31. Elimian A, Goodman J, Escobedo M, Nightingale L, Knudtson E, Williams M. Immediate compared with delayed cord clamping in the preterm neonate: a randomized controlled trial. Obstet Gynecol 2014;124:1075-9.

32. Krueger MS, Eyal FG, Peevy KJ, Hamm CR, Whitehurst RM, Lewis DF. Delayed cord clamping with and without cord stripping: a prospective randomized trial of preterm neonates. Am J Obstet Gynecol 2015;212:394.e1-5.

50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Tuberous Sclerosis: From Phenotype to Genotype

Hurwitz S, Irwin B. White Spots in Tuberous Sclerosis. J Pediatr 1970;77:587-94.

Much was already understood in 1970 about tuberous sclerosis, including many of its classical phenotypic characteristics with skin, central nervous system, eye, heart, kidney, lung, and bone findings. Neurocutaneous stigmata of adenoma sebaceum, shagreen patches, periungual and gingival fibromas, and hypopigmented macules were described at the time. Hurwitz and Braverman detailed the cutaneous findings in 23 patients with tuberous sclerosis and compared pigmentary lesions in these children with those found in 55 children with neurologic disorders exclusive of tuberous sclerosis, and 100 neurologically typical children. The majority of children with tuberous sclerosis in their sample (78%) had hypopigmented macules, a finding in only one of the children in the comparator groups. There was considerable variability in the size and shape of the lesions in this sample compared with the classic lance-ovate shape similar to the leaf of the mountain ash tree described by Fitzpatrick et al in 1968, with additional description of confetti lesions, which are now recognized in the diagnostic criteria.[1,2]

Fifty years ago, there was appropriate emphasis on the clinical diagnosis of tuberous sclerosis and other neurocutaneous disorders. Clinical diagnosis of tuberous sclerosis using major and minor criteria remains an important tool, particularly when attempting to make rapid treatment decisions in a patient presenting with new-onset infantile spasms with neurocutaneous features. The increasing accuracy and availability of genetic testing has changed diagnostic practices for tuberous sclerosis. Importantly, the 2012 update in the diagnostic criteria for tuberous sclerosis complex includes genetic criteria, with identification of either a *TSC1* or *TSC2* pathogenic mutation sufficient to make a definitive diagnosis of tuberous sclerosis.[2] As genetic testing continues to evolve, the yield of these analyses continues to increase. Sanger sequencing enabled the detection of point mutations in coding regions and intron and exon boundaries of *TSC1* and *TSC2*, with a diagnostic yield of 75%-90% when combined with deletion and duplication analysis.[3] Next-generation sequencing *TSC1* and *TSC2* panels have even further increased the ability to identify pathogenic variants.[3] As genetic testing continues to expand in both availability and affordability, there will likely be further emphasis on early genetic diagnosis and genetic confirmation of clinical diagnosis. However, there is no substitute for evaluation and recognition of clinical features to guide further diagnostics.

Amanda G. Sandoval Karamian, MD
Division of Child Neurology
Lucile Packard Children's Hospital
Palo Alto, California

References

1. Fitzpatrick TB, Szabo G, Hori Y, Simone AA, Reed WB, Greenberg MH. White leaf-shaped macules, earliest visible sign of tuberous sclerosis. Arch Dermatol 1968;98:1-6.
2. Northrup H, Krueger DA , International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric Neurol 2013;49:243-54.
3. Peron A, Au K, Northrup H. Genetics, genomics, and genotype-phenotype correlations of TSC: insights for clinical practice. Am J Med Genet C Semin Med Genet 2018;178:281-90.