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Short Communication

The association between educational attainment and SCA 3 age of onset and disease course

Katherine Iannuzzelli [a], Rosa Shi [b], Reece Carter [b], Rachel Huynh [c], Owen Morgan [a], Sheng-Han Kuo [d,e], Jee Bang [a], Kelly A. Mills [a], Kristin Baranano [a], David S. Zee [a], Emile Moukheiber [a], Ricardo Roda [a], Ankur Butala [a], Cherie Marvel [a], Michelle Joyce [a], Ximin Li [f], Jiangxia Wang [f], Liana S. Rosenthal [a,*]

[a] Department of Neurology, Johns Hopkins School of Medicine, United States
[b] Department of Arts and Sciences, Johns Hopkins University, United States
[c] Department of Medicine, Utah Health Sciences, United States
[d] Department of Neurology, Columbia University, United States
[e] Initiative for Columbia Ataxia and Tremor, Columbia University, United States
[f] Johns Hopkins Bloomberg School of Public Health, United States

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ABSTRACT

Background: The number of trinucleotide CAG repeats is inversely correlated with the age at onset (AAO) of motor symptoms in individuals with Spinocerebellar Ataxia type 3 (SCA 3) and may be responsible for 50%–60% of the variability in AAO. Drawing from a social determinants of health model, we sought to determine if educational attainment further contributes to the AAO and motor symptom progression of SCA 3.
Methods: We performed a retrospective chart review in which twenty individuals met criteria for inclusion and had been seen by an ataxia specialist at our hospital between January 2005 and July 2019. AAO of motor symptoms and Scale for Assessment and Rating of Ataxia (SARA) scores were used as primary outcome measures.
Results: Using a linear regression, we found that having greater CAG repeat length and greater than 16 years of education results in an earlier AAO. The importance of the CAG repeat length on AAO, however, is greater amongst individuals with lower education. Using a linear mixed model evaluating SARA score over time with AAO, we found that less than 16 years of education is associated with faster progression of the disease.
Conclusion: In our group of SCA 3 patients, level of education correlated with both the AAO and SARA scores. Though our findings need to be confirmed with a larger cohort, our study suggests that level of education can have a strong influence on health outcomes in SCA 3 and possibly other groups of patients with ataxia.

1. Introduction

Spinocerebellar Ataxias (SCAs) are neurodegenerative diseases that follow autosomal dominant inheritance. SCA type 3 is caused by pathologically expanded CAG repeats in the *ATXN3* gene (14q21). Clinical features of SCA 3 include the core features of cerebellar ataxia and sometimes additional characteristics of ophthalmoplegia, pyramidal signs, basal ganglia symptoms and peripheral neuropathy. Individuals with at least 45 CAG expansions in *ATXN3* develop symptoms, and greater CAG repeat lengths are associated with earlier age at onset (AAO). CAG repeat length is thought to determine approximately 50%–60% of variability in AAO in SCA 3 patients [1]. The relationship between CAG repeat length and disease progression, however, is not as clear. Some studies have found that greater CAG repeat length is associated with faster ataxia progression [2] while others have found that disease duration, but not CAG repeat length, correlates with the Scale for Assessment and Rating of Ataxia (SARA) scores, motor changes, and MRI markers of ongoing cerebellar degeneration [3]. Recent studies have found that ethnicity and geographic origin further contribute to differences in AAO and disease progression [4].

Social determinants of health, as defined by the World Health Organization, are "the conditions in which people are born, grow, live, work and age" and are "the fundamental drivers of these conditions" [5]. Educational attainment is one of the most commonly used social

* Corresponding author. 10751 Falls Road, Suite 250 Lutherville, MD, 21093, United States.
E-mail address: liana.rosenthal@jhmi.edu (L.S. Rosenthal).

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determinants of health because it can be assessed in most members of the population, and higher educational attainment is usually predictive of higher incomes, more affluent neighborhoods, and healthier working conditions [6].

The role of educational attainment in the severity of genetic diseases is not well understood. We sought to determine if self-reported educational attainment, contributes to AAO or disease course of SCA 3 patients.

2. Patients and methods

2.1. Ethics

With the approval of the Johns Hopkins Institutional Review Board, we conducted a retrospective chart review of patients from the Johns Hopkins Ataxia Center with a genetic diagnosis of SCA 3. Data was collected from patients who visited the clinic between January 2005 and July 2019.

2.2. Subjects

Twenty-nine people with a clinical diagnosis of SCA 3 were identified as having been seen in our clinic since 2013. CAG repeat length was determined based on genetic testing results from a CLIA approved lab and educational attainment was based on self-report. We therefore excluded five people who did not have the results of genetic testing, three people who did not have self-reported educational attainment, and one person who was pre-symptomatic. The remaining twenty patients had a clearly described AAO, defined as the age at which the patient noticed ataxia symptoms as reported during their first clinic visit to our institution, and were included in the analysis for AAO. Sixteen of these patients with follow-up visit data had at least one reliable SARA score conducted by a neurologist or physical therapist and were used to analyze the progression of the disease. To determine the household income for all participants, we used publicly available records reporting the median household income in the zip code of the participants' address.

2.3. Statistical analysis

Continuous variables were compared across educational groups with the *t*-test and Wilcoxon rank sum tests. Categorial variables were compared using the Fisher's exact test. Linear regression was used to model AAO on pathological CAG repeat length, education, and interaction between pathological CAG repeat length and education. CAG repeat length was centered at the mean of 71 for our model; therefore, we were evaluating the difference in CAG repeat length from 71. Linear mixed model was used to model total SARA score on time since AAO, education and interaction between time and education with patients as random intercept. All analyses were conducted in R version 3.6.2. Test results were considered significant at the 0.05 level (two-sided).

3. Results

3.1. Demographics

Demographic data for all patients is presented in Table 1 and stratified by educational attainment being above or below the median of 16 years. Our sample included an equal number of men and women; 55% identified as White or Caucasian, and 45% identified as Black or African American. The average AAO was 41.1 years, and the median CAG repeat length was 71. The median household income was $84,340. Patients with follow-up used for analysis of progression of the disease had similar demographic characteristics except an equal number of Whites and Blacks (See Supplemental Table 1).

There was a significant difference in race when comparing the two educational groups with more White than Black individuals in the "16 years or higher" educational group (10 vs. 4; p = 0.05). Further, the lower educational group had significantly more visits and naturally, more SARA scores than did the higher educational group. Amongst those patients with follow-up, there were no differences in educational attainment and number of SARA scores.

Table 1
Descriptive table of all patients stratified by educational attainment split at 16 years of education.

Group	Education 16 years or higher (n = 14)	Education less than 16 years (n = 6)	p-value (n = 6)	All Patients (n = 20)
Race (n, %)				
Black	4 (28.6%)	5 (83.3%)	0.05	9 (45%)
White	10 (71.4%)	1 (16.7%)		11 (55%)
Gender (n, %)				
Female	8 (57.1%)	2 (33.3%)	0.63	10 (50%)
Male	6 (42.9%)	4 (66.7%)		10 (50%)
Number of visits with SARA (median [IQR])	1.00 [0.25, 3.50]	4.00 [3.25, 5.50]	0.05	2.50 [1.00, 4.25]
Age at onset (mean, (SD))	41.1 (9.0)	41.2 (17.1)	0.99	41.1 (11.5)
Years of education	17 [16, 18]	14 [13.25, 14]	<0.01	16 [14,18]
Median household income based on ZIP code (median [IQR])	$88,868 [$63,917, $131,960]	$55,630.5 [$35,740.75, $83,111.75]	0.13	$84,340 [$48,762, $102,578]
Pathological CAG repeat length (median [IQR])	70 [67.25, 72.75]	72.50 [70.25, 74]	0.39	71 [67.75, 74.00]

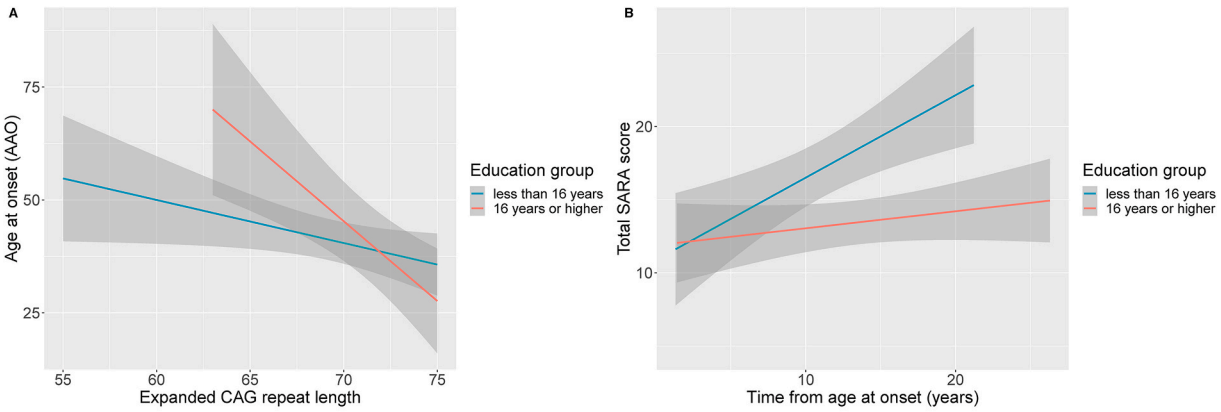
p-value for comparison of individuals with 16 years of education or higher versus those with less than 16 years of education.

3.2. Influence of education on AAO

We first sought to determine whether educational attainment influences AAO in SCA 3 patients. A linear regression was used to model AAO based on self-reported educational attainment (16 years or higher vs. less than 16 years) and pathological CAG repeat length (Fig. 1A and C). Pathological repeat length is indeed a large influence on AAO but the effect size was greater amongst individuals in the lower education group (2.25 years, 95% CI: −5.85, 10.36). Specifically, the rate at which the AAO of the less educated group decreased per 1 unit increase of pathological CAG repeat length was higher than for the more educated group (−2.58 years, 95% CI: −4.44, −0.7). For the more educated group (16 years or higher), every 1 unit increase of pathological CAG repeat length was associated with a −0.95 year (95% CI: 1.84, −0.07) change in AAO. For the less educated group, every 1 unit increase of pathological CAG repeat length was associated with a −3.53 year (95% CI: −5.05, −2.01) change in AAO.

3.3. Influence of education on SCA 3 disease progression

Next, we asked whether educational attainment influenced disease progression in SCA 3 patients. A linear mixed model was used to model SARA score based on years since AAO and educational attainment (16 years or higher vs. less than 16 years) (Fig. 1B and D). As expected, time since AAO was associated with higher SARA scores. The less educated group increased faster (0.58, 95% CI: 0.01, 1.14) in SARA score compared to that of the more educated group. For the less educated group, every 1-year increase of time since AAO was associated with a 0.96 (95% CI: 0.53, 1.39) increase in SARA score. For the more educated group, every 1-year increase of time since AAO was associated with a 0.38 (95% CI: 0.03, 0.74) increase in SARA score.



C

	Est	95%CI
Intercept	39.5	(34.9, 44.1)
CAG repeat length	−0.95	(−1.84, −0.07)
Education:< 16yr	2.25	(−5.85, 10.36)
Interaction between CAG & Edu:<16yr	−2.58	(−4.44, −0.71)

D

	Est	95%CI
Intercept	7.45	(1.42, 13.47)
time from AAO	0.96	(0.52, 1.4)
Education:< 16yr	1.12	(−7.42, 9.66)
Interaction between time & Edu:<16yr	−0.58	(−1.14, −0.01)

Fig. 1. A and C (n = 20 patients). Results from the linear regression calculated to predict AAO based on self-reported educational attainment (16 years or higher vs. less than 16 years) and pathological CAG repeat length. B and D (n = 56 visits from 16 patients). Results from linear mixed model calculated to predict SARA score based on years since AAO) and educational attainment (16 years or higher vs. less than 16 years). EDU: Education; CAG: CAG repeat length.

4. Discussion

Our study aimed to determine the association between educational attainment and AAO and disease course among individuals with SCA 3. In line with previous studies, we have shown that CAG repeat length was negatively associated with the age of symptom onset for SCA 3 [7]. We further determined that while higher educational attainment was associated with earlier AAO, it seems to mitigate the impact of CAG repeat length on AAO. Higher education was also associated with slower disease progression. Our findings, while preliminarily given our small cohort, fit within the social determinants of health model highlighting the importance of educational attainment in patient outcomes.

Our analysis highlights that educational attainment may account for some of the non-genetic variability of AAO. First, we found that having less than 16 years of education was associated with an older AAO, which is similar to the relationship found in Huntington's disease, another CAG repeat neurodegenerative disease [8]. However, the effect of education on AAO in our patients was more complex when considering its interaction with CAG repeat length. That is, as seen in Fig. 1A, the negative linear relationship between AAO and CAG repeat length was significantly steeper in those with less than 16 years of education.

Educational attainment may also contribute to differences in disease progression. We found that having less than 16 years of education was significantly associated with higher SARA scores over length of time from AAO. As seen in Fig. 1B, having 16 years or more of education is associated with a less steep increase of SARA scores over time from AAO relative to those with less than 16 years of education. This finding suggests that education is a protective factor when it comes to disease progression of SCA 3. This may relate to individuals with higher socioeconomic status having more resources for specialized care such as physical therapy, personal training, speech therapy or occupational therapy that improve functional outcomes.

One explanation for both findings, however, is that individuals who develop symptoms later in life progress faster. This would be consistent with findings in other neurodegenerative conditions. For example, in Parkinson's individuals with earlier symptom onset of PD seem to progress at a slower rate than those with later symptom onset [9]. Amongst individuals with Huntington's disease, AAO also affects disease duration with the fastest progression amongst juvenile and late onset individuals [10]. This relationship has not been investigated in the SCAs, and our findings suggest that education may be an important modifier or even driver of this correlation between AAO and disease progression.

There are some limitations to our analysis. First, the sample size was small due to the limited number of patients with confirmed genetic SCA 3 diagnosis. While we were interested in the relationship between SARA score and time from AAO, this relationship may differ by patient. Due to our small sample size we had to assume that the rate of change in SARA score was linear and the same for all individuals and could not allow for differences in rate of change of the SARA score over time. While the significant findings of the regression analysis lack statistical power due to the small sample size, we still believe the results are clinically relevant and merit reporting.

Further, our cohort may not be representative of all individuals with SCA 3. Specifically, they were more educated and lived in areas of higher median income than the average US resident in 2018 [11,12]. This cohort also only included people with confirmed genetic testing, which requires either financial means or insurance coverage. Put together, the variance in AAO and progression rate related to educational attainment could be underestimated in this cohort.

Despite these limitations, our analyses highlight the importance of including socioeconomic variables in future research for diseases like SCA 3. Our research emphasizes the importance of including nongenetic factors on the health outcomes of patients with familial degenerative neurological diseases, including SCA 3.

Author contributions

All authors contributed to the study conceptualization and design. Data collection was performed by Katherine Iannuzzelli, Rosa Shi, Reece Carter, and Rachel Huynh. Statistical analyses was performed by Ximin Li and Jiangxia Wang. The first draft of the manuscript was written by Katherine Iannuzzelli and Liana Rosenthal and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.02.025.

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