Limb Deformity Treatment and Diagnosis in Freeman-Burian syndrome

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We read with interest the article, “Holistic rehabilitation of a rare case of distal arthrogryposis: Freeman Sheldon syndrome,” by Drs Sreeja, Sahoo, Barman, and Baral.[1] It is wonderful to see this 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 appearing to some other conditions, especially distal arthrogryposes, 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 use the classification, 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 speak of, “skeletal deformities”, “skeletal anomalies”, “skeletal features”, and “skeletal abnormalities”.[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.[6] This fibrose tissue acts as

constricting bands, the way collagen behaves in severe burns.[6] 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.[6] Misunderstanding of etiology in FBS has led to inappropriate treatment plans, especially surgeries, and has resulted in tragic, lifelong impairments.[4,6-7] As such, it is exceedingly rare for the types of operative hand and foot therapies described in this article to be helpful in FBS.

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.[4-5,8] All inherited cases are believed to be autosomal dominant. Overall, most cases are not inherited (sporadic).[4-5] Moreover, prenatal ultrasound is not considered diagnostic.[6] In general, prenatal diagnosis is not considered feasible.[6] For women with FBS, testing polar bodies during *in vitro* fertilization is the best way to prevent FBS.[6]

Regarding the cardinal clinical findings in the syndrome, the authors describe common findings, some of which are included in the diagnostic criteria, but most are not.[1,4-5] The authors do not delineate the 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] Arriving at a correct diagnosis is paramount in FBS, as patient outcomes depend on it.[9] Similar-appearing conditions (i.e., distal arthrogryposes) react far more favourably than FBS to surgery.[1] In FBS, surgery to address foot deformities often has poor outcomes, and even more successful surgeries, such as craniofacial surgery, may require multiple revisions to overcome fibrose constricting band development.[6] The diagnostic clinical criteria is also strongly correlated with the presence of *MYH3* mutations.[6]

The authors paradoxically suggest windmill vane deformity and ulnar deviation are separate findings,[1] but they are synonyms. The authors also speak of kyphosis, which is somewhat rare in FBS, but they do not mention scoliosis, which is common.[1,4] Spina bifida occulta is not part of FBS, and while pterygium colli occurs in FBS, it is a required finding in Sheldon-Hall syndrome.[1,4-5]

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.[10] There is no evidence that MH is associated with FBS, though FBS anesthesia practice guidelines still suggest following an MH protocol.[10]

The patient’s description does not include any of the diagnostically required craniofacial findings, and while photographs are provided, the resolution is insufficient.[1,4-5] As FBS has an estimated false-positive rate of 30-60%,[4] the absence of evidence that the patient met the criteria for FBS raises serious doubt concerning the patient’s diagnosis. Without objective evidence for the patient’s FBS diagnosis, the purpose of the case report is lost.

We applaud the authors’ encouraging, hopeful, and optimistic tone and message that is lacking in so many articles.[1] We feel it is critical to express a realistically optimistic outlook for these patients. Expressing an optimistic perspective can encourage colleagues and patients’ families, possibly improving patient outcomes on many levels.

Ten English-language case reports have been published between 2020-2022 purportedly describing FBS that contained similar, preventable errors.[1,11-19] Not conducting a thorough literature search and omitting recent articles was the common denominator among the articles.[20] In trying to address the shortcomings of each, we have responded to nine, with four letters already published.[20-23] This article illustrates the potential perils of describing a rare condition despite the best intentions.

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