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SLEEP MEDICINE PEARLS

FOXP1 Syndrome and Severe Obstructive Sleep Apnea

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A 3-year-old male with a history of macrocephaly, developmental delay, snoring and apneas, despite adenoidectomy, presented for evaluation of sleep-disordered breathing.

He was the product of a full-term pregnancy without any pre/postnatal complications. Medical history was significant for empty sella syndrome, chronic nasal congestion and recurrent otitis media. He had global developmental delays, most notably speech delay. He also had behavioral problems including aggression and hyperactivity. Surgical history was positive for adenoidectomy and multiple bilateral myringotomy tube placements. His family history was unremarkable for sleep disorders, intellectual disability or genetic syndromes.

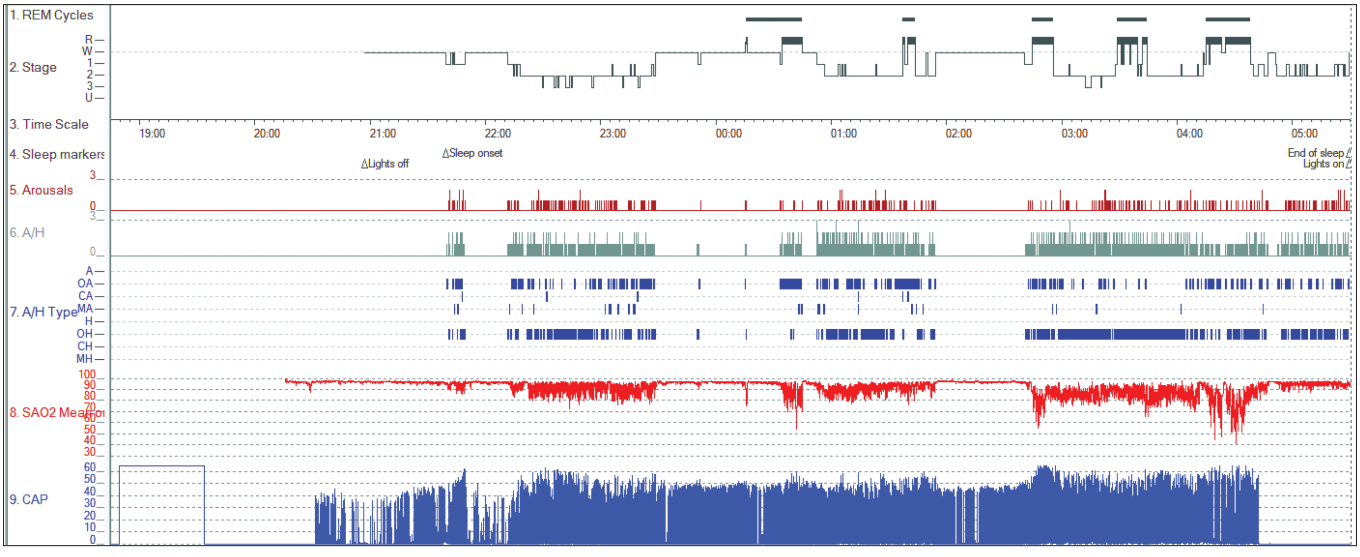
On physical examination, he was a pleasant, interactive boy in no acute distress. His vital signs were normal. His weight was 16.6 kg (49th percentile), height 96.5 cm (5th percentile), head circumference was 54.5 cm (> 99th percentile). He had dysmorphic facial features including macrocephaly, frontal bossing and intermittent strabismus. Oropharyngeal examination revealed high arched palate, Mallampati class III, tonsils 2+. Cardiac examination revealed a grade 3 systolic murmur. He had bilateral fifth finger clinodactyly and mild hypotonia. The rest of his physical examination was unremarkable.

Polysomnography revealed severe obstructive sleep apnea (OSA) with an obstructive apnea-hypopnea index (oAHI) of 144.7 events/h, prolonged desaturations to a nadir of 42%, peak end-tidal CO_2 was 67 mmHg with end-tidal CO_2 > 50 mmHg for 11% of total sleep time (**Figure 1**).

He underwent urgent adenotonsillectomy. Follow up polysomnogram (6 weeks after adenotonsillectomy) demonstrated persistent severe obstructive sleep apnea with an oAHI of 101.5 events/h (oxygen saturation nadir was 49%) (**Figure 2**). A sleep titration study revealed that continuous positive airway pressure at 8 cmH_2O was effective in controlling his sleep-disordered breathing (**Figure 3**).

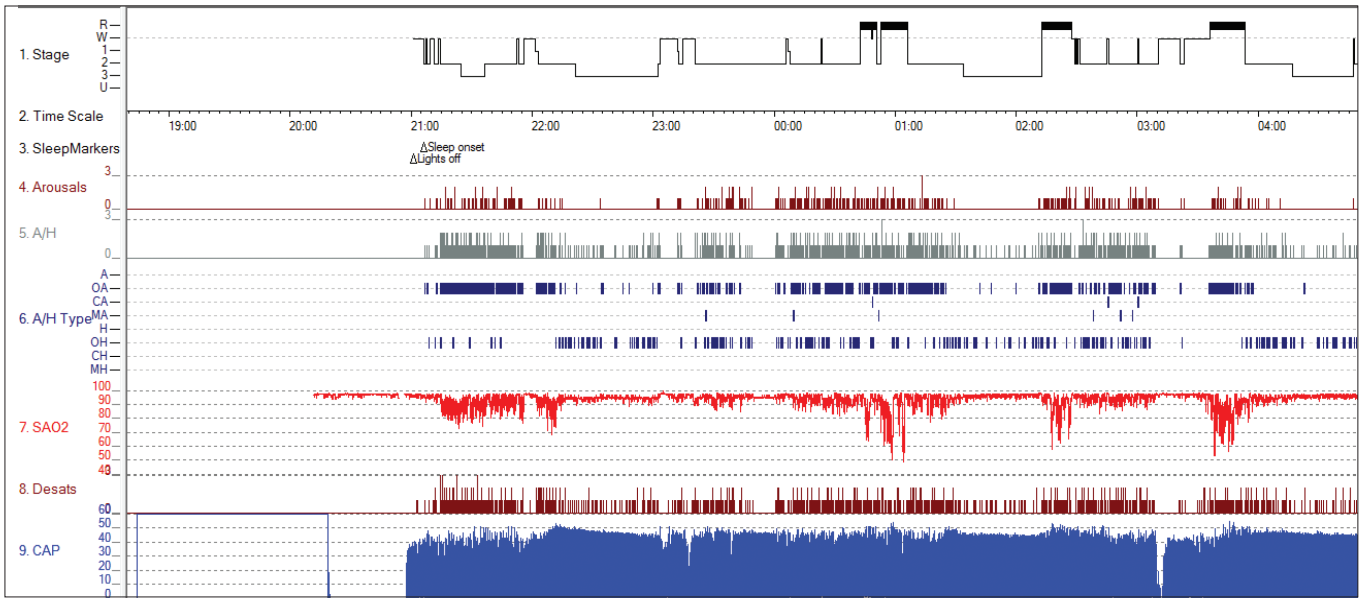
QUESTION: Given the patient's clinical examination findings and medical history, for what evaluation should the patient be referred?

Figure 1—Baseline polysomnography overview.



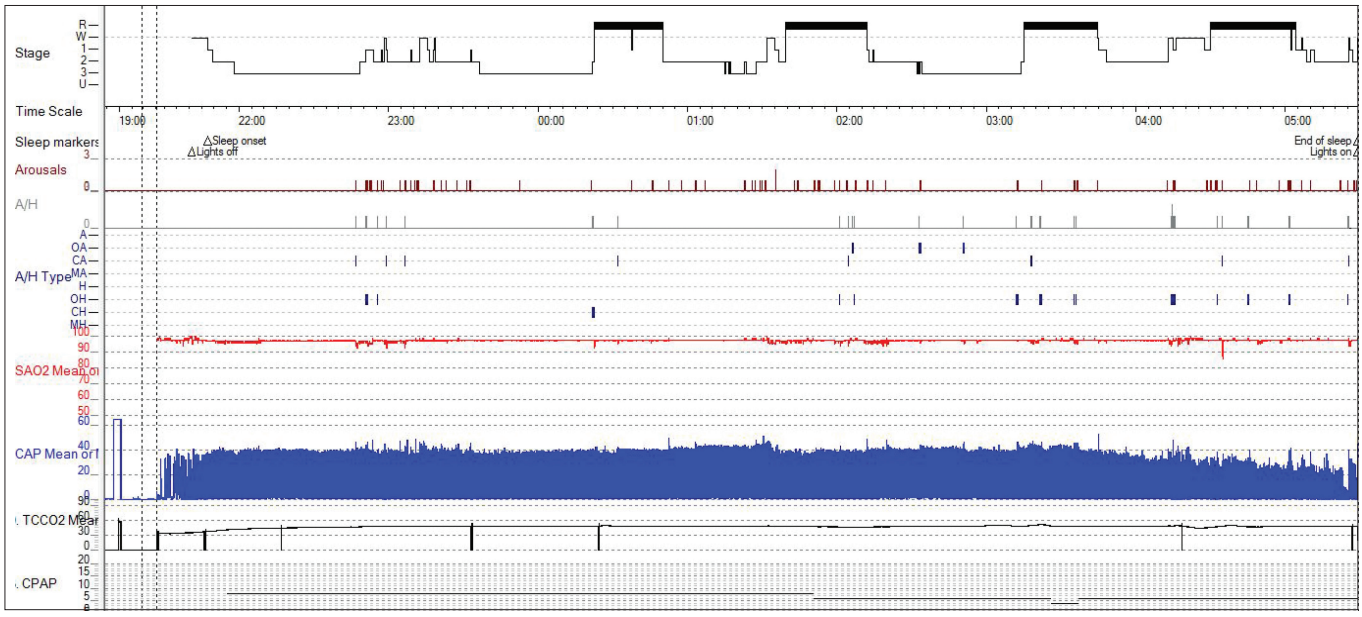
1 = stage N1 sleep, 2 = stage N2 sleep, 3 = stage N3 sleep, A = apnea, CA = central apnea, CAP = capnography, CH = central hypopnea, H = hypopnea, MA = mixed apnea, MH = mixed hypopnea, OA = obstructive apnea, OH = obstructive hypopnea, R = stage R sleep (REM sleep), REM = rapid eye movement, SaO2 = oxygen saturation, W = awake.

Figure 2—Postoperative polysomnography 6 weeks after adenotonsillectomy depicting a high number of residual breathing events and significant desaturations.



1 = stage N1 sleep, 2 = stage N2 sleep, 3 = stage N3 sleep, A = apnea, CA = central apnea, CAP = capnography, CH = central hypopnea, Desats = desaturations, H = hypopnea, MA = mixed apnea, MH = mixed hypopnea, OA = obstructive apnea, OH = obstructive hypopnea, R = stage R sleep (REM sleep), REM = rapid eye movement, SaO2 = oxygen saturation, W = awake.

Figure 3—CPAP titration study.



A pressure of 8 cmH_2O was effective in eliminating breathing events. 1 = stage N1 sleep, 2 = stage N2 sleep, 3 = stage N3 sleep, A = apnea, CA = central apnea, CAP = capnography, CH = central hypopnea, CPAP = continuous positive airway pressure, H = hypopnea, MA = mixed apnea, MH = mixed hypopnea, OA = obstructive apnea, OH = obstructive hypopnea, R = stage R sleep (REM sleep), REM = rapid eye movement, SaO2 = oxygen saturation, TCCO2 = transcutaneous carbon dioxide, W = awake.

ANSWER: Genetics evaluation.

DISCUSSION

Due to his clinical examination findings and medical history, he was referred for genetics evaluation. A full exome sequencing revealed a de novo heterozygous splicing mutation in the *FOXP1* gene.

FOXP1 syndrome results from haploinsufficiency of the forkhead-box protein 1 (FOXP1).[1,2] It is a rare genetic neurodevelopmental syndrome characterized by mild dysmorphic features, intellectual disability, language impairment and behavioral issues.[1,2] Expressive language is more severely affected than receptive.[1] Characteristic dysmorphic features include macrocephaly, a broad forehead, bulbus nose and clinodactyly.[1,2] Recurrent otitis media and strabismus are very common.[2] Cardiac, renal and urinary tract anomalies have been reported.[2] Pulmonary anomalies are rare with one reported case requiring nocturnal oxygen.[2] Sleep problems in the form of difficulty initiating sleep and multiple awakenings throughout the night may also occur.[2]

To the best of our knowledge, this is the second reported case of OSA in a patient with FOXP1 syndrome.[3] Pathophysiology may be multifactorial including craniofacial features and neuromuscular control of the upper airway. Specifically in our patient, characteristic dysmorphic features including ones that are likely associated with residual severe OSA were a high and broad prominent forehead, downslanting palpebral fissures, short nose, wide mouth with down turned corners and open mouth appearance, as well as hypotonia. Of particular concern is that sleep-disordered breathing, if present, may be severe with severe desaturations, and not resolved with adenotonsillectomy.

Finally, OSA may be underdiagnosed and undertreated and may contribute to exacerbation of FOXP1 syndrome neuropsychiatric and behavioral manifestations.[4]

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1. The severe OSA found in our patient, combined with previous reports of sleep problems in children with FOXP1 syndrome, suggest that evaluation for OSA should be considered for patients with this rare genetic disorder.
2. Children with FOXP1 syndrome may have residual severe OSA despite adenotonsillectomy given their dysmorphic features.
3. Untreated OSA may contribute to irritability, aggression, hyperactivity frequently found in FOXP1 syndrome.

CITATION

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DISCLOSURE STATEMENT

The authors have read and approved the manuscript in its current form. The authors report no conflicts of interest.