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Original Article NEUROLOGY

Epidemiological study of congenital myasthenic syndromes based on national electronic health database of Turkiye

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ABSTRACT

OBJECTIVE: Congenital myasthenic syndromes (CMS) represent a group of genetically heterogenous disorders characterized by defective signal transmission at the neuromuscular junction. Although global prevalence of CMS remains uncertain, regional studies have reported varying prevalence rates. This study aimed to define the incidence and prevalence of CMS in Turkiye utilizing data from the national electronic health registry. Additionally, the rate of pyridostigmine prescriptions among patients with CMS was assessed.

METHODS: The study was a retrospective national cohort study, and patients with at least three G70.2 ICD-10 code entries between 1 January 2015 and 22 May 2024 were included. While calculating incidence and prevalence rates official census data from the Turkish Statistical Institute were used.

RESULTS: A total of 406 patients were included in the study, with females comprising 48.8% of the cohort. The mean age at diagnosis was 20.59±21.65 years (median: 12.00, min-max: 0-86). Among the cohort, 58.6% were diagnosed before the age of 18, and 12.3% before the age of one. Pyridostigmine was prescribed at least once to 68.2% of the patients. The annual incidence of CMS ranged from 0.28 to 0.59 per million between 2016 and 2023. In 2023, the incidence and prevalence rates of CMS were calculated as 0.63 and 4.49 per million, respectively.

CONCLUSION: This study represents the first comprehensive nationwide epidemiological analysis of CMS in Turkiye utilizing the national electronic health registry. The study enhances the understanding of the epidemiological landscape of CMS in the country by reporting the current incidence, prevalence, and pyridostigmine prescription rates and underscores the significance of this rare but impactful neuromuscular disorder.

Keywords: Congenital myasthenic syndromes; epidemiology; incidence; prevalence.

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Congenital myasthenic syndromes (CMS) comprise a group of genetically heterogenous disorders characterized by defective signal transmission at the neuromuscular junction [1]. Based on the localization of mutated protein, CMS are classified into presynaptic, synaptic, and postsynaptic subtypes [2]. The clinical onset typical-

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ly occurs at birth or during early childhood with fatigable weakness of the ocular, bulbar, and limb muscles. However, milder cases may remain undiagnosed until early adulthood. Late-onset cases predominantly affect axial and proximal limb muscles [3, 4].

Although the global prevalence of CMS remains unknown, various regional studies have reported prevalence rates ranging from 9.2 to 22.2 per million in pediatric population [5–7] and from 1.8 to 3.1 per million in the general population [7–9]. Early diagnosis of CMS is essential due to the potential for effective therapeutic interventions [2, 10]. However, treatment strategies must be tailored to specific CMS subtypes, as medications beneficial for one form may exacerbate symptoms in another.

In this study, we primarily aimed to elucidate the epidemiological profile of CMS in Turkiye. Secondarily, we assessed the rate of pyridostigmine prescriptions among patients with CMS.

Highlight key points

- This study represents the first comprehensive nationwide epidemiological analysis of CMS in Turkiye, utilizing the national electronic health registry.
- In 2023, the prevalence rate of CMS was 4.49 per million in the general population and 10.00 per million among children.
- Between 2016 and 2023, the annual incidence of CMS ranged from 0.28 to 0.59 cases per million in the general population, and from 0.63 and 1.35 per million in the pediatric population.

MATERIALS AND METHODS

This study was conducted in collaboration with the Health Policy Development Working Group of the Republic of Turkiye Ministry of Health (RTMH). We identified patients with CMS based on International Classification of Diseases, 10th revision (ICD-10) coding within the e-Nabiz and Health Record Reporting System (HRRS) registries, both managed by RTMH.

e-Nabiz and HRRS Registries

In Turkiye, national health data are mainly managed by RTMH via e-Nabiz and HRRS, while the Social Security Institution administers the state-funded universal health insurance system that provides a coverage for most of the population. HRRS serves as a platform for recording and reporting healthcare data, facilitating more effective health service management. e-Nabiz is a digital interface enabling patients and healthcare providers to access medical records collected across healthcare facilities. For this study, all data were anonymized and handled in strict adherence to the data protection regulations.

Case Identification, Incidence and Prevalence Calculations

The HRRS database was queried for ICD-10 code G70.2 (congenital and developmental myasthenia) entries between 1 January 2015 and 22 May 2024. As diagnostic codes, whether preliminary, definitive or used for prescription, are permanently stored in the database, a case of CMS was defined as having at least three G70.2 code entries. This threshold was adopted from previous epidemiological studies of autoimmune myasthenia gravis [11, 12] to enhance diagnostic reliability (Fig. 1).

Demographic and clinical variables including sex, date of birth, age at diagnosis, province of residence, and the total number of G70.2 ICD-10 code entries were collected. The initial entry date of the G70.2 code in HRRS was designated as the date of diagnosis. Prescription data for pyridostigmine were identified using Anatomical Therapeutic Chemical (ATC) code N07AA02.

Since e-Nabiz was implemented in 2015 and prior data were retrospectively integrated that same year, prevalence estimates were calculated without temporal restrictions. However, incidence analyses were confined to the 2016–2023 period to avoid bias from retrospective data aggregation in 2015. Population data including total and sex-disaggregated provincial and Turkiye census data, and total and sex-disaggregated census data for children (<18 years) were obtained from the Turkish Statistical Institute website [13] for the corresponding years.

Statistical Analysis

Descriptive statistics were expressed as mean±standard deviation or median (minimum–maximum) for continuous variables and as frequency (percentage) for categorical variables. Statistical analyses were performed using IBM SPSS Statistics version 23.0 for Windows (Armonk, New York: IBM Corp.), and graphical visualizations were generated using GraphPad Prism version 10.2.3 for Mac, GraphPad Software, Boston, Massachusetts, USA (www.graphpad.com). A p-value <0.05 was considered statistically significant.

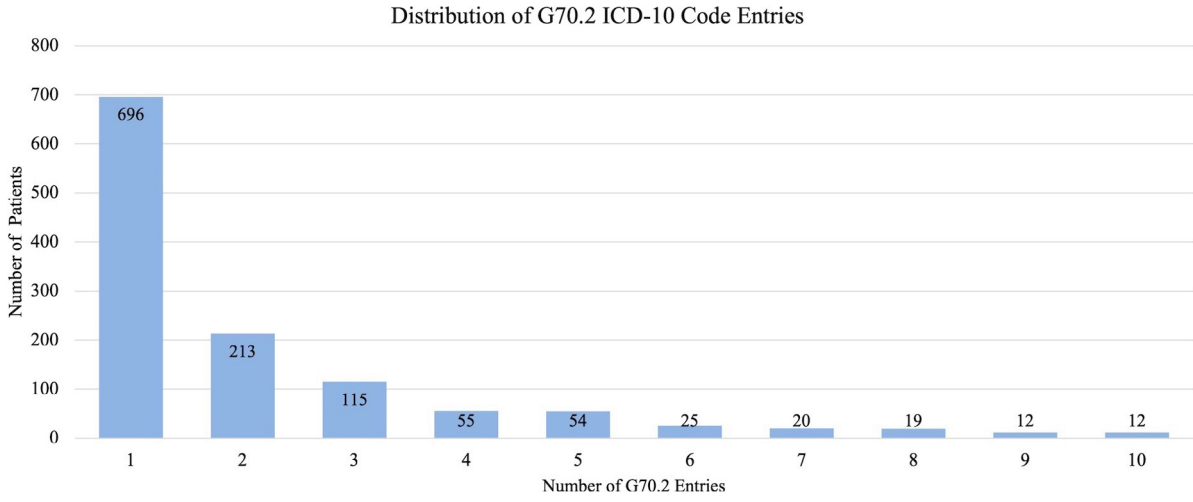

Figure 1. The graph showing the number of patients according to the number of G70.2 code entries.
ICD: International classification of diseases.

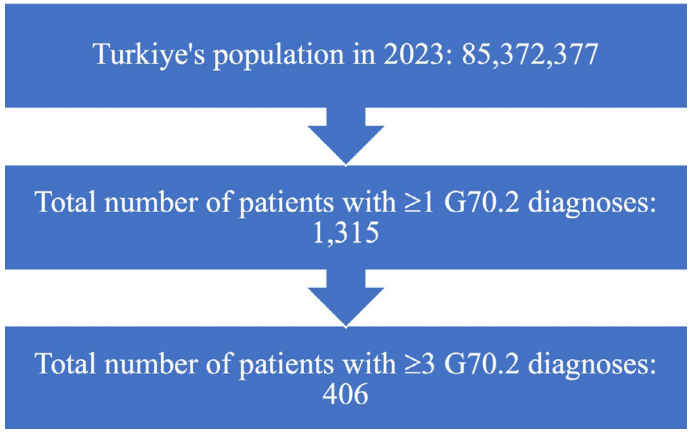

Figure 2. Study flowchart.

Ethical Approval

This study was conducted in line with the principles of the Declaration of Helsinki. Ethical approval was obtained from both the Republic of Turkiye Ministry of Health and University of Gulhane ethics committee (approval number and date: 2024-365, 28/06/2024). The requirement for informed consent was waived due to the retrospective nature of the study.

RESULTS

A comprehensive search of the RTMH database revealed 1,315 individuals with at least one G70.2 code entry. Among these, 406 individuals (198 females, 208 males) had ≥3 G70.2 entries and were thus included in the study cohort (Fig. 2). The female-to-male ratio was 0.95, indicating no notable sex predominance. The mean age at the diagnosis was 20.59±21.65 years (median: 12.00, min–max: 0–86). Of these, 238 patients (58.6%) received a diagnosis before the age of 18, and 50 (12.3%) were diagnosed before one year of age. Demographical characteristics and age at the time of initial diagnosis are presented in Table 1 and Figure 3.

Regional differences in diagnostic age were observed, with the lowest mean age at diagnosis reported in the Southeastern Anatolia region and the highest in the Mediterranean region (Fig. 4). Pyridostigmine was prescribed at least once to 277 patients (68.2%) overall. Subgroup analyses revealed prescription rates of 58.4% (n=139) among pediatric patients and 82.1% (n=138) among adults.

For nationwide prevalence calculation, individuals diagnosed in 2024 and those who had died prior to 2023 were excluded. We excluded three additional cases due to missing provincial data during regional prevalence calculations.

Between 2016 and 2023, the annual incidence of CMS in the general population ranged from 0.28 to 0.59 cases per million, while incidence in the pediatric population varied between 0.63 and 1.35 per million. The peak incidence occurred in 2017, with the lowest rate observed in 2023. As expected, incidence rates were consistently higher in children compared to the total population (Fig. 5a, b). The prevalence of CMS in 2023 was calculated as 4.49 per million in the general population, 10.00 per million in children, and 2.55 per million in

TABLE 1. Classification of the patients according to the age at the diagnosis

	Female		Male		Total	
	n	Age at diagnosis Mean±SD (Median, Min–Max)	n	Age at diagnosis Mean±SD (Median, Min–Max)	n	Age at diagnosis Mean±SD (Median, Min–Max)
Children	125	5.73±4.63 (5.00, 0–16)	113	6.27±4.77 (5.00, 0–17)	238	5.99±4.67 (5.00, 0–17)
Adults	73	39.11±17.88 (38.00, 18–86)	95	42.96±20.19 (38.00, 18–86)	168	41.29±19.26 (38.00, 18–86)
All population	198	18.04±19.77 (10.00, 0–86)	208	23.03±23.09 (13.50, 0–86)	406	20.59±21.65 (12.00, 0–86)

SD: Standard deviation; Min: Minimum; Max: Maximum.

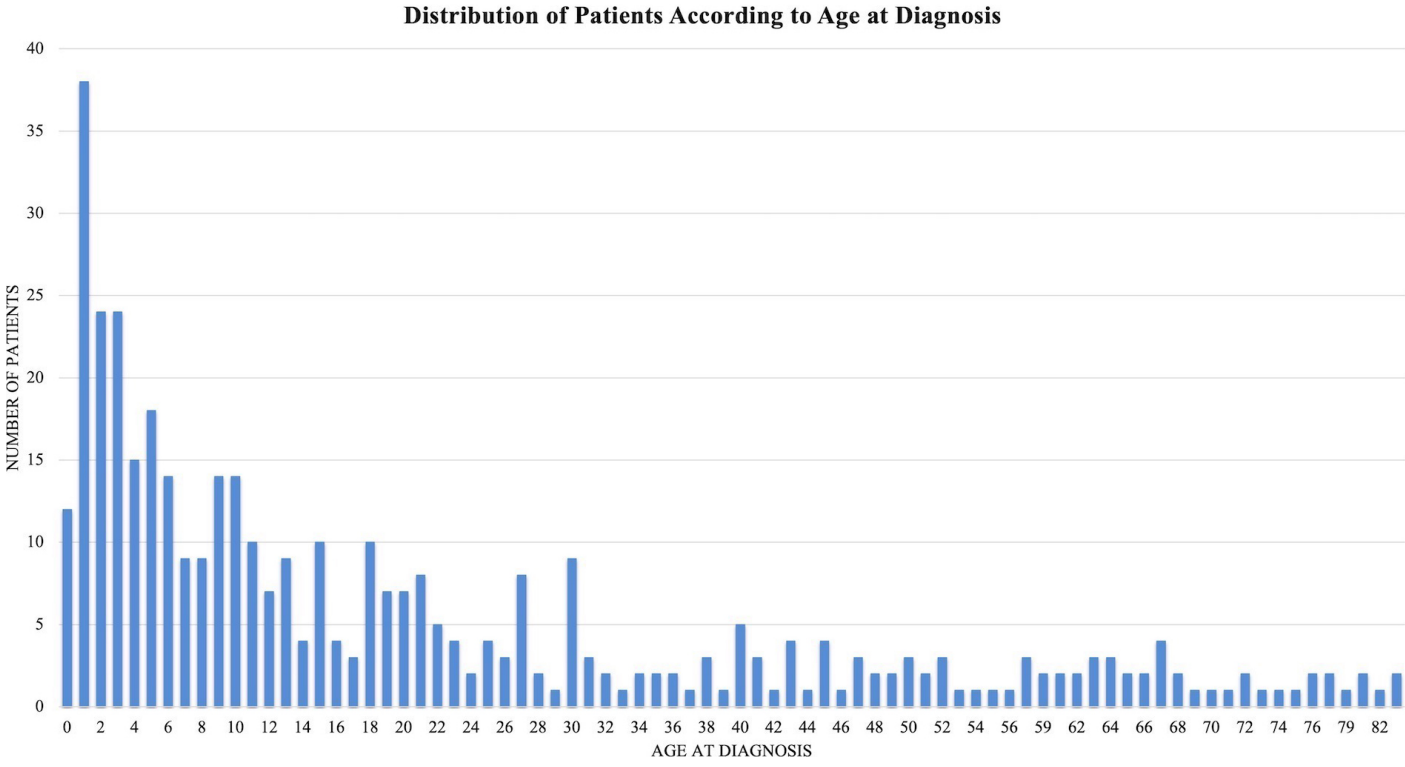

FIGURE 3. The graph showing the distribution of the patients according to the age at the initial diagnosis.

adults (Table 2). The cities with the highest number of patients were Istanbul, Izmir and Ankara, respectively. When examined by geographical regions, the Aegean region exhibited the highest prevalence rate, while the Black Sea region reported the lowest (Fig. 6).

DISCUSSION

CMS are exceedingly rare disorders, and their exact global prevalence remains undetermined. However, several epidemiological studies from different countries have reported prevalence rates ranging from 2.8 to 22.2 per million in pediatric age group [5–7], and from 1.8 to 3.1 per million in the general population [7–9]. Although several genetically confirmed, institution-based CMS studies have been reported from Turkiye, this study represents the first nationwide epidemiological investigation utilizing national electronic health records. It also constitutes one of the largest population-based studies on CMS globally [2, 5–7, 9].

In 2023, the incidence of CMS in individuals under 18 years of age was 0.63 cases per million, while it was 0.28

Table 2. Prevalence of congenital myasthenic syndromes according to the age groups in 2023

	Female		Male		Total	
	n	Prevalence (per million)	n	Prevalence (per million)	n	Prevalence (per million)
Children	116	10.73	106	9.30	222	10.00
Adults	72	2.26	89	2.84	161	2.55
All population	188	4.41	195	4.56	383	4.49

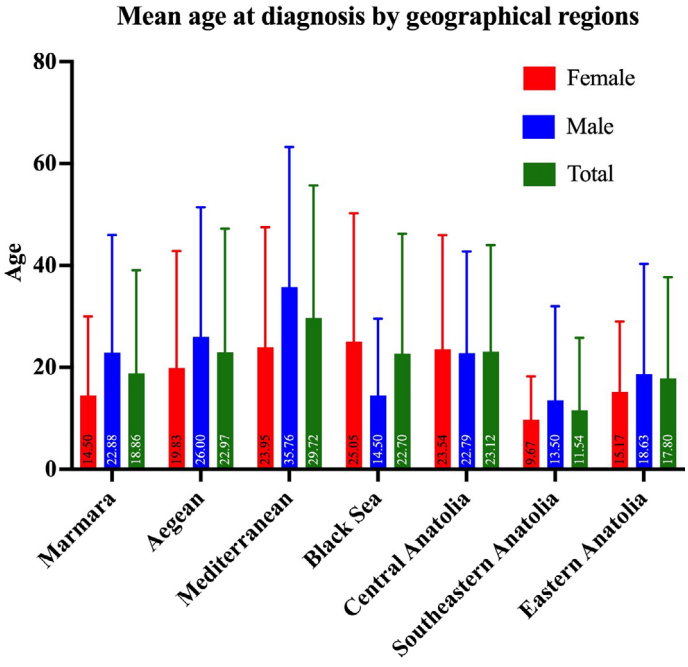

Figure 4. The graph showing the mean age at the initial diagnosis of patients by geographical regions in Turkiye

per million in the overall population. The corresponding prevalence rates were 10.00 per million in children and 4.49 per million in the general population. The pediatric prevalence in Turkiye aligns closely with that of Austria (10.5 per million) [7] and United Kingdom (9.2 per million) [5], but remains significantly lower than that reported in Slovenia (22.2 per million) [6]. For the general population, the prevalence in Turkiye exceeds that of Belgium (3.2 per million) [2], Austria (3.1 per million) [7], Brazil (1.8 per million) [8] and Spain (1.8 per million) [9].

No significant sex-based difference in prevalence was observed in this study, with females comprising 48.8% of the cohort. This is consistent with findings from previous Turkish studies [14, 15], as well as those from the

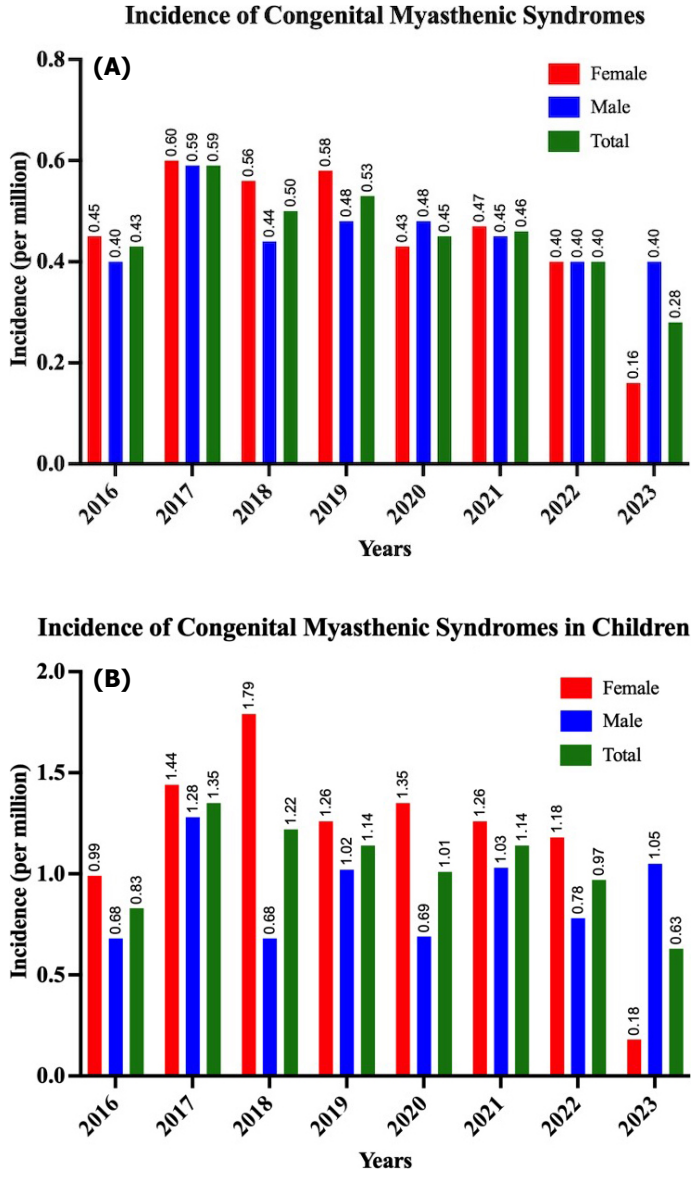

Figure 5. The graphs showing the incidence rates of congenital myasthenic syndromes. **(A)** In all population **(B)** In children.

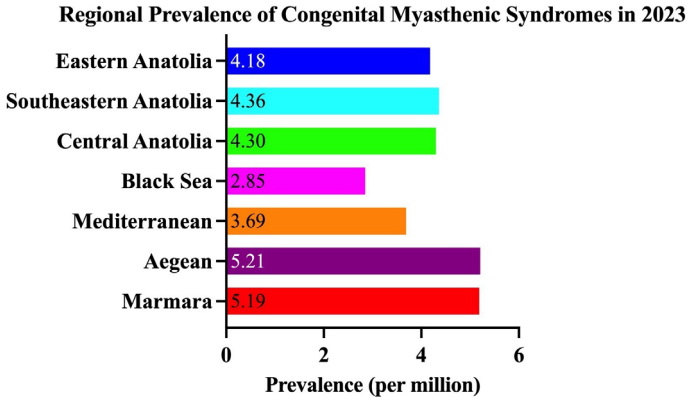

FIGURE 6. The graph showing the prevalence rates of congenital myasthenic syndromes in 2023 by geographical regions in Turkiye.

United Kingdom [5] and Japan [16]. However, other studies have reported a slight female [6–9, 17, 18] or male [10] predominance.

In this study, the mean age at the initial diagnosis was 20.6 years (median: 12), with 58.6% of the patients diagnosed before the age of 18 and 12.3% within the first year of life. In contrast, previous single-center studies from Turkiye reported lower mean diagnostic ages, ranging from 4.8 to 7.8 years [10, 14, 17, 18], and over half of the patients were diagnosed during the first year of life [10, 15]. This discrepancy may be attributed to the nature of those studies, which were conducted in tertiary care centers with a focus on genetically confirmed cases, potentially limiting their generalizability to the broader population. Furthermore, the rate of patients diagnosed before the age of 18 in Belgium (81%) [2], and those diagnosed before the age of one in Austria (50%) [7] were also higher than the rates observed in our cohort.

Although there is no curative treatment for CMS, early diagnosis remains critical, as the majority of patients respond favorably to symptomatic pharmacological treatment [3, 4, 19]. Pyridostigmine, an acetylcholinesterase inhibitor, is the most frequently used treatment and acts by enhancing acetylcholine (Ach) availability at the neuromuscular junction [3, 4, 20]. Pyridostigmine is generally effective in cases of Ach receptor deficiency, fast-channel syndrome, rapsyn deficiency, and glycosylation defects [19]. However, it may worsen symptoms in subtypes such as slow-channel syndrome, collagen Q, DOK7, and muscle-specific kinase [3, 4]. Unfortunately, genetic data were not available in this study. Nevertheless, 68.2% of patients in our cohort received at least one prescription for pyridostigmine, a rate comparable to the Austrian cohort (71.4%) [7], but lower than the rates reported in other studies, which ranged from 83.3 to 100% [2, 6, 16].

This study has several limitations that should be acknowledged. First, the identification of the cases was based solely on G70.2 diagnostic code entries without access to clinical and electrophysiological findings, or genetic test results. Additionally, any diagnoses entered into the registry, preliminary or definitive or for prescription purposes, remain unchanged even if a patient later receives a different final diagnosis. Therefore, to mitigate this limitation and to increase diagnostic accuracy, we applied a conservative inclusion criterion as having at least three G70.2 code entries. However, this approach may have resulted in the exclusion of some recently diagnosed cases.

Conclusion

This study is the first comprehensive nationwide epidemiological analysis of CMS in Turkiye based on national electronic health records. The study enhances the understanding of the epidemiological profile of CMS in the country by reporting the current incidence, prevalence, and pyridostigmine prescription rates and highlight the importance of awareness and early detection, particularly given the impact of CMS on neurodevelopment during childhood. These data are expected to contribute to the development of regional and national health policies and the planning of healthcare services to improve patient care.

Ethics Committee Approval: The Gülhane Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 28.06.2024, number: 2024-365).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: No conflict of interest was declared by the authors.

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