Misinformation and Misdiagnosis in Freeman-Burian syndrome

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We read with interest the article, "Freeman-Sheldon Syndrome with Stiff Knee Gait – A Case Report," by Drs Sehrawat, Sural, Sugumar, Khan, Kar, and Jeyaraman.[1] It is wonderful to see this rare syndrome discussed. Unfortunately, there were several unclear or inaccurate points, and recent publications were omitted, suggesting an incomplete literature search. As Freeman-Sheldon syndrome, now Freeman-Burian syndrome (FBS),[2] is exquisitely rare, many who believe they have encountered it in clinical practice are eager to publish their experience, despite the perils.

The authors present FBS as a variant of distal arthrogryposis,[1] but FBS is a unique condition.[3] Though similar in physical appearance, FBS is genetically unique and has a unique clinical course.[3] Two studies have provided evidence that certain craniofacial findings are pathognomonic for FBS,[4-5] and a meta-analysis found distal arthrogryposes are not required for diagnosis.[4] Though many continue to do so, FBS can no longer be cogently classed as a distal arthrogryposis syndrome in the face of such evidence, and the most reasonable classification seems to be as a complex congenital myopathic craniofacial syndrome.[3]

The authors next discuss the patient's copper beaten skull appearance.[1] They do not detail any workup or treatment.[1] The authors postulate it is related to craniosynostosis but quickly dismiss it. It is concerning that they seemed to have focused on a suspected diagnosis of a well-known rare syndrome and ignored a concerning neurologic finding.

The authors describe FBS as an, "autosomal dominant trait and in rare cases as autosomal recessive and x-linked recessive".[1] It is believed that inherited cases either have a parent with clinical evidence of FBS or rarely are germline mosaicisms[4-6].

The authors next speak of, "skeletal abnormalities" and "skeletal malformations".[1] In the syndrome, problems involving the skeletal system are secondary effects of the primary myopathic process of fibrose tissue replacement of normal muscle fibers.[7] This fibrose tissue acts as constricting bands, the way collagen behaves in severe burns.[7] This is correlated with *in vitro* molecular myophysiology observations showing problems with the metabolic process for contraction and extreme muscle stiffness that reduces muscular work and power.[7] Misunderstanding of etiology in FBS has led to inappropriate treatment plans, especially surgeries, and has resulted in tragic, lifelong impairments.[4,7-8] We applaud the authors for their caution toward surgery and explanation of its potential for unfavorable outcomes.[1]

Unlike many similar case reports to which we have responded over the past 2-years, the authors clearly state the standard clinical diagnostic criteria (microstomia, pursed lips, deep nasolabial folds, and H or V-shaped chin defect and two major arthrogryposes—typically, camptodactyly with ulnar deviation and equinovarus).[1,4-5] They also provide a somewhat fair description of FBS, except as noted.[1] A major failing of their description of FBS is their summary of findings suggestive of FBS, Sheldon-Hall syndrome (SHS), and Schwartz Jampel syndrome.[1] The table lists some required findings as, "Features not favoring FSS".[1,4-5] Generally, the construction of the table is misleading, as structured diagnostic criteria exist for FBS and SHS.[4-5]

The authors also present a very clear description of their patient, with acceptable figures.[1] It is mystifying that—despite correctly stating the FBS diagnostic criteria twice—they diagnosed their patient with FBS, though she clearly did not meet the diagnostic criteria.[1,4-5] The patient lacked the V or H-shaped chin defect and had a small mouth but not microstomia, as judged from included photographs.[1] The patient's appearance seems consistent with SHS, exhibiting a small mouth, short neck, small chin, obvious nasolabial folds, and triangular face.[1] Such an error is not uncommon; FBS has an estimated false-positive rate of 30-60%.[4-5]

The authors state there is an association of malignant hyperthermia (MH) with FBS and urge caution.[1] Some patients with FBS do, indeed, develop hyperpyrexia during general anesthesia, but these hyperpyrexia events, which may include tachycardia and increased muscle rigidity, respond to ibuprofen and also occur where a malignant hyperthermia protocol was followed and in stressful, non-operative stress situations.[9] There is no evidence that MH is associated with FBS, though FBS anesthesia practice guidelines still suggest following an MH protocol.[9]

Prenatal ultrasound is not considered diagnostic, and prenatal diagnosis is not considered generally feasible.[6] As suggested by the authors, molecular diagnosis is very expensive and is not clinically helpful or needed, given the strong correlation of the clinical diagnostic criteria with the presence of *MYH3* mutations.[1,6] For women with clinically diagnosed FBS undergoing *in vitro* fertilization and wishing to avoid use of an FBS-affected egg, polar bodies testing has been used successfully, as the authors correctly state.[1,6]

Ten English-language case reports have been published between 2020-2022 purportedly describing FBS that contained similar, preventable errors.[1,10-18] Not conducting a thorough literature search and omitting recent articles was the common denominator among the articles.[19] In trying to address the shortcomings of each, we have responded to all ten, with four letters already published.[19-22] This article illustrates the potential perils of describing a rare condition despite the best intentions.

References

1. Sehrawat S, Sural S, Sugumar PA, Khan S, Kar S, Jeyaraman M. Freeman-Sheldon Syndrome with Stiff Knee Gait – A Case Report. Journal of Orthopaedic Case Reports 2021 November;11(11):64-68. doi: 10.13107/jocr.2021.v11.i11.2518
2. Poling MI, Dufresne CR. Revisiting the many names of Freeman-Sheldon syndrome. J Craniofac Surg. 2018;29(8):2176–2178. doi: 10.1097/SCS.0000000000004802
3. Poling MI, Dufresne CR. Head first, not feet first: Freeman-Sheldon syndrome as primarily a craniofacial condition. Cleft Palate-Craniofac J. 2018;55(5):787-788. doi: 10.1177/1055665617753482

4. Poling MI, Dufresne CR, Chamberlain RL. Findings, Phenotypes, Diagnostic Accuracy, and Treatment in Freeman-Burian Syndrome. J Craniofac Surg. 2020;31:1063-1069. doi: 10.1097/SCS.0000000000006299
5. Stevenson DA, Carey JC, Palumbos J, Rutherford A, Dolcourt J, Bamshad MJ. Clinical characteristics and natural history of Freeman-Sheldon syndrome. Pediatrics. 2006;117:754-762. doi: 10.1542/peds.2005-1219
6. Hague J, Delon I, Brugger K, Martin H, Abbs S, Park SM. Molecularly proven mosaicism in phenotypically normal parent of a girl with Freeman-Sheldon Syndrome caused by a pathogenic *MYH3* mutation. Am J Med Genet A. 2016;170(6):1608-1612. doi: 10.1002/ajmg.a.37631
7. Poling MI, Dufresne CR, Chamberlain RL. Freeman-Burian syndrome. Orphanet J Rare Dis. 2019;14:14. doi: 10.1186/s13023-018-0984-2
8. Poling MI, Dufresne CR, McCormick RJ. Identification and Recent Approaches for Evaluation and Management of Rehabilitation Concerns for Patients with Freeman-Burian Syndrome: Principles for Global Treatment. J Ped Genet. 2020;09(03):158-163. doi: 10.1055/s-0040-1710339
9. Poling MI, Dufresne CR. Freeman-Burian syndrome. Anästh Intensivmed. 2019;60(1):S8-S17. doi: 10.19224/ai2019.S008
10. Kamal G, Shah SB, Gupta A. Anesthesia Challenges in the Management of Freeman-Sheldon Syndrome: Report of Two Cases and Literature Review. AANA J. 2020;88(1):35-38. PMID: 32008616.
11. Park J, Kang SW, Choi WA, Lee Y, Cho HE. Precise Pulmonary Function Evaluation and Management of a Patient With Freeman-Sheldon Syndrome Associated With Recurrent Pneumonia and Chronic Respiratory Insufficiency. Ann Rehabil Med. 2020;44(2):165-170. doi: 10.5535/arm.2020.44.2.165
12. Wróblewska-Seniuk K, Jarząbek-Bielecka G, Kędzia W. Freeman-Sheldon syndrome - a course of the disease from birth to adulthood. Clin Exp Obstet Gynecol. 2020;47(6): 978-982. doi: 10.31083/j.ceog.2020.06.5430
13. Sato Boku A, Sento Y, Hasegawa T, Tsutsumi K, Kamimura Y, So M, Kako E, Sobue K. Anesthetic management of a patient with Freeman-Sheldon syndrome undergoing oral surgery: a case report. Clin Case Rep. 2021;9(6):e04358. Published 2021 Jun 9. doi: 10.1002/ccr3.4358
14. Kiliçbay F, Küçük Kurtulgan H , Sidar Duman Y, Tunç G. A Case Report of Freeman-Sheldon Syndrome with Gastrointestinal Dysmotility in a Premature Newborn Delivered Due to Polyhydramnios. Turkiye Klinikleri J Case Rep. 2021;29(4):230-3. doi: 10.5336/caserep.2021-83838.
15. Wu TM, Chin LS. Treatment results of teratologic arthrogryposis in a case of Freeman-Sheldon syndrome: A 25-year follow-up. Formos J Surg. 2021;54:66-9. doi: 10.4103/fjs.fjs_79_20
16. Sreeja KS, Sahoo J, Barman A, Baral D. Holistic rehabilitation of a rare case of distal arthrogryposis: Freeman Sheldon syndrome. International Journal of Scientific Research. 2021;10(5). Available at: *https://www.worldwidejournals.com/international-journal-of-scientific-research-(IJSR)/fileview/holistic-rehabilitation-of-a-rare-case-of-distal-arthrogryposis-freeman-sheldon-syndrome_May_2021_6121064717_8726505.pdf*
17. Fayed M, Giska MA, Shievitz RC, Attali A, Younger J. Emergent Cesarean Delivery in a Patient With Freeman-Sheldon Syndrome Complicated by Preeclampsia, Acute Pulmonary Embolism, and Pulmonary Edema: A Case Report. Cureus. 2021;13(12):e20802. doi: 10.7759/cureus.20802
18. Bowman S, Noble G, Rahmani B, Mets M, Ranaivo HR, Castelluccio V. A case of blepharophimosis: Freeman Sheldon syndrome. Ophthalmic Genet. 2021. doi: 10.1080/13816810.2021.1989603
19. Poling MI, Dufresne CR. Unsafe Care and Misunderstanding Diagnosis in Freeman-Burian syndrome: Problems in Writing Case Reports Involving Rare Conditions and Strategies for Improvement. Version: 3. Authorea [Preprint]. January 26, 2022. doi: 10.22541/au.164303994.43963430/v3
20. Poling MI, Dufresne CR. Letter. AANA J. 2020;88(5):54. Available at: https://www.aana.com/docs/default-source/aana-journal-web-documents-1/20-oct-letters.pdf?sfvrsn=7aa229e4_6
21. Poling MI, Dufresne CR. Letter: Precise Pulmonary Function Evaluation and Management of a Patient With Freeman-Sheldon Syndrome Associated With Recurrent Pneumonia and Chronic Respiratory Insufficiency. Ann Rehabil Med. 2020;44(5):409-410. doi: 10.5535/arm.20110
22. Poling MI, Dufresne CR. Accuracy of Facts About Freeman-Sheldon syndrome. Clin Exp Obstet Gyne-

col. 2021;48(5):997-998. doi: 10.31083/j.ceog4805160