Dear Editor,

We were intrigued to read the article by Martos et al.1 about a boy affected by progressive dystonia, spasticity, retinitis pigmentosa, and psychomotor delay. They labeled this boy as having “HARP,” a term coined almost 3 decades ago to summarize a clinical syndrome of “hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration.”2 As acknowledged in their contribution’s title, “HARP” has long been established as allelic with pantothenate kinase-associated neurodegeneration (PKAN).3,4 We are therefore perplexed as to why the boy’s condition is not merely termed PKAN, and even more so why it is labeled “incomplete HARP syndrome,” justified according to the authors by the failed detection of “hypoprebetalipoproteinemia.” Such redundant as well as nonsensical terminology perpetuates the use of diagnostic terms that convey no relevant meaning, and distracts from focusing on the possible significance, if any, of observations hidden in a seemingly attractive acronym.

We initially raised this concern some years ago5 when we explained that the term “hypoprebetalipoproteinemia” had originated in “a bygone era when gel or paper electrophoresis was used to separate plasma lipoproteins.” The “prebeta” fraction migrates faster than low-density lipoprotein (LDL, or “betalipoprotein”) and in ultracentrifugally separated plasma corresponds to particles known today, respectively, as lipoprotein(a) [Lp(a)] and very-low-density lipoproteins (VLDL). Modern biochemical methods can precisely quantitate both, eliminating the requirement for semiquantitative electrophoresis.

We emphasized then that “hypoprebetalipoproteinemia” and “aprebetalipoproteinemia” are meaningless from a metabolic perspective and are absent from the lipoprotein literature.5 Neither isolated low plasma VLDL nor Lp(a) have since been connected to pathophysiological consequences, and both research and clinical experience have confirmed that no clinically meaningful entities correspond to these terms. VLDL and its end product LDL each contain one molecule of apolipoprotein B; it is impossible for humans to have isolated VLDL deficiency (i.e., “hypoprebetalipoproteinemia”) without concurrent LDL deficiency. This inappropriately named phenotype has never been documented using modern quantification methods. However, while terms with “..prebeta..” should be discontinued, “abetalipoproteinemia” (ABL, Bassen-Kornzweig syndrome; OMIM #200100) and “hypobetalipoproteinemia” (FHBL1, OMIM #615558; FHBL1, OMIM # 605019) refer to underlying entities that actually do exist and are characterized by concurrent deficiencies of VLDL and LDL particles.

Even if only a single additional case6 received the “HARP” label since its creation in 1992,2 the acronym persists despite the
term’s uselessness. It is, however, helpful to remember that it was coined a decade before the genetic bases were elucidated for conditions such as PKAN, once collected under the now defunct and deserving obsolete “Hallervorden-Spatz” eponym.

Disease taxonomy is an evolving field, and in the current era of molecular medicine arguments are being made for the association of a disease with its causative mechanisms or, even more appropriately, genetic etiology. The field of medicine is successively abandoning not only eponymous designations and incomplete descriptors but also acronyms that appear pleasing, yet ultimately result in diagnostic confusion. This clearly applies to the cases termed “HARP” (with or without the nonsensical “hypoprebetalipoproteinemia”): their proper diagnosis is PKAN.1,3,4

Continued use of the “HARP” acronym can no longer be justified. With respect to PKAN, questions remain regarding the frequency of retinal involvement and of acanthocytosis (and hence potential confusion with other disorders under the “neuroacanthocytosis” umbrella) and the search for mechanisms underlying these manifestations.

Conflicts of Interest
The authors have no financial conflicts of interest.

Acknowledgments
None.

Author Contributions
Conceptualization: Ruth Helen Walker. Writing—original draft: all authors.

REFERENCES
1. Martos ML, Reyes MJ, Iglesias RM, Moro CG, Gutierrez ML, Pedregosa LE. A new allelic variant in the PANK2 gene in a patient with incomplete HARP syndrome. J Mov Disord 2020;13:229-231.
2. Higgins JJ, Patterson MC, Papadopoulos NM, Brady RO, Pentchev PG, Barton NW. Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP syndrome). Neurology 1992; 42:194-198.
3. Ching KHL, Westaway SK, Gitschier J, Higgins JJ, Hayflick SJ. HARP syndrome is allelic with pantothenate kinase-associated neurodegeneration. Neurology 2002;58:1673-1674.
4. Houlden H, Lincoln S, Farrer M, Cleland PG, Hardy J, Orrell RW. Compound heterozygous PANK2 mutations confirm HARP and Hallervorden-Spatz syndromes are allelic. Neurology 2003;61:1423-1426.
5. Danek A, Hegle RA. Compound heterozygous PANK2 mutations confirm HARP and Hallervorden-Spatz syndromes are allelic [Internet]. Neurology; 2004. Available at: https://n.neurology.org/content/compound-heterozygous-pank2-mutations-confirm-harp-and-hallervorden-spatz-syndromes-are.
6. Orrell RW, Amrolia PJ, Heald A, Cleland PG, Owen JS, Morgan-Hughes JA, et al. Acanthocytosis, retinitis pigmentosa, and pallidal degeneration: a report of three patients, including the second reported case with hypoprebetalipoproteinemia (HARP syndrome). Neurology 1995;45(3 Pt 1):487-492.