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Original Article

Pediatric-Onset Multiple Sclerosis Disease Progression in Kuwait: A Retrospective Analysis

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ABSTRACT

BACKGROUND: Pediatric and adults patients share basic aspects of multiple sclerosis; however, pediatric patients may have distinctive clinical features and disease course. **OBJECTIVE:** To compare the demographic and clinical characteristics between patients of pediatric-onset and adult-onset multiple sclerosis. **METHODS:** Using the Kuwait National Multiple Sclerosis Registry , multiple sclerosis patients with disease onset at age ≤17 years (pediatric-onset multiple sclerosis) or >17 years (adult-adult multiple sclerosis) were identified. Several demographics and clinical characteristics were analyzed. Disability measures and time to reach secondary progressive multiple sclerosis were compared between the two cohorts using chi-square and Student *t* tests. **RESULTS:** A total of 984 records of multiple sclerosis patients were assessed, of which 111 (11.3%) had disease onset at age ≤17 years. The female to male ratio did not differ between the two groups ($P = 0.19$). The mean age at onset of pediatric- and adult-onset multiple sclerosis was 14.9 and 27.68 years, respectively. Pediatric-onset multiple sclerosis patients were more likely to have brainstem/cerebellar ($P < 0.03$) and multifocal ($P < 0.01$) presentations at onset. The mean number of relapses did not differ between the two cohorts (3.4 ± 2.1 versus 3.05 ± 2.2; $P = 0.14$). The mean expanded disability status scale score at last visit was lower in the pediatric-onset cohort compared with the adult-onset cohort (2.38 ± 1.72 versus 3.02 ± 2.18; $P = 0.003$). The time to develop secondary progressive multiple sclerosis was longer in the pediatric-onset cohort (14.6 ± 4.6 years versus 11.0 ± 5.3 years; $P < 0.04$). **CONCLUSIONS:** Pediatric-onset multiple sclerosis patients were more likely to have brainstem/cerebellar and multifocal symptoms at onset. Although the number of relapses was comparable to the adult-onset cohort, multiple sclerosis patients with pediatric-onset had lower expanded disability status scale scores and a longer time to reach secondary progressive course at last follow-up visits.

Keywords: multiple sclerosis, pediatric, Kuwait, disability, progression

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Introduction

Early-onset multiple sclerosis (MS) accounts for 2% to 10% of all MS cases, representing the most frequent neuroimmunological disorder in children and young adolescents.[1] Studying epidemiological changes in early MS is important in determining the risk of development and progression of MS in the pediatric population. Although pediatric MS patients share similar pathogenesis with adults, they may have distinct phenotypic characteristics and disease course. Despite an early and an intense inflammatory course, the initial recovery is reportedly better and disease progression is slower in children when compared with the disease course in adults.[1,2] We compared the demographics, clinical characteristics, and progression of MS between pediatric- and adult-onset MS patients.

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Patients and Methods

We conducted a retrospective analysis using the Kuwait National MS Registry.[3,4] The registry was established in 2010 after combining the databases of all major hospitals including MS clinics, which together accounted for nearly 98% of the MS patients diagnosed in the country. MS patients' data were retrieved from patient records and were screened for accuracy before entering them in the registry. Patients were subsequently followed on regular basis (at least two visits per year) and their clinical data were prospectively updated in the registry. The data were extracted from the registry on August 30, 2014. The most recent data entry was used for analysis. Patients were divided into two groups: pediatric-onset MS if the disease onset occurred before age 17 years and adult-onset MS if the disease onset occurred after age 17 years. Demographics (age, sex) and clinical characteristics (age at disease onset, symptom presentation at onset, disease duration, course of the disease, number of relapses, initial and last follow-up expanded disability status scale [EDSS] scores,[5] time to reach secondary progressive course and the use of prior disease modifying therapies) were extracted. EDSS assessments were scored initially by the treating physicians and confirmed subsequently by neurologists who completed the neurostatus certification.[6] Sustained EDSS scores at last follow-up visits were used in the final analysis. Patients with incomplete data, clinically isolated syndrome, and other demyelinating disorders such as neuromyelitis optica or acute disseminated encephalomyelitis were excluded. The symptom presentations at onset were localized into optic, supratentorial, brainstem/cerebellar, and spinal cord systems. A disabling relapse was defined as any relapse, which fulfilled one or more of the following criteria: a motor or cerebellar relapse with incomplete recovery, a relapse that affected the patient's activity of daily living or ability to work, or a relapse requiring hospitalization.[7,8] Disease progression was defined as progressive worsening of a patient's neurological status resulting in an increase of at least 1 point on the EDSS and sustained for at least 6 months, thus excluding any transient worsening of disability related to relapses. An aggressive disease course was defined as having at least two relapses within 1 year or a disabling relapse with at least one gadolinium-enhancing lesion on magnetic resonance imaging performed within the past 3 months.[9] Breakthrough disease was defined as having persistent relapses and magnetic resonance imaging activity after instituting first-line disease modifying therapies for at least 1 year.[10] The outcome measure was to compare several demographics and clinical variables between the pediatric-onset MS and adult-onset MS cohorts, with emphasis on the proportion of patients who reached secondary progressive course.

Descriptive statistics (i.e., mean) and standard deviations were calculated. Student *t* test and chi-square analysis were used to compare numerical values and nonnumerical values respectively between the two groups. A correlation coefficient test was calculated to measure the strength of association between quantitative data. Multivariate analysis was performed to determine variables predictive of secondary progressive MS course. Hazard ratios (HR) and their 95% confidence intervals (CI) were computed from the parameters' estimates of the final multivariable analysis and used for interpretation of the results. A probability of $P \leq 0.05$ was accepted as significant. The local ethical committee approved data collection. Patients aged 18 or older signed informed consent forms. Parents of patients aged younger than 18 years completed parental informed consent forms and additional assents forms were obtained from patients aged 12 to 18 years for their data to be stored and to be used for research purposes.

Results

A total of 984 complete records of MS patients were evaluated, of which 111 (11.3%) were pediatric-onset MS cases who had disease onset at age ≤17 years. Of 111 pediatric-onset MS patients, 19 (17.1%) were aged younger than 12 years. Basic demographics and clinical characteristics were outlined in Table 1. The female to male ratio did not differ between the two cohorts ($P = 0.19$). Pediatric-onset MS and adult-onset MS cohorts were followed for mean durations of 3.50 ± 1.44 and 3.27 ± 1.36 years, respectively. The mean age at onset of pediatric- and adult-onset MS was 14.9 ± 1.9 (range, 9.0-16.9) and 27.68 ± 8.5 (range, 17.0-52.8) years, respectively. Family history was reported in 12.6% of pediatric-onset MS compared with 15.25% of adult-onset MS cohort ($P = 0.47$). Pediatric-onset MS patients were more likely to have cerebellar/brainstem (36% versus 26.5%; $P < 0.03$) and multifocal symptoms (15.3% versus 8.1%; $P < 0.01$) at onset. The average of the total number of relapses did not differ between the two groups (3.4 ± 2.1 versus 3.05 ± 2.2; $P = 0.14$). There was a trend toward an aggressive course in the pediatric cohort (14.4% versus 8.8%, $P = 0.06$). Although a higher proportion of pediatric-onset MS patients had breakthrough disease ($P = 0.03$), the mean EDSS score was significantly lower (2.38 ± 1.72 versus 3.02 ± 2.18; $P = 0.003$) at the end of the observational period. The distribution of EDSS scores at last visits of the both cohorts was plotted in the Figure. The time to develop secondary progressive MS was significantly longer in pediatric-onset MS cohort (14.63 ± 4.64 versus 11.03 ± 5.33; $P < 0.04$).

Additional analysis using independent Student *t* test was performed to compare the EDSS means between the two cohorts based on disease duration (Table 2). Pediatric-onset MS cohort had a significantly higher mean EDSS in the first 5 years (3.0 ± 1.57 versus 2.14 ± 1.65; $P = 0.002$), whereas a higher mean EDSS was observed in adult-onset MS patients who had disease duration of more than 10 years (3.98 ± 2.30 versus 2.45 ± 1.45; $P = 0.002$). The mean age of patients who reached secondary progressive MS in pediatric- and adult-onset MS was 29.6 ± 4.0 and 40.1 ± 9.1 years, respectively. Younger age at onset was significantly associated with longer duration to reach secondary progressive course ($r = -0.094$, $P < 0.001$). However, there was no statistically significant correlation between early aggressive course and time to reach secondary progressive course ($r = -0.017$; $P = 0.961$). With respect to exposure to disease-modifying therapies, a higher proportion of pediatric-onset MS had received natalizumab (29.7% versus 16.7%; $P < 0.0001$) either as a first-line therapy in aggressive patients (12.6%) or as a second-line therapy secondary to disease breakthrough (17.1%), whereas most adult-onset MS patients had continued first-line therapies (45% versus 34.2%; $P = 0.03$). Multivariate analyses revealed that sex was not associated with conversion to secondary progressive course (adjusted HR = 1.07; 95% CI: 0.51-2.23; $P = 0.87$) as shown in Table 3. Patients presented with optic neuritis at onset were less likely to reach secondary progressive course (adjusted HR = 0.4; 95% CI: 0.2-0.8; $P = 0.01$), whereas patients presented with brainstem/cerebellar (adjusted HR = 3.5; 95% CI: 1.2-9.8; $P = 0.02$) or multifocal symptoms at onset (adjusted HR = 4.4; 95 %CI: 1.5-13.1; $P = 0.01$) were more likely to reach secondary progressive course.

Discussion

Our pediatric-onset MS cohort had different clinical characteristics at baseline and had slower disease progression throughout the observational period. Pediatric-onset MS patients were more likely to present with brainstem/