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REVIEW

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Cluster headache diagnostic delay and its predictors: a systematic review with a meta-analysis

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Abstract

Background Despite its characteristic clinical expression, cluster headache (CH) often remains unrecognized in clinical practice, with patients suffering from CH having to wait a long time before receiving a correct diagnosis and benefit from appropriate treatment.

Methods This work is a systematic review of data accessible through PubMed and published up to December 2024, focusing on the delay in CH diagnosis and its predictors. A meta-analysis was performed to estimate the mean CH diagnostic delay using the inverse of variance as the weight. A qualitative analysis was performed to identify predictors of this delay.

Results Among the 108 studies identified, 22 and 11 were selected for the qualitative analysis and meta-analysis respectively. These selected studies included a total of 8654 subjects (range 23–1604). This whole population was composed of 6383 men, 2180 women and 91 subjects with sex not specified. CH form was indicated for 7177 subjects with 5808, 1182 and 187 with episodic CH, chronic CH and undetermined form respectively. Meta-analysis estimated the overall CH diagnostic delay at 10,43 years (95% CI [9.09; 11.77]) with a reduction in the CH diagnostic delay over time since the sixties and the continuation of such a reduction every decade since 2000. Qualitative analyses identified several predictors of this diagnostic delay. Autonomic symptoms were associated with a decrease in the delay of diagnosis, whereas lower age of CH onset, alternating attack side and nocturnal headaches were associated with an increase in the delay of diagnosis.

Conclusion This systematic review including meta-analysis confirms an important unmet need in terms of CH diagnosis. Further work is needed to identify more precisely the predictors of this delay for better management of patients suffering from CH.

Trial registration The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 01/10/2025 (registration number: CRD42025630779).

Keywords Cluster headache, Systematic review, Diagnostic delay

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Background

Cluster headache (CH), which is the most common of the trigeminal autonomic cephalalgias (TACs), is characterized by attacks of severe to very severe unilateral pain orbital, supraorbital and/or temporal pain lasting from 15 to 180 min (when untreated) associated with ipsilateral autonomic symptoms and/or with restlessness or agitation [1]. Attacks have a frequency between one every other day and eight per day during cluster bouts that occur with pain-free periods of at least 3 months in the episodic CH (ECH) and without remission or with remissions lasting less than 3 months in the chronic CH (CCH) [1]. This primary headache displays also rhythmic patterns with a circadian rhythmicity (nocturnal preference of attack occurrence) and a circannual rhythmicity (occurrence of bouts at specific times of the year) [2].

Despite this characteristic clinical expression, CH often remains unrecognized in clinical practice, with patients suffering from CH having to wait a long time before receiving a correct diagnosis and being able to benefit from an appropriate treatment [3]. This unmet need can be explained by the rarity of this primary headache, the life-time prevalence of which being estimated at 124/100000 of the general population [4]. However, this failure to diagnose is probably due to other factors that need to be clarified to remedy the unsatisfactory situation.

Buture and colleagues published a systematic review on the delay in the diagnosis and misdiagnosis of CH, considering publications from January 1978 to May 2017 [5]. The aim of our work is to extend this systematic review to data published up to December 2024, focusing on the delay in the diagnosis of CH and its predictors.

Methods

This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [6]. In accordance with these guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 01/10/2025 (registration number: CRD42025630779).

Search strategy

A comprehensive search on PubMed database was carried out in December 2024. The search terms were 'delays in diagnosis' OR 'delay in diagnosis' OR 'diagnostic delay' OR 'diagnostic delays' OR 'late diagnosis' OR 'delayed diagnosis'. These were combined with a search for 'cluster headache' OR 'cluster-like headache'. In addition to this electronic search, we screened the reference lists of the selected articles and relevant literature known by the authors.

Inclusion criteria were: i) prospective and retrospective studies, case series and survey on delay in the diagnosis of CH and its predictors; ii) adult or children subjects with a diagnosis of cluster headache according to International Classification od Headache Disorders (ICHD) criteria or according to the International Classification of Diseases (ICD); iii) no restrictions by date; iv) no restrictions by geographical location; v) English language articles. Exclusion criteria were: i) case reports; ii) adult or children subjects with a diagnosis of CH not based on ICHD or ICD; iii) studies less than 10 participants. According to these inclusion/exclusion criteria, two authors (VOE and LMM) independently assessed all title and abstracts for inclusion. Full-text papers were retrieved for articles meeting the eligible criteria and for articles for which these criteria could not be verified solely by the title and abstract. All full-text articles were assessed independently by two authors (VOE and LMM) and disagreement was resolved by discussion to reach consensus.

Data extraction

Data were independently extracted by two authors (VOE and LMM). Data extracted included the study design, methods of data acquisition, population (number of participants, adult and/or children, men: women ratio, percentage of participants with ECH and CCH), year of CH onset (if available), mean (with standard deviation if available) and median (with range if available) of the CH diagnosis delay (time between the first CH attack and the correct diagnosis), predictors of CH diagnosis delay (if studied). The discrepancies were resolved by discussion to reach consensus amongst VOE and LMM.

Risk of bias (quality) assessment

Quality assessment of studies selected in this systematic review was performed using the Joanna Briggs Institute (JBI) Appraisal Checklist tool [7] for case series studies and the Oxford Centre for Evidence-Based Medicine (OCEBM) critical appraisal tool [8] for survey studies. The studies were independently assessed by two authors (VEO and LMM) and the discrepancies were resolved by discussion to reach consensus.

Statistical analysis

For the meta-analysis, the weighted mean of CH diagnostic delay was calculated using the inverse of variance as the weight. The 95% confidence interval was indicated. Study heterogeneity was performed using I^2 (less than 25% viewed as low heterogeneity, between 25

and 50% as moderate, and over 50% as high heterogeneity). The rma function in the Metafor package of R-4.3.0 software was used.

No statistical analysis was performed for qualitative analysis. For this analysis, we considered as CH diagnostic delay predictors, a clinical characteristic having the same influence on the CH diagnostic delay in at least two independent studies and no contrary result in the other studies.

Results

Studies selected

The search carried out on data related to CH diagnostic delay published up to December 2024 is summarized in the PRISMA flow chart presented in Fig. 1. This search identified 108 unique articles published between January 1978 and October 2024. All articles were screened by title and abstract and 72 articles were excluded at this stage. Full-text articles were assessed for the remaining 36 articles and finally 22 articles, published between June 1992 and October 2024, were selected for the systematic review (Table 1). Among the 22 studies included, 18 were case series studies [9–26] and 4 survey studies [27–30]. Nineteen were national studies that 12 took place in Europe [10–12, 14–16, 18, 19, 21, 22, 26, 28], 3 in the USA [9, 20, 29], 3 in Asia [13, 23, 24] and 1 in Africa [25] whereas 1 was a multinational study performed in four European countries [17] and 2 were international performed via internet [27, 30]. Most of these studies were recruited from tertiary headache centers [9–11, 14, 15, 17–19, 21–26] or neurology clinics [12, 13, 16, 28]. These selected studies included a total of 8654 subjects (range 23–1604). This whole population was composed of 6383 men, 2180 women and 91 subjects with sex not specified. CH form was indicated for 7177 subjects with 5808, 1182 and 187 with ECH, CCH and undetermined form respectively.

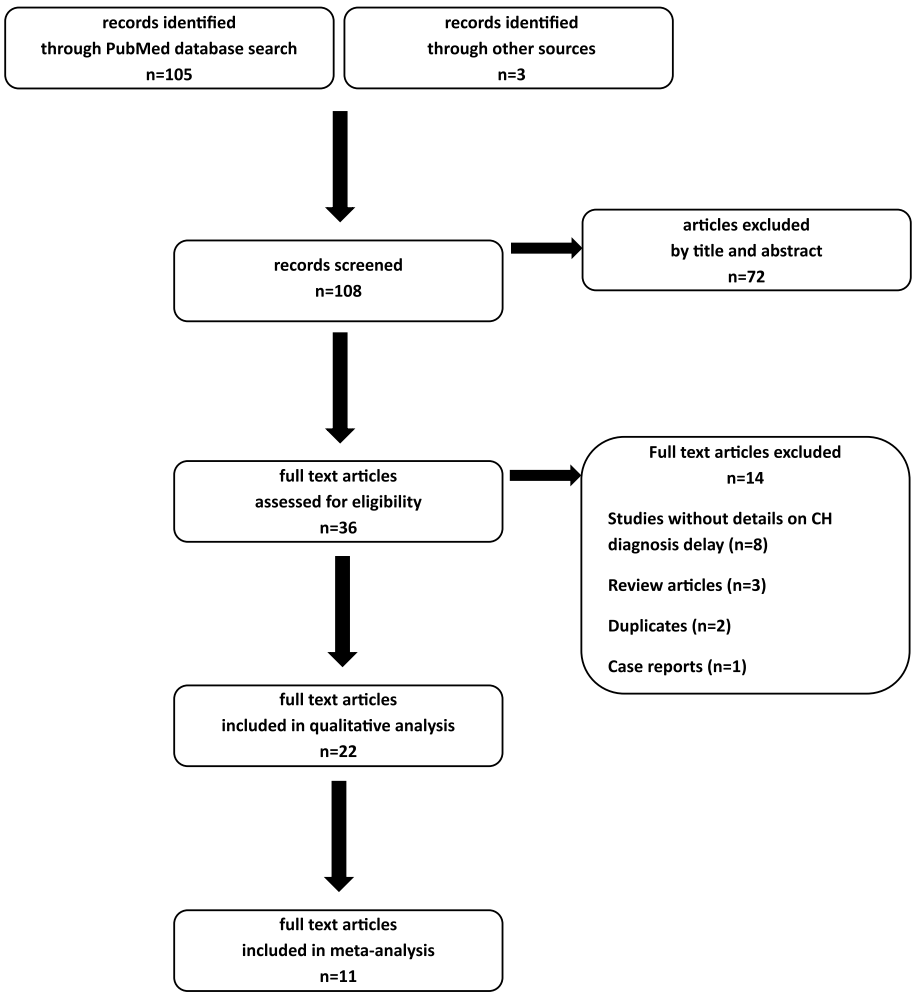

Fig. 1 PRISMA flow diagram studies selection

Table 1 Description of selected studies

Ref	Authors	Year	Country	Study design	Data acquisition	Recruitment origin	Subjects number	Men/Women/ not specified	ECH/CCH/ Undetermined
[9]	Maytal et al	1992	USA	Case series	Phone interview or Questionnaire	Headache center	35	30/5	NR[a]
[27]	Klapper et al	2000	International	Survey	Internet	General population	789	600/189	671/118/0
[28]	Van Vliet et al	2003	Netherlands	Survey	Questionnaire	Neurological center or Primary care	1163	913/250	849/244/70
[10]	Bahra & Goadsby	2004	UK	Case series	Face-face	Headache center or Patients' association	230	166/64	182/48/0
[11]	Jensen et al	2007	Denmark	Case series	Face-face	Headache center	85	56/29	59/15/11
[12]	Van Alboom et al	2009	Belgium	Case series	Questionnaire	Neurological center	85	77/8	67/18/0
[29]	Rozen & Fishman	2011	USA	Survey	Internet	General population	1134	816/318	NR
[13]	Imai et al	2011	Japan	Case series	Face-face	Neurological center	86	68/18	83/3/0
[14]	Sanchez del Rio et al	2014	Spain	Case series	Questionnaire	Headache center	75	67/8	NR
[15]	Zidverc-Trajkovic et al	2014	Serbia	Case series	Face-face	Headache center	182	121/61	164/18/0
[16]	Bekkelund et al	2014	Norway	Case series	Questionnaire	Neurological center	70	58/12	NR
[17]	Voiticovki-Iosob et al	2014	Europe[b]	Case series	Face-face or Phone interview	Headache center	144	106/38	144/0/0
[18]	Vikelis & Rapoport	2016	Greece	Case series	Face-face	Headache center	302	237/65	234/68/0
[19]	Taga et al	2016	Italy	Case series	Face-face	Headache center	785	569/216	686/99/0
[20]	Joshi et al	2017	USA	Case series	Medical records	Health registry	75	60/15	NR
[21]	Taga et al	2017	Italy	Case series	Face-face	Headache center	38	20/18	31/7/0
[22]	Fredericksen et al	2020	Denmark	Case series	Face- face or Phone interview	Headache center	400	268/132	253/147/0
[30]	Schor et al	2021	International	Survey	Internet	General population	1604	1104/497/3	1245/351/8
[23]	Kim et al	2022	Corea	Case series	Medical records	Headache center	445	365/80	328/19/98
[24]	Zhang et al	2022	China	Case series	Medical records	Headache center	816	663/153	797/19/0
[25]	Nada et a	2024	Egypt	Case series	Face-face	Headache center	23	19/4	15/8/0
[26]	Membrilla et al	2024	Spain	Case series	Medical records	Headache center	88	NR[a]	NR[a]

[a] *NR* Not reported

[b] Italy, Moldova, Ukraine and Bulgaria

Data extracted

Data extracted in the 22 selected studies is presented in Table 2. Eleven studies reported the mean of CH diagnosis delay and its standard deviation for the whole population included in the study and/or for sub-populations [12, 13, 15, 17, 19, 21–23, 25, 26, 30]. Only these eleven studies were selected for the quantitative analysis. Seven studies reported the mean of CH diagnosis delay without its standard deviation [9–11, 14, 18, 20, 27]. Four studies reported the median of CH diagnosis delay with its range [12, 16, 18, 28]. Two studies reported neither the mean nor the median of the CH diagnosis delay but the proportion of subjects whose CH diagnosis was made at different times after the first attack [24, 29]. Four studies reported an analysis of CH diagnostic delay predictors [12, 18, 22, 28].

Risk of bias of individual studies

Assessment of selected case series using Joanna JBI Appraisal Checklist tool is summarized in Table 3 and assessment of selected surveys using OCEBM critical appraisal tool is summarized in Table 4. Selected studies

Table 2 Data extracted in selected studies

Ref	Authors	Year	Group & sub-groups	CH diagnosis delay (in years)				Predictors	% delays (y : years)
				Mean	SD[a]	Median	Range		
[9]	Maytal et al	1992	**Total** ($n=35$)	**8.5**	NR[b]	NR	**0–34**	no	
[27]	Klapper et al	2000	**Total** ($n=789$)	**6.6**	NR	NR	NR	**no**	
[28]	Van Vliet et al	2003	**Total** ($n=1163$)	NR	NR	**3**	**0–48**	**yes**	
[10]	Bahra & Goadsby	2004	**Total** ($n=230$)	NR	NR	NR	NR	no	
			Diagnosis < 1950 ($n=1$)	**12**	NR	NR	NR		
			Diagnosis 1950–59 ($n=6$)	**22.3**	NR	NR	NR		
			Diagnosis 1960–69 ($n=21$)	**17.2**	NR	NR	NR		
			Diagnosis 1970–79 ($n=46$)	**9.5**	NR	NR	NR		
			Diagnosis 1980–89 ($n=89$)	**6.4**	NR	NR	NR		
			Diagnosis 1990–99 ($n=66$)	**2.6**	NR	NR	NR		
[11]	Jensen et al	2007	**Total** ($n=85$)	**9**	NR	NR	**0–39**	no	
			ECH ($n=59$)	**8**	NR	NR	**0–35**		
			CCH ($n=15$)	**9**	NR	NR	**0–39**		
			probable CH $n=10$)	**18**	NR	NR	**0–38**		
[12]	Van Alboom et al	2009	**Total** ($n=85$)	**3.7**	**6.3**	**1**	**0–40**	**yes**	
[29]	Rozen & Fishman	2011	**Total** ($n=1134$)	NR	NR	NR	NR	**no**	**< 1 y: 25%** **1–5 y: 39%** **6–9 y: 14%** **≥ 10 y: 22%**
[13]	Imai et al	2011	**Total** ($n=85$)	**7.3**	**6.9**	NR	NR	no	
[14]	Sanchez del Rio et al	2014	**Total** ($n=75$)	**4.9**	NR	NR	0–28	no	
[15]	Zidverc-Trajkovic et al	2014	**Total** ($n=182$)	**7.8**	**8**	NR	NR	no	
			Onset < 20 years old ($n=29$)	**13.9**	**9.7**	NR	NR		
			Onset 20–40 years old ($n=104$)	**7.9**	**7.6**	NR	NR		
			Onset > 40 years old ($n=49$)	**4 .2**	**2.1**	NR	NR		
[16]	Bekkelund	2014	**Total** (n = 70)	NR	NR	**4**	**0–30**	no	
[17]	Voiticovki-Iosob et al	2014	**Total** ($n=144$)	**5.3**	**6.4**	NR	**0–30**	no	
			Italy ($n=116$)	**5.6**	**6.9**	NR	NR		
			Eastern Europe[c]($n=28$)	**4**	**3.7**	NR	NR		
[18]	Vikelis & Rapoport	2016	**Total** ($n=302$)	**7.2**	NR	**5**	**0–45**	**yes**	
			Onset < 1989 ($n=30$)	NR	NR	**20**	**0–45**		
			Onset 1990–1999 ($n=69$)	NR	NR	**12**	**2–21**		
			Onset 2000–2009 ($n=124$)	NR	NR	**5**	**0–14**		
			Onset ≥ 2010 ($n=79$)	NR	NR	**1**	**0–7**		
[19]	Taga et al	2016	**Total** ($n=785$)	NR	NR	NR	NR	no	
			With migrainous features ($n=362$)	**10.4**	**9.4**	NR	NR		
			Without migrainous features ($n=423$)	**9 .6**	**9.1**	NR	NR		
[20]	Joshi et al	2017	**Total** ($n=75$)	**12.7**	NR	NR	**1–51**	no	

Table 2 (continued)

Ref	Authors	Year	Group & sub-groups	CH diagnosis delay (in years)				Predictors	% delays (y : years)
				Mean	SD[a]	Median	Range		
[21]	Taga et al	2017	**Total** ($n=114$)	NR	NR	NR	NR	no	
			Pediatric population ($n=38$)	**21.2**	**12.4**	NR	NR		
			Adult population ($n=76$)	**11.7**	**9.5**	NR	NR		
[22]	Fredericksen et al	2020	**Total** ($n=400$)	**6.3**	NR	NR	NR	**yes**	
			Onset ≤ 1959 ($n=1$)	**39**	**0**	NR	NR		
			Onset 1960–69 ($n=7$)	**25.1**	**16.8**	NR	NR		
			Onset 1970–79 ($n=19$)	**20.8**	**11.5**	NR	NR		
			Onset 1980–89($n=52$)	**12.1**	**8.7**	NR	NR		
			Onset 1990–99 ($n=85$)	**6.6**	**6.1**	NR	NR		
			Onset 2000–09 ($n=160$)	**3.9**	**4.1**	NR	NR		
			Onset ≥ 2010 ($n=76$)	**0.9**	**1.2**	NR	NR		
			Onset < 20 years old (($n=87$)	**18.8**	NR	NR	NR		
			Onset 20–40 years old ($n=200$)	**5.4**	NR	NR	NR		
			Onset > 40 years old ($n=113$)	**2.1**	NR	NR	NR		
[30]	Schor et al	2021	**Total** ($n=1604$)	**6.2**	**7**	NR	NR	no	
			Onset pediatric ($n=341$)	**11.1**	**9.9**	NR	NR		
			Onset adult ($n=1242$)	**4 .9**	**5.5**	NR	NR		
[23]	Kim et al	2022	**Total** ($n=445$)	**5.7**	**6.7**	NR	NR	no	
[24]	Zhang et al	2022	**Total** ($n=816$)	NR	NR	NR	NR	no	**< 1 y: 11.81%** **1–5 y: 30.88%** **6–9 y: 18.01%** **≥ 10 y: 39.22%**
[25]	Nada et al	2024	**Total** ($n=23$)	**9.8**	**7.9**	NR	NR	no	
			Men ($n=19$)	**13.1**	**9.1**	NR	NR		
			Women (n-4)	**8.6**	**8.9**	NR	NR		
			ECH ($n=15$)	**13**	**10.1**	NR	NR		
			CCH ($n=8$)	**12.1**	**6.9**	NR	NR		
[26]	Membrilla et al	2024	**Total** ($n=88$)	NR	NR	NR	NR	no	
			Refractory CH ($n=60$)	**4.6**	**7.1**	NR	NR		
			Non-refractory CH ($n=28$)	**3.2**	**3.7**	NR	NR		

[a] *SD* Standard deviation

[b] *NR* Not reported

[c] Moldava, Ukraine, Bulgaria

Table 3 The Joanna Briggs Institute (JBI) critical appraisal tool for case series

Ref	Authors	Were there clear criteria for inclusion?	Was the condition measured in a standard reliable way for all participants?	Were valid methods used for identification of the condition for all participants?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting in the demographic of the participants?	Were the outcomes of follow-up results of case clearly reported?	Was there clear reporting in the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?
[9]	Maytal et al (1992)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[10]	Bahra & Goadsby (2004)	yes	yes	yes	no	no	yes	yes	yes	yes
[11]	Jensen et al (2007)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[12]	Van Alboom et al (2009)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[13]	Imai et al (2010)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[14]	Sanchez del Rio et al (2014)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[15]	Zidverc-Trajkovic et al (2014)	Yys	yes	yes	no	no	yes	yes	yes	yes
[16]	Bekkelund et al (2014)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[17]	Voiticovki-Iosob et al (2014)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[18]	Vikelis & Rapoport (2016)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[19]	Taga et al (2016)	yes	yes	Yes	yes	yes	yes	yes	yes	yes
[20]	Joshi et al (2017)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[21]	Taga et al (2017)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[22]	Fredericksen et al (2020	yes	yes	yes	no	no	yes	yes	yes	yes
[23]	Kim et al (2022)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[24]	Zhang et al (2022)	yes	yes	yes	yes	yes	yes	yes	yes	yes

Table 3 (continued)

Ref	Authors	Were there clear criteria for inclusion?	Was the condition measured in a standard reliable way for all participants?	Were valid methods used for identification of the condition for all participants?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting in the demographic of the participants?	Were the outcomes of follow-up results of case clearly reported?	Was there clear reporting in the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?
[25]	Nada et al (2024)	yes	yes	yes	yes	yes	yes	yes	yes	yes
[26]	Membrilla et al (2024)	yes	yes	yes	yes	yes	yes	yes	yes	yes

Table 4 Oxford Centre for Evidence-Based Medicine (OCEBM) critical appraisal of survey studies

Ref	Authors	Did the study address a clearly focused question issue?	Is the study design appropriate for answering the research question?	Is the method of selection of subjects clearly described?	Could the way the sample was obtained introduce selection bias?	Was the sample of subjects' representative with regard to the population to which the findings will be referred?	Was the sample size based on pre-study consideration of statistical power?	Was a satisfactory response rate achieved?	Are the measurements likely to be valid and reliable?	Was the statistical significance assessed?	Are the confidence intervals given for the main results?	Could there be confounding factors that haven't been accounted for?	Can be results be applied to your organization?
[27]	Klapper et al (2000)	yes	yes	yes	no	yes	no	yes	yes	no	no	no	yes
[28]	Van Vliet et al (2003)	yes	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes
[29]	Rozen & Fishman (2011)	yes	yes	yes	no	yes	no	yes	yes	no	yes	no	yes
[30]	Schor et al (2021)	yes	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes

were not excluded based on their quality appraisal. The studies selected for quantitative analysis [12, 13, 15, 17, 19, 21–23, 25, 26, 30] were unbiased, with the exception of two case-series which did not rely on consecutive and complete inclusion of participants [15, 22], and one survey whose sample size was not based on pre-study consideration of statistical power [30].

Diagnostic delay in cluster headache

Overall CH diagnostic delay

Considering the eleven studies (3955 subjects) for which the mean and standard deviation of the time between first attack and diagnosis were reported and which were included in the meta-analysis [13, 19, 21–23, 25, 26, 29, 30], I^2 was estimated to 27.89%. Forest-plot of the delay in cluster headache diagnosis is presented in Fig. 2. The overall delay in cluster headache diagnosis was estimated at 10.43 years (95%CI [9.09; 11.77]).

CH diagnostic delay in sub-populations

Two studies showed a large and significant reduction in the mean CH diagnosis delay over time with a drop from 22.3 years (SD not reported) between 1950 and 1960 to 2.6 years (SD not reported) between 1990 and 1999 in the UK [10] and from 25.1 years (SD not reported) between 1960 and 1969 to 0.9 years (SD not reported) after 2010 in Denmark [22]. Such a significant reduction was also found in Greece where a median time to diagnosis was reported as decreasing from 20 years (range 0–45) before 1989 to 1 year (range 0–7) after 2010 [18].

Two studies have estimated the mean CH diagnostic delay according to the age of CH onset: 13.9 ± 9.7 years for onset before age 20, 7.9 ± 7.6 years for onset between age 20 and 40, 4.2 ± 2,1 years for onset after age 40 in Serbia [15] and 18.8 years (SD not reported) for onset before age 20, 5.4 years (SD not reported) for onset between age 20 and 40, 2.1 years (SD not reported) for onset after age 40 in Denmark [22]. In both studies, CH diagnostic delay was significantly longer in the early onset group (before age 20) than the common onset group (between age 20 and 40) and significantly shorter in late onset group (after age 40) than in the common onset group, showing a decrease in CH diagnostic delay with increase of CH onset age. A relationship between CH onset age and mean delay to CH diagnosis was also found in two studies comparing pediatric onset and adult onset of CH: 21.2 ± 12.4 years for pediatric onset, 11.7 ± 9.5 years for adult onset in Italy [21] and 11.1 ± 9.9 years for pediatric onset, 4.9 ± 5.5 years for adult onset in an international survey [30].

Two studies [11, 25] have estimated the diagnostic delay according to the CH form (ECH vs CCH) and one study [25] according to the patient gender, but the results are inconclusive given the small numbers of patients involved (Table 2). In a previous UK study [10], the authors claimed that there was no significant difference in time of CH diagnosis between men and women (unfortunately no data were presented).

One study [19] has estimated the CH diagnostic delay according to the presence of migraine-like features (MLF) showing no significant difference between

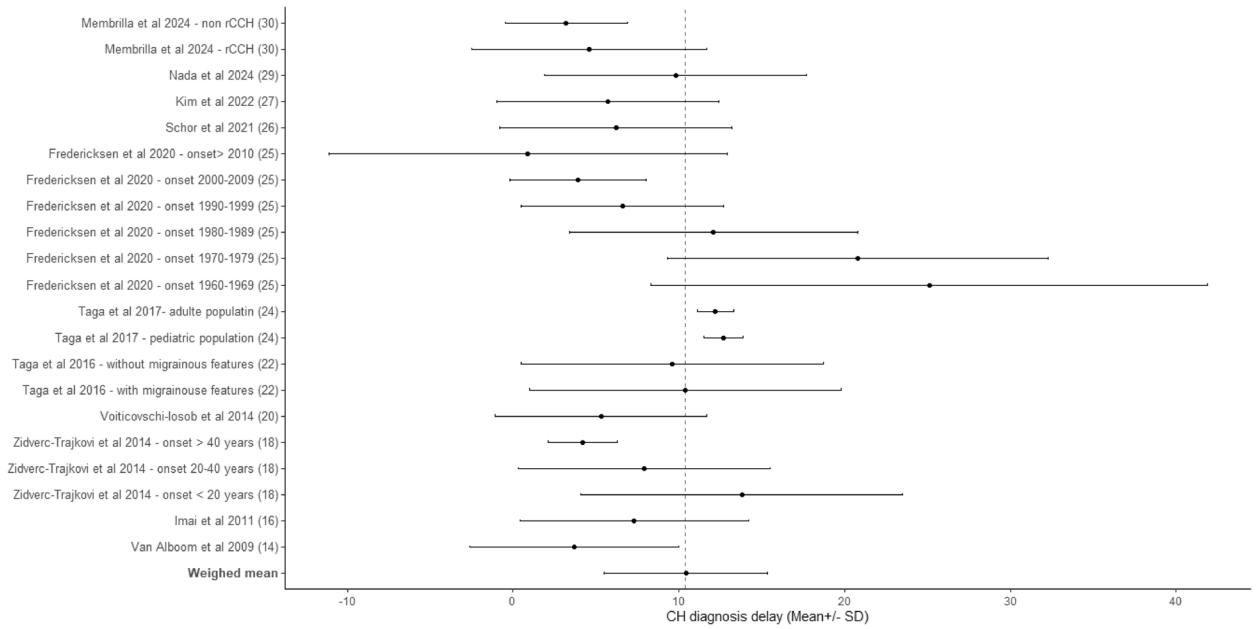

Fig. 2 Mean cluster headache diagnostic delay

subjects with (10.4 ± 9.4) and without (9.6 ± 9.1) MLF. Another study [26] showed that the delay in the diagnosis of CH was significantly longer in patients with refractory CCH (4.6 ± 7.1) compared to patients with non-refractory CCH (3.2 ± 3.7).

Predictors of diagnostic delay in cluster headache

Over and above the evaluation of the delay in various sub-populations presented in the previous chapter, predictors of CH diagnostic delay were specifically studied in four studies [12, 18, 22, 28].

Investigating whether certain clinical features considered individually influenced the delay in diagnosis of CH, a Dutch series found that the presence of photophobia and phonophobia, presence of nausea and/or vomiting during attacks, episodic CH pattern, alternating attack side, nocturnal attacks, and a lower age at CH onset were associated with a longer diagnostic delay. In contrast, sex, interictal headache, circadian rhythm, restlessness during attacks and pain radiation to jaw did not appear to influence the diagnostic delay of CH [28].

In a study performed in Belgian Flanders with a similar methodology, van Alboom et al. found that lower age of CH onset and pain that does not reach its peak in the first 5 min during attacks were associated with a significant longer diagnostic delay. In contrast the presence of phonophobia, photophobia and/or nausea during attacks, episodic CH pattern, alternating attack side did not influence the diagnostic delay. However higher number of autonomic symptoms during attacks was associated with a significant shorter diagnostic delay [12].

In a study performed in Greece with a similar methodology, Vikelis and Rappoport found that alternating attack side, pain location in the face and in the back of the head, presence of photophobia during attacks, presence of forehead and facial sweating, aggravation by physical activities and absence of autonomic symptoms during attacks were associated with a significant longer diagnostic delay whereas, as indicated previously, this study confirmed a significant reduction in CH diagnostic delay with each decade other the past fifty years [18].

In a study performed in Denmark using a more sophisticated statistical approach with a gamma regression model applied because of the skewed distribution of the diagnostic delay, Frederincksen et al. evaluated eleven selected clinical characteristics believed to be relevant for CH diagnostic delay [22]. The risk (OR [95% CI]) of longer diagnostic delay was thus assessed for female sex (0.83 [0.7–1.1]), episodic CH pattern (1.01 [0.8–1.3]), occurrence after 1990 (0.28[0.2–0.4]), CH family disposition (1.34 [1.0–1.8]), attack duration > 180 min. (1.62 [1.0–2.5]), alternating attack side (1.15 [0.9–1.4)], less than very severe pain intensity (1.13 [0.9–1.4]), absence of restlessness and agitation (0.92 [0.7–1.2]), migraine-like features (1.3 [1.0–1.7]), nocturnal attacks (1.39 [1.1–1.8]) and co-existing migraine (0.97 [0.7–1.4]) [22].

All the predictors studied in these four studies and their influence on CH diagnostic delay are summarized in Table 5. If we consider the predictors having the same influence on the CH diagnostic delay in at least two independent studies and no contrary result in the other studies, it appears that: the occurrence of CH after 1990–2000 is associated with decreased diagnostic delay, lower age of CH onset and nocturnal attacks are associated with an increase of the delay in CH diagnosis and female sex is not associated with diagnostic delay. For four other predictors studied (episodic CH pattern, alternating attack side, migraine-like features, pain location) the results are contradictory, depending on the study. The remaining predictors were investigated in only one of the studies. However, considering the mirror effect of the absence of autonomic symptoms (assessed once) and the presence of a high number of autonomic symptoms (assessed once), presence of autonomic symptoms can be considered as a predictor for a shorter diagnostic delay.

Discussion

Before this work, the only systematic review available on the CH diagnostic delay was that of Buture et al. related to data published from January 1978 to May 2017 [5]. Aims of our work were to: i) update this systematic review with data published up to December 2024, ii) perform a meta-analysis to estimate the mean CH diagnostic delay and iii) identify predictors of the CH diagnostic delay using a qualitative analysis. Our work confirms an important unmet need in terms of CH diagnosis with a mean delay of 10,43 years (95% CI [9.09, 11.77]). As Martelletti and Curto rightly put it: "the simplicity of the clinical manifestation, though dramatic, makes this delay inexplicable" [31].

With a majority of selected studies carried out in Europe, it has not been possible to highlight a regional difference in the CH diagnostic delay. Furthermore, the comparison of the results of the various studies selected must be cautious because they concerned patients whose CH diagnosis was made over a period ranging from the 1950s to the present day. Indeed, the qualitative analysis of this systematic review shows a regular reduction in the CH diagnostic delay over time since the sixties and highlights the continuation of such a reduction every decade since 2000 [18, 22]. This reduction in diagnostic delay over time has been interpreted as resulting from dissemination of the ICHD diagnostic criteria, easier access to neurologists, but also easier access to information about CH on the internet [22]. Data suggesting an influence of autonomic symptoms on the reduction of

Table 5 Predictors of CH diagnostic delay (DD)

	Fredericksen et al. [22]	Vikelis & Rappoport [18]	Van Alboom et al. [12]	Van Vielt et al. [28]
Occurrence after 1990–2000	associated with decreased DD	associated with decreased DD	factor not considered	factor not considered
Lower age of CH onset	factor not considered	factor not considered	associated with increased DD	associated with increased DD
Female sex	not associated with DD	factor not considered	factor not considered	not associated with DD
Episodic CH pattern	not associated with DD	factor not considered	not associated with DD	associated with increased DD
CH familial disposition	not associated with DD	factor not considered	factor not considered	factor not considered
Attack duration > 180′	associated with increased DD	factor not considered	factor not considered	factor not considered
Alternating attack side	not associated with DD	associated with increased DD	not associated with DD	associated with increased DD
Absence of restlessness/agitation	not associated with DD	factor not considered	factor not considered	factor not considered
Presence of restlessness/agitation	factor not considered	factor not considered	factor not considered	not associated with DD
Absence of autonomic symptoms	factor not considered	associated with increased DD	factor not considered	factor not considered
High number of autonomic symptoms	factor not considered	factor not considered	associated with decreased DD	factor not considered
Migraine-like features	associated with increased DD	associated with increased DD	not associated with DD	associated with increased DD
Nocturnal attacks	associated with increased DD	factor not considered	factor not considered	associated with increased DD
Pain extension	factor not considered	associated with increased DD	factor not considered	not associated with DD
Pain intensity less than very severe	not associated with DD	factor not considered	factor not considered	factor not considered
Pain that does not reach its peak in the first 5 min	factor not considered	factor not considered	associated with increased DD	factor not considered
Sweating of forehead or face	factor not considered	associated with increased DD	factor not considered	factor not considered
Interictal headache	factor not considered	factor not considered	factor not considered	not associated with DD
Circadian rhythmicity	factor not considered	factor not considered	factor not considered	not associated with DD
Aggravation by physical activities	factor not considered	associated with increased DD	factor not considered	factor not considered
Co-existing migraine	not associated with DD	factor not considered	factor not considered	factor not considered

this delay is consistent with a better knowledge of this disease. However, other clinical features more often observed in migraine (such as alternating pain, migraine-like signs and pain location) have not been confirmed as predictors of CH diagnostic delay while female gender, more commonly associated with migraine than with CH, is not associated with CH diagnostic delay. In addition, the episodic occurrence of attacks, corresponding to the characteristic rhythmicity of the CH, does not contribute to earlier CH diagnosis and the occurrence of nocturnal attacks, more frequent in CH than in other primary headaches, is associated with an increase of the CH diagnostic delay. Finally, our systematic review shows that CH diagnostic delay decreases with increase of CH onset age. This result had already been highlighted by Buture et al. [5], who suggested that clinicians are more suspicious of a secondary headache if the patient is older and refer more frequently to a neurologist. However, the assumption that CH diagnostic accuracy of neurologists is superior to that of general practitioners has not been formally established. Indeed, the study performed by Alboom et al. showed that neurologists correctly diagnose 80% of cases [12] whereas Vikelis and Rapoport reported that 40% of the patients included in their case series had been seen by a neurologist who missed the diagnosis [18].

In addition to the traditional approach of identifying predictors of CH diagnostic delay through association studies, such as those included in our systematic review, it seems essential to encourage qualitative research to better identify the obstacles of rapid and correct CH

diagnosis among healthcare professionals. Such an approach was used by Buture et al., who confirmed difficulties in diagnosing CH in both general practitioners and neurologists [32]. Qualitative research needs to be continued and extended to other healthcare professionals, such as ENT specialists, ophthalmologists, dentists and emergency physicians, who are often consulted by patients at the start of their illness. Another way to improve CH diagnostics is to develop CH screening tools. Several screening questionnaires have been developed and validated [33–36], but in spite of their good sensitivity and specificity, none has yet established itself in clinical practice. Among these questionnaires, the one proposed by Buture et al. is original because it comprises images depicting pain headache that do not clearly discriminate between CH and migraine [36]. The contribution of visual aids to the recognition of CH is interesting but videos would probably be more effective in conveying the intensity of the pain and the behavior so particular during the CH attack. Such screening videos would facilitate early self-diagnosis via Internet and social networks. In this perspective, it is noteworthy that, 10 years ago, 15% of CH patients already said they had self-diagnosed using different sources of information before seeking medical confirmation [17].

Conclusions

Using a meta-analysis, this review estimated the overall CH diagnostic delay at 10,43 years (95% CI [9.09, 11.77]). Even if this delay seems to be getting shorter with time, such a result confirms an important unmet need in terms of CH diagnostic. Further work is needed to better identify the predictors of this delay for better management of patients suffering from CH.

Authors' contributions

E.V.O. and M.L.M. conceived the study. E.V.O and M.L.M. performed studies selection, data extraction and data analysis. R.F. performed statistical analysis. E.V.O. and M.L.M. drafted the manuscript. All authors revised and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This systematic review did not require the authorization of an ethics committee. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 01/10/2025 (registration number: CRD42025630779).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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