Neuroacanthocytosis Syndromes
– A Current Overview

R.H. Walker, S. Saiki, and A. Danek

Abstract Neuroacanthocytosis syndromes are characterized by the presence of “thorny” red blood cells and neurodegeneration of the basal ganglia, along with peripheral neuromuscular findings, seizures, and a variety of neuropsychiatric features. In recent years significant progress has been made in understanding the molecular pathophysiology of these disorders; cases are now identified as autosomal recessive chorea-acanthocytosis, X-linked McLeod syndrome, or more rarely, pantothenate kinase-associated neurodegeneration or Huntington’s disease-like 2. Molecular analysis of classic reports of neuroacanthocytosis will clarify nomenclature and improve understanding of genotype-phenotype correlations. In addition, there are issues of atypical inheritance patterns which remain to be elucidated. A relatively high incidence of chorea-acanthocytosis in Japan may indicate a genetic founder effect, and has led to significant developments from Japanese researchers.

R.H. Walker
Departments of Neurology, James J. Peters Veterans Affairs Medical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY, USA
ruth.walker@mssm.edu

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1 Advances in Neuroacanthocytosis

This volume follows up on “Neuroacanthocytosis syndromes” [2], which summarized the proceedings of a symposium which took place in Seeon, Bavaria, in May 2002. That meeting brought together a diverse group of researchers from around the world, including movement disorder neurologists, molecular biologists, hematologists, and neurogeneticists, and many others involved in studying this group of rare diseases. The group explored “New perspectives for the study of basal ganglia degeneration”, following the discovery by scientists in England and Japan of the genetic basis of the core neuroacanthocytosis (NA) syndromes, McLeod syndrome (MLS) and chorea-acanthocytosis (ChAc) [43, 100, 142].

The collaborations initiated at this meeting led to the second Neuroacanthocytosis Symposium (Montreal Neurological Institute, Montreal, Canada, April 2005) and the third symposium, a satellite meeting of the 10th International Congress of Parkinson’s disease and Movement Disorders, organised by the Movement Disorder Society, in Kyoto, Japan, October 2006 (Figs. 1 and 2 of the Foreword). An interim meeting was convened at the Third International Congress on Vascular Dementia in Prague, Czech Republic, October 2003 [27].

The present volume expands on the abstracts of the Kyoto [111] and Montreal [7] symposia. Major scientific developments since the first meeting in 2002 have included the publication of the reference method for acanthocyte detection [127], the description of XK mutations without full-blown MLS [54, 150], and the discovery of additional members, XPLAC and XTES, of the XK family [18]. The genes related to CHAC were found to belong to a conserved gene family involved in vacuolar protein sorting, thus leading to the renaming of CHAC as VPS13A [143]. The use of chorein antibodies for diagnosis of ChAc using Western blot assay [30] was a major clinical advance, obviating the need for molecular analysis of the large VPS13A gene for diagnosis in most cases.

Major developments from Japan included the observation of cellular inclusions in ChAc muscle [133] and the first animal model for ChAc [137], mice with the VPS13A deletion-mutation found in the Ehime province [71, 87].

The nosology of NA syndromes has evolved since the Seeon meeting. A family reported there with autosomal dominant NA [148] was identified as having Huntington’s disease-like 2 [144, 146, 147, 149] (see chapter by Margolis).

The fourth “core” NA syndrome, pantothenate-kinase associated neurodegeneration (PKAN), has been better delineated with the availability of genetic testing for PANK2 mutations. The so-called HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, pallidal degeneration), of which only two cases have been reported, was proven to be allelic with PKAN [26, 46, 95]. The occurrence of acanthocytes as a feature of PKAN – in at least 8% of patients – has lately become more appreciated [39, 97].

Here we discuss the history of NA in Japan and in the English medical literature, including the appropriateness of the use of the “Levine–Critchley” eponym and the confusion in diagnosis of NA syndromes prior to the molecular era. We discuss recent developments in ChAc and issues related to the genetics of this disorder.