Available online at www.sciencedirect.com

SciVerse ScienceDirect

Neuromuscular Disorders 24 (2014) 48–55

www.elsevier.com/locate/nmd

The absence of curly hair is associated with a milder phenotype in Giant Axonal Neuropathy

Lisa A. Roth [a,*], Bethany L. Johnson-Kerner [a], Jonathan D. Marra [b], Nicole H. LaMarca [b], Douglas M. Sproule [b]

[a] College of Physicians and Surgeons, Columbia University Medical Center, New York, NY, United States
[b] Division of Pediatric Neurology, Department of Neurology, Columbia University Medical Center, New York, NY, United States

Received 5 March 2013; received in revised form 29 May 2013; accepted 11 June 2013

Abstract

Giant Axonal Neuropathy is a pediatric neurodegenerative disorder caused by autosomal recessive mutations in the *GAN* gene on chromosome 16q24.1. Mutations in the *GAN* gene lead to functional impairment of the cytoskeletal protein gigaxonin and a generalized disorder of intermediate filaments, including neurofilaments in axons. Tightly curled hair is a common but not universal feature of Giant Axonal Neuropathy. The pathogenesis of curly hair is unknown, although disruption of keratin architecture is thought to play a role. As part of a broader natural history study of Giant Axonal Neuropathy, we found that the absence of curly hair is correlated with superior motor function ($p = 0.013$) when controlling for age, as measured by the Gross Motor Function Measure. Theoretically, higher levels of functional gigaxonin protein or compensatory mechanisms could produce fewer abnormalities of neurofilaments and keratin, accounting for this phenotype. We suggest that straight-haired patients with Giant Axonal Neuropathy are potentially underdiagnosed due to their divergence from the classic phenotype of the disease. Due to their non-specific features of an axonal neuropathy, these patients may be misdiagnosed with Charcot–Marie–Tooth Disease type 2. Genetic testing for Giant Axonal Neuropathy should be considered in relevant cases of Charcot–Marie–Tooth Disease type 2.

Keywords: Giant Axonal Neuropathy; GAN; Gigaxonin; Charcot–Marie–Tooth disease; Straight hair; Gross Motor Function Measure

1. Introduction

Giant Axonal Neuropathy (GAN) is a pediatric degenerative disorder of the central and peripheral nervous systems. In 1972, Asbury et al. [1] and Burg et al. [2] first reported GAN in a 6-year-old girl who met her early developmental milestones, but experienced a progressive decline in motor function in the first few years of life. She had distal and proximal weakness, clumsiness, dysarthria, areflexia, and distally impaired sensation. Her photograph [2] is most remarkable for the "Shirley Temple-like" curls in her hair. Asbury and Berg describe her hair as "kinky," although this word more aptly connotes the steel wool-like hair of Menkes Disease than her tightly wound curls. Sural nerve biopsy showed a reduced population of nerve fibers, with the remaining myelinated and unmyelinated fibers featuring "giant" axons filled with neurofilaments.

The true incidence of GAN is unknown, but it has since been reported in approximately 100 patients worldwide [3]. Asbury and Berg's description still encapsulates the classic phenotype of GAN, but subsequent cases have enriched and expanded our knowledge of the disease. GAN's known effects include dysphagia [4], nystagmus [5], dysmetria [6], precocious puberty [7], and possibly mental retardation, although many patients with the later have

* Corresponding author. Address: Columbia University, Pediatric Neurology, 180 Fort Washington Avenue, Harkness Pavilion, Rm 503, New York, NY 10032, United States. Tel.: +1 212 342 2920; fax: +1 212 342 2893.
E-mail address: Lr2253@columbia.edu (L.A. Roth).

0960-8966/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.nmd.2013.06.007

consanguineous parents and, hence, other possible genetic causes for this symptom [8,9]. The overall disease course involves relentless progression of weakness and ataxia, with loss of ambulation before 10 years and death from respiratory failure in the third decade.

A unique and striking feature of GAN is the presence of tightly curled hair in many patients. However, there have been cases of straight-haired patients with giant axons on nerve biopsy [10–15], some of whom were reported to have milder symptoms and a slower disease course [16]. Further confounding this phenotypic variability was the discovery of giant axons on histopathology in diseases other than GAN, including toxic neuropathies caused by exposure to industrial chemicals [17,18], Charcot–Marie–Tooth disease type 2 [19], infantile neuroaxonal dystrophy [20], and, more recently, *BAG3*-associated myofibrillar myopathy [21]. The giant axons in these reports are essentially indistinguishable from those in GAN (although somewhat less ubiquitous). Hence, although giant axons on nerve biopsy are suggestive of GAN, they are not pathognomonic. In the earlier literature, the phenotypic variability within GAN and the presence of giant axons in other syndromes suggested that the label of "GAN" was being used to describe multiple, distinct diseases.

These ambiguities were resolved in 2000, when Bomont et al. discovered that autosomal recessive mutations in the *GAN* gene, coding for the protein gigaxonin, form the genetic basis of GAN [22]. The exact function of gigaxonin has yet to be determined, but its loss is thought to produce the large-scale disruption of intermediate filament architecture associated with GAN, affecting neurofilaments in neurons and vimentin in fibroblasts. However, there has been little progress in correlating genotype with the phenotypic variations seen within the disease [23,24]. Additionally, Asbury and Berg's classic phenotype still remains a powerful predictor of disease – to the authors' knowledge, no patient with tightly curly hair and the typical clinical syndrome has even been proven not to have a *GAN* mutation. However, recognition of the *GAN* gene has clarified the diagnosis in cases of phenotypic uncertainty, especially in patients with milder disease and straight hair. In this study, we explore the relationship between the presence of curly hair and disease severity among patients with GAN.

2. Methods

2.1. Natural history study

This study draws upon baseline data obtained as part of a comprehensive study of the natural history of Giant Axonal Neuropathy (GAN). Thirteen subjects with a genetic or clinical diagnosis of GAN were recruited. As part of the longitudinal study, subjects will be assessed at 6-month intervals over a 2-year period. Study procedures include standardized measures of clinical function, nerve conduction studies, motor unit number estimation, brain and spine MRI, cerebrospinal fluid and serum collection, skin biopsy, standardized measures of cognitive ability, and standardized assessments of quality of life. We aim to elucidate the clinical features of GAN and their rate of progression, as well as variability within the disease.

2.2. Clinical assessment

A full medical history and physical exam was performed for all subjects. Motor function was assessed with the Charcot Marie Tooth Neuropathy Score (CMT-NS) [25], Friedreich Ataxia Rating Scale (FARS) [26,27], Gross Motor Function Measure (GMFM) [28,29], Jebsen Taylor Timed Test ("Jebsen") [30], and Six-Minute Walk Test (6MWT) [31]. Baseline testing revealed limitations in some of these measures – the CMTNS and 6MWT had limited applicability in non-ambulatory subjects, and subjects with hand contractures or impaired fine movements were unable to perform the Jebsen. The GMFM was successfully performed in 12/13 subjects and the FARS in 11/13; younger patients had difficulty understanding some of the required tasks.

2.3. Statistical analysis

Our primary hypothesis was that straight hair is associated with improved motor function compared to curly hair when controlling for age. Multiple linear regression analysis was used to assess the relationship of the FARS and GMFM scores to the following variables: age (continuous), sex, and hair texture (straight or curly). This model assumes a linear relationship between the outcome measures and age. Analysis was performed with SAS Enterprise Guide software. A two-sided p-value of less than 0.05 was considered statistically significant.

3. Results

Thirteen subjects with Giant Axonal Neuropathy (GAN) were enrolled in the natural history study. Their genetic and clinical features are listed in Table 1. 10/13 subjects had a genetic diagnosis of GAN. The remaining 3/13 subjects were diagnosed based on the expected clinical features and diagnostic work-up. Nerve biopsies were performed on seven subjects, but only the pathology reports were available for six of these biopsies. All subjects exhibited giant myelinated and unmyelinated axons filled with irregularly oriented neurofilaments and without signs of inflammation (Fig. 1). No discrepancy in the severity of the histopathology between subjects could be ascertained from the reports based on age or other clinical features.

Two subjects had a history of parental consanguinity. One subject was adopted and his family history could not be confirmed. Genetic testing of at least one unaffected