

## Clarity on Diagnosis in Freeman-Burian Syndrome

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We read with interest an article published in your Journal, “A Case Report of Freeman-Sheldon Syndrome with Gastrointestinal Dysmotility in a Premature Newborn Delivered Due to Polyhydramnios.”<sup>1</sup> It is wonderful seeing this syndrome correctly identified. Unfortunately, there were several unclear or inaccurate points, suggesting an incomplete literature search.<sup>1-4</sup> As Freeman-Sheldon syndrome, now Freeman-Burian syndrome (FBS), is exquisitely rare, many encountering it are eager to publish, despite the perils.<sup>3,4</sup>

In describing the syndrome and their patient, the authors omit the diagnostic criteria (microstomia, pursed lips, deep nasolabial folds, and H or V-shaped chin defect and two major arthrogryposes—often, camptodactyly, ulnar deviation, equinovarus, and metatarsus varus).<sup>1,3,5</sup> Instead, the authors list common findings, some of which are included in the diagnostic criteria, but most are not.<sup>1,3,5</sup> Omitting the diagnostic criteria, listing non-diagnostic findings, and not stating findings the patient had that satisfied the diagnostic criteria lead to confusion for those unfamiliar with FBS.

In FBS, “skeletal malformations” are secondary effects of fibrose tissue constricting bands replacing

normal muscle fibers.<sup>4</sup> The constricting bands behave like collagen does in severe burns.<sup>4</sup> These observations correlate with *in vitro* molecular myophysiology studies demonstrating impairments of the metabolic process for contraction and extreme muscle stiffness that reduces muscular work and power.<sup>4</sup> Failure to appreciate FBS’s etiology has precipitated inappropriate therapeutic strategies—notably, operative interventions, sometimes causing tragic, lifelong impairments.<sup>2,4</sup>

As FBS is a “complex congenital myopathic craniofacial syndrome” and limb malformations and other features being non-diagnostic, referral and most care is best provided by plastic or craniofacial surgeons.<sup>4</sup> Although given as a possible cause and paradoxically dismissed, dysphagia is the generally expected cause of polyhydramnios in FBS pregnancies. Autosomal recessive inheritance is no longer accepted, with all inherited cases believed to be autosomal dominant and rarely germline mosaicisms; however, most cases are not inherited.<sup>4</sup> Notwithstanding a couple of case reports, prenatal diagnosis is not generally considered feasible.<sup>4</sup> For women with FBS, testing polar bodies during *in vitro* fertilization is the best way to prevent FBS.<sup>4</sup> FBS is not associated with malignant hyperthermia, but non-

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MH hyperthermia may occur with physiologically stressful situations in FBS.<sup>4</sup>

This is the tenth case report in the last 2-years with similar errors easily preventable by a prudent literature search. We have responded to seven, with four letters already published. While factually problematic, the article demonstrates the hazards of describing a rare disease.

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### Authorship Contributions

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