Recommendations for Evaluation and Monitoring of Patients with Joubert Syndrome and Related Disorders

Dear Healthcare Professional,

Joubert Syndrome and Related Disorders are a group of developmental brain disorders characterized clinically by disturbances of breathing rhythm, ataxia, oculomotor abnormalities, developmental delays, and hypotonia. These disorders are characterized on brain imaging by cerebellar vermis hypoplasia and the "molar-tooth" sign of the brainstem. From our review of clinical records from patients in the Joubert Syndrome Foundation, we have found many with co-existing medical conditions at a frequency sufficient to **warrant a set of guidelines for the evaluation and monitoring of all patients with Joubert Syndrome and Related Disorders.** These evaluations are necessary for two reasons. First is for proper diagnosis of the child, as we find that approximately 20% of patients display features indicating a subtype of Joubert syndrome or a related syndrome. Second is to try to prevent medical complications from these associated conditions, which through proper screening might be avoided. However, because our total knowledge of Joubert syndrome and its complications are limited, our recommendations will need to be evaluated and changed as new information becomes available.

Patients with Joubert Syndrome and Related Disorders, in addition to the features mentioned above, have displayed the following features:

1. Abnormal electroretinogram, indicating co-existent retinal dysplasia and visual impairment.
2. Optic colobomas, which may also limit vision.
3. Kidney disease, which may include juvenile nephronophthisis or cystic dysplastic kidneys. In some patients, the kidney disease has progressed to end-stage renal failure that required dialysis or transplantation.
4. Liver fibrosis with or without compromised liver function.
5. Tongue tumors (hamartomas), enlarged tongues, multiple frenulae or other unusual anomalies of the mouth.
6. Polydactyly of fingers or toes that may be simple or complex.
7. Hypothalamic disorders, sometimes related to a hypothalamic hamartoma.
8. Additional subtle variation in the appearance of brain structures, including polymicrogyria or encephalocele.

Because of these findings, we recommend the following evaluations for patients with Joubert Syndrome and Related Disorders.

Diagnostic Evaluations (Initial)

1. Careful physical examination to look specifically for these co-existent features.
2. Pediatric neurological evaluation for careful assessment of development and cerebellar function.
3. Medical genetics evaluation with attention focused on genealogy, growth, polydactyly, micro/macrocephaly, facial dysmorphism, clefts, lingual nodules, genitalia, and other anomalies.
4. Evaluation of oromotor function by a trained occupational or speech therapist
5. Brain MRI with axial, coronal, sagittal images (ideally with 3 mm axial planes through midbrain and pons) and review of the images by one of the Medical Advisors of the Joubert Syndrome Foundation.
6. Developmental assessment using the Bayley Scale for children less than 3 years and specific age-appropriate motor/speech/language testing for older children.

7. Sleep history with attention to apnea/hyperpnea. Polysomnogram in all children diagnosed under the age of 1. After the age of 1, this test may be useful if the child has symptoms of sleep apnea.
8. Baseline pediatric ophthalmologic dilated eye exam to test for retinal dysplasia and coloboma. If visual problems are suspected, a visual evoked potential (VEP) study may be a useful test that does not require sedation and can be performed as early as 6 months of age.
9. Baseline electroretinogram (ERG) if possible. Ideally, this should be done between the ages of 8 months and 3 years, when the sedation required is minimal.
10. Specific ocular motility examination (with electrooculogram in older children).
11. Abdominal ultrasound scan with attention to kidneys and liver.
12. Renal evaluation: Blood urea nitrogen (BUN), creatinine, complete blood count (CBC), and first-morning void urinalysis with specific gravity for concentrating ability. A baseline blood pressure should be obtained.
13. Liver function tests (LFTs) to include transaminases, albumin and bilirubin.
14. High resolution karyotype.
15. Referral of the child to one of the Medical Advisors of the Joubert Syndrome Foundation to discuss results of testing or for questions.

Annual Evaluations (Yearly)

1. Annual pediatric and neurological evaluation to monitor systemic or motor abnormalities.
2. Patients may have progressive kidney failure with the first manifestation being reduced urine concentrating ability or anemia. Therefore, annual abdominal ultrasounds, BUN, creatinine, CBC, first- morning void urinalysis, and blood pressure measurements, are recommended until at least age 20 years.
3. Ophthalmologic abnormalities may be progressive. Therefore, annual ophthalmologic evaluation of retina is recommended with follow-up ERG if indicated by the ophthalmologist.
4. Annually monitor growth and sexual maturation with endocrinologic evaluation if indicated
5. Neuropsychological evaluation when patient is able to cooperate with testing.
6. Periodic developmental assessments as appropriate.
7. Liver evaluation by annual ultrasound (as for kidneys) and liver function tests.
8. Patients may have problems with swallowing from large tongues, thus need ongoing evaluation for oromotor function and symptoms of obstructive apnea.

These are guidelines only. Individual patients may have unique needs and management may need to be individualized. If you have any questions about Joubert Syndrome and Related Disorders, the Joubert Syndrome Foundation, or other matters, please do not hesitate to contact one of us.

Sincerely,

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Medical Advisors of the Joubert Syndrome Foundation