osteolysis, recurrent infections, vascular events, and recent nutritional decline secondary to dysphagia. Treatment has focused on bisphosphonates, with gaps in dosing potentially contributing to progression. Current concerns include severe malnutrition, chronic pain, and inflammatory skin manifestations.

Summarized Section on Typical HCS Experiences and Biochemistry Leading to Newer Medicines

HCS typically manifests with a spectrum of symptoms that evolve over a lifetime, driven by the NOTCH2 mutation's impact on cellular signaling pathways. Biochemically, NOTCH2 regulates bone remodeling by influencing the balance between osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells). The mutation results in a gain-of-function effect, leading to persistent NOTCH2 activation. This upregulates downstream pathways like NF-κB, which in turn elevates RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) expression. RANKL is a cytokine that binds to RANK receptors on osteoclast precursors, promoting their maturation and activity, while OPG (osteoprotegerin) acts as a natural decoy to inhibit RANKL. In HCS, the RANKL/OPG ratio skews toward excessive osteoclastogenesis, causing accelerated bone resorption analogous to a demolition crew operating without oversight.

Typical experiences include:

- Childhood (0-10 years) Early acro-osteolysis (finger/toe resorption, clubbing), short stature, craniofacial dysmorphisms (e.g., wide-set eyes, small jaw), joint hyperlaxity, and recurrent respiratory infections from thoracic deformities restricting lung function. Immune overactivity may exacerbate infections.

*- **Adolescence (10-20 years):** Progressive skeletal deformities, fractures from minor trauma, reduced range of motion (ROM) in neck/joints, and growth delays. Vascular fragility may emerge as epistaxis or clots.*

*- **Adulthood (20+ years):** Worsening osteoporosis with vertebral instability (e.g., spondylolisthesis, basilar invagination risking neurological issues), chronic pain, neuropathy (numbness, sensory aberrations), inflammatory skin conditions (e.g., psoriasis due to immune dysregulation), and systemic complications like malnutrition from dysphagia (TMJ erosion).*

This biochemistry has led to newer medicines beyond bisphosphonates (which inhibit osteoclasts but don't address RANKL directly). RANKL inhibitors like denosumab bind RANKL to prevent osteoclast activation, while sclerostin inhibitors like romosozumab boost osteoblasts and indirectly reduce RANKL. These target the NOTCH2-RANKL axis more precisely, offering dual bone-building/resorption reduction, with 2025 studies showing 8-15% BMD gains in HCS cases.

Thomas's Chronological Medical History:

- Neonatal Period (1980): Born at term with average weight and length. Developed neonatal jaundice, which resolved without long-term sequelae. No immediate skeletal abnormalities noted, though retrospective assessment suggests possible early subtle manifestations.

- Early Childhood (1983-1990): Diagnosis of HCS at age 3-4, prompted by emerging skeletal features such as finger deformities; there were no facial or other deformities or issues. Onset of clubbed fingers at age 3-4, beginning with one thumb and progressing to both hands, with associated 2-3 phases of resorption over subsequent years totaling 2-3 episodes over all the fingers over the course of 44 years. Recurrent upper respiratory infections, including pneumonia (every other year), sinusitis, and eye/ear infections (with one episode risking blindness due to severe ocular involvement). A slightly deformed rib cage was noted, contributing to respiratory vulnerability, possibly exacerbated by immune overactivity. No surgical interventions during this period.

- Adolescence (1990-1998): Continued pneumonia episodes roughly biennially, with increased minor sports-related injuries during volleyball (grades 5, 6, 8), basketball (grade 7) but nothing to warrant a trip to AHS. Notable trauma at age 15 (knocked unconscious by basketball), with subsequent neck range of motion (ROM) reduced to 75%-70%. Weight maintained around 145 lbs at the peak. Spent this decade growing up working on farms doing all the manual labour expected of a healthy kid and my brothers. There were no issues to visit AHS over however I felt a lot of arthritis in my joints and my range of motion in my neck was limited, my wrists could not bend backwards since I was an infant, maybe. I could not make a fist, I could not sit cross legged, I could not raise my arms straight above my head nor hang off them like the other kids. Pullups were so painful I could only do a few. My ankles still had their range of motion and while I was typically the slowest runner at least I could run. It was around 1995 that I got shingles the first time.

- Early Adulthood (1999-2004): Initiated smoking (gradual increase to a pack every few days), correlating with perceived worsening of skeletal health. Toe fracture and ankle injury during slow-pitch softball exacerbated the necessity of orthotic support. Shoulder pain emerged, impacting work activities (e.g., apron discomfort in kitchen role). Bisphosphonate therapy started circa 2004 with Aclasta, transitioned to Alendronate due to gastrointestinal intolerance. Pneumonia incidence declined post-age 22. I played softball from 1999-2006 in a beer league. My throwing was not good, but I filled a spot. My shoulders inhibited my ROM while throwing and there was not normal strength due to inability to use muscles properly. I graduated with my power engineering 4th class and part of my 3rd class but was uninsurable by the industry due to my fragile and unknown condition.

- Mid-Adulthood (2004-2015): Progressive shoulder and clavicle deformities limited upper extremity function, requiring adaptive techniques (e.g., elbow assistance for reaching high into cupboards or changing lights, I had little strength with my arms above my shoulders). Neck ROM further declined to 60% from additional injuries (chiropractic manipulation (1993), waterslide impact (1995), mid-back trauma (1997), body-check incident). Alendronate interrupted from 2008-2013 due to ulcer recurrence, potentially allowing exacerbation of bone loss. Though there were a few years of treatment with another bisphosphonate. Surgical excision of a buttock cyst in 2014. Severe epistaxis (three episodes within 24 hours) in 2015, followed by neck deep vein thrombosis (DVT) in 2016-2017 shortly (1 month) after getting a lump removed. Dental care absent from 2000-2017, with no cavities identified when I went in. There was an impacted wisdom tooth that needed to be surgically removed under mild anesthesia.

- Recent Years (2015-2025): Further deterioration of hands, feet, and shoulders led to work cessation by 2018-2019. Second episode of herpes zoster (shingles 2018), the second managed earlier with antivirals. Foot surgery (2021) resulted in persistent numbness (tingling in some toes, skin patches on right foot, undetected athlete's foot infection occurred (2024). Sensory aberration in shoulders (rubbing elicits neck-perceived sensation- since spinal fusion). Spinal fusion surgery in 2022 following a sledding accident worsening the C3 alignment and overall stability, complicated by pneumonia and weight loss from 122 lbs to 95 lbs (brief recovery to 120 lbs, then declined again after getting out of hospital). Height reduction from 5'11" to 5'10" due to vertebral compression and head tilted forward. Psoriasis recurrence: initially bilateral ankles (resolved with medication), now affecting left knee, both elbows, with dry skin behind earlobes, eyebrows, forehead, scalp, and occasionally chin. Vascular access challenges during blood draws (veins mobile or difficult to cannulate). Current bisphosphonate regimen (Zoledronic acid) administered intravenously at 12–16-month intervals.

Current Symptoms and Functional Status:

- Musculoskeletal: Severe osteoporosis with temporomandibular joint dislocation (right condyle absent, left partially eroded), contributing to dysphagia. Cervical spine fusion with anterior bulge obstructs swallowing, causing food impaction and heart rate elevation (>100 bpm per wearable data). Non-healing rib fractures and hip pain noted.

- Nutritional: Inability to consume solid foods effectively, reliance on mushy or pureed diets or swallowing down under-chewed foods, leading to exhaustion and inadequate caloric intake (BMI ~13.6, indicative of severe malnutrition). Frequent watery bowel movements exacerbate nutritional decline.

- Dermatological: Active psoriasis with scaling and erythema on left knee, elbows, and dry patches on scalp, face, and ears, suggesting systemic inflammation.

In Thomas's case, the presence of erythema alongside scaling on the left knee, elbows, and dry patches on the scalp, face, and ears suggests an ongoing inflammatory skin process, consistent with active psoriasis.

- Neurological: Numbness in feet, sensory misperception in shoulders, and fatigue impacting daily function.

-Noticeable cognitive decline – making new memories, remembering things from earlier in the day or previous days. Difficult to concentrate and form my usual complex thoughts.

- Cardiovascular/Vascular: History of deep vein thrombosis and epistaxis, with potential implications for vascular fragility.

Diagnostic Imaging Analysis (Based on Provided Screenshots):

- Skull/Jaw CT: Asymmetrical mandible with eroded temporomandibular joint condyles, indicating advanced bone resorption and joint instability, consistent with chronic osteolysis.

- Foot CT: Distal phalangeal resorption with sclerotic changes in the ankle, reflective of a degenerative process and contributing to sensory deficits.

- Cervical Spine X-ray/MRI: Post-fusion hardware intact, with anterior bulge at C2-C3 causing pharyngeal obstruction and possible mild cord compression, explaining dysphagia and functional limitations.

Current Medications and Interventions:

- Zoledronic acid (IV, variable 12–18-month intervals) as primary osteoporosis management.

- Past Alendronate (discontinued due to ulcer).

- Antiviral therapy for shingles (recent episode).

- Prior unspecified medications for initial psoriasis resolution.

- Codeine 2x15mg 2-3 x daily

- Tylenol 2-3 gm daily

- Duloxetine 60mg

- Pregabalin 3x daily

- 1mg daily aripiprazole

-Iron – 150mg bidaily

Allergies and Adverse Reactions:

- Gastrointestinal intolerance to Alendronate (ulceration).

- No documented drug allergies.

Social and Lifestyle Factors:

- Former smoker (pack every few days, started when I was 19 until I was 37). Quit 7 years ago.

- Previously active in sports (volleyball, basketball, softball), now sedentary due to disability.

- Occupational history in kitchen work (2000-2012), terminated due to physical limitations.

-Grew up playing and farming then went onto playing sports and learning.

- Currently Vapes cannabis - wants to stop

Pending Investigations and Recommendations:

- Urgent referral to a speech-language pathologist for dysphagia assessment (e.g., video fluoroscopy) to optimize swallowing mechanics and reduce aspiration risk.

- Consultation with a gastroenterologist to evaluate pharyngeal obstruction and consider enteral feeding options (e.g., nasogastric tube) if oral intake remains insufficient.

- Dermatological evaluation for psoriasis management, potentially with topical corticosteroids or biologics, assessing systemic inflammation links.

- Neurological assessment (MRI follow-up) to monitor cervical cord integrity post-fusion.

- Nutritional consultation with a dietitian to design a high-calorie, dysphagia-friendly diet (e.g., pureed foods, nutritional shakes) targeting weight restoration (goal 120-140 lbs).

- Review of bisphosphonate regimen for adherence and efficacy, with consideration of alternative agents (e.g., denosumab and romosozumab) pending discussion of risks/benefits.

- Serial imaging (CT/MRI) to track jaw erosion and spinal stability. Those lower vertebrae are being forced to twist a lot more than usual with the fusion, osteophyte/wedge fracture, and the non-uniting ribs going on.

Critical Alerts:

- Severe malnutrition (BMI 13.6) poses immediate risk of muscle wasting, immune compromise, and organ dysfunction. Expedited nutritional intervention required.

- Potential aspiration pneumonia risk due to dysphagia—monitor for coughing, fever, or respiratory distress.

- Vascular history (DVT, epistaxis) warrants cardiovascular screening prior to new therapies.

-Absent bone density examination?

Physician Notes:

This synopsis presents a complex case of progressive skeletal deterioration, nutritional decline, and inflammatory skin disease, necessitating a tailored therapeutic approach. The patient's unique presentation, including jaw dislocation and cervical obstruction, suggests structural challenges beyond typical metabolic bone disease. Prior reluctance to escalate therapy (e.g., denosumab, combo-therapy, Ro) may reflect conservative management; however, the current severity justifies re-evaluation. Please integrate imaging findings with clinical correlation and prioritize multidisciplinary input to address acute risks and long-term stability.

Case Studies Involving HCS and RankL:

https://pmc.ncbi.nlm.nih.gov/articles/PMC7820303/pdf/main.pdf

https://pmc.ncbi.nlm.nih.gov/articles/PMC8431733/pdf/ijerph-18-09099.pdf

https://link.springer.com/article/10.1007/s00198-021-05914-6

Case Studies Involving Romosozumab:

Romosozumab, marketed as EVENITY, is a monoclonal antibody that acts as a sclerostin inhibitor, promoting bone formation while simultaneously reducing bone resorption. It is administered via subcutaneous injection at a dose of 210 mg monthly (delivered as two 105 mg prefilled syringes) for a maximum duration of 12 months, as approved by Health Canada. This treatment is indicated for osteoporosis in postmenopausal women at high risk of fracture, defined by a history of osteoporotic fracture or multiple risk factors. It represents a dual-action anabolic agent, distinguishing it from traditional antiresorptive therapies such as bisphosphonates or RANKL inhibitors.

Clinical Studies on Romosozumab:

https://www.sciencedirect.com/science/article/pii/S2352187224000706

https://pmc.ncbi.nlm.nih.gov/articles/PMC10690408/

https://pubmed.ncbi.nlm.nih.gov/40742575/

There are several other case studies however, they are focusing on post Menopausal women, elderly with completely different conditions than HCS such as Vitiligo

Clinical evidence supports the efficacy of romosozumab in reducing fracture risk, with key trials demonstrating superior outcomes in bone mineral density (BMD) improvements and fracture

prevention compared to placebo or other agents. The FRAME trial (NCT01575834), a multinational phase 3 study involving postmenopausal women with osteoporosis, showed that 12 months of romosozumab treatment reduced the risk of new vertebral fractures by 73% and clinical fractures by 36% relative to placebo, with subsequent transition to denosumab maintaining these benefits. The ARCH trial, another phase 3 randomized controlled study, compared romosozumab followed by alendronate to alendronate alone, reporting a 48% reduction in vertebral fracture risk and a 19% reduction in hip fracture risk over 24 months.

In Canadian contexts, the Canadian Agency for Drugs and Technologies in Health (CADTH) reviewed romosozumab based on these trials, noting its clinical benefits in high-risk patients but highlighting a slightly elevated risk of cardiovascular events (e.g., 2.5% incidence versus 1.9% in controls in the ARCH trial). A CADTH pharmacoeconomic analysis further evaluated its cost-effectiveness, concluding that it provides incremental benefits at an acceptable cost in specific subpopulations when priced appropriately. Health Canada's approval in 2019 was informed by these studies, with post-marketing surveillance in Canada aligning with global safety data, emphasizing monitoring for cardiovascular risks.

Efficacy, Costs, and Status of Bone-Targeting Medications in Hajdu-Cheney Syndrome

Drug	BMD Increase (% LS)	Duration Observed.	Annual Cost to Albertans (CAD)	Approved for Severe Osteoporosis
Romosozumab	+13%	12 months	$7,881 cda-amc.ca	Y cda-amc.ca
Teriparatide	+13%	24 months	$10,000–$15,000 pmc.ncbi.nlm.nih.gov	Y aafp.org
Abaloparatide	+11%	18 months	~$25,000	Y cda-amc.ca