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Incidence and Etiology of Presumed Fourth Cranial Nerve Palsy: A Population-based Study

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Abstract

Purpose—To determine the incidence of isolated, presumed fourth nerve palsy in a defined population, and to report the frequency of each cause.

Design—Retrospective, population-based case-series.

Methods—A population-based database was used to identify all cases of isolated fourth nerve palsy in Olmsted County, MN, USA diagnosed over a 15-year period (January 1, 1978 to December 31, 1992). The most likely etiology was determined by review of the entire medical record by two ophthalmologists. A priori definitions were applied for assigning cause. The incidence of fourth nerve palsy and the frequency of each etiology were calculated. Decade of life at presentation was recorded.

Results—73 patients, (74 episodes, 70 [95%] unilateral) were identified. Mean age at presentation was 41.8 (range 3.3 to 81.6) years. The age- and sex-adjusted annual incidence rate was 5.73 per 100,000 per year (95% Confidence Interval [CI] 4.31–7.14). The most common etiology was presumed congenital (49%) followed by hypertension (18%) and trauma (18%). One patient (1%) had fourth nerve palsy due to a known intracranial neoplasm. For 3 patients (4%) the cause of fourth nerve palsy was undetermined. The most common decade of presentation overall was the fourth decade, including for presumed congenital cases.

Conclusions—In this population-based study, the majority of isolated fourth nerve palsies were presumed congenital, even though they presented throughout adulthood. Other etiologies such as hypertension and trauma were less frequent, and in no case was an isolated fourth nerve palsy the presenting sign of an intracranial tumor.

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In this retrospective, population-based case-series (January 1, 1978 and December 31, 1992, in Olmsted County, MN, USA), the age- and gender-adjusted incidence of isolated, presumed fourth nerve palsy was 5.73 per 100,000 per year (95% Confidence Interval [CI] 4.31–7.14). The most likely etiologies (determined by review of the entire medical record) were presumed congenital (49%), hypertension (18%), and trauma (18%). Presentation was most commonly the fourth decade of life, including presumed congenital.

Introduction

Fourth cranial nerve palsy is commonly encountered in both pediatric and adult strabismus practices. Nevertheless, the frequency with which fourth nerve palsy occurs in the general population, across all age groups and etiologies, has not been previously studied. In addition, while several previous studies have reported the frequency of various etiologies of fourth nerve palsy,^{1–17} these estimates vary considerably across studies due to differences in referral patterns and definitions.

Population-based studies have the advantage of providing estimates of frequency that reflect true incidence in the general population, rather than the frequency encountered by the subspecialist or in tertiary referral centers. In the present study, we evaluated the incidence of presumed fourth nerve palsy, and the frequency of etiologies, in a defined population.

Materials and Methods

The procedures used in this retrospective population-based study conformed to the Declaration of Helsinki and were approved by the Institutional Review Board of the Mayo Clinic, Rochester, Minnesota.

Using the Rochester Epidemiology Project database, (REP)^{18–20} we retrospectively identified patients diagnosed with fourth cranial nerve palsy between January 1, 1978 and December 31, 1992. All included patients were residents of Olmsted County, Minnesota at the time of onset of the fourth nerve palsy. The population of Olmsted County, Minnesota is relatively isolated from other urban areas, and virtually all medical care is provided to residents of the county by the Mayo Clinic, or by the Olmsted Medical Group and their affiliated medical centers.

Patients

Patients with a diagnosis of isolated fourth cranial nerve palsy (unilateral and bilateral) were identified by searching the REP databases using a hospital adaptation of “International Classification of Diseases 8” codes. All diagnoses had been coded by trained coding personnel based on review of the entire medical record. In addition, billing records were searched for “International Classification of Diseases 9” codes for fourth cranial nerve palsy. We also searched both the REP databases and billing databases for cases of fourth cranial nerve palsy that might have been coded using codes such as strabismus associated with neuromuscular diseases, miscellaneous ophthalmoplegia, and strabismus. Trained residency

checkers also verified the patient's county of residence at the onset of the fourth nerve palsy. All patients who were not residents of the Olmsted County at the time of the onset of the palsy were excluded.

For each patient, the entire medical record through December 2010 was reviewed by study ophthalmologists to: 1) confirm the diagnosis of presumed unilateral or bilateral fourth nerve palsy (for unilateral: hypertropia in straight ahead gaze, increasing with opposite lateral gaze and same head tilt, with no other paretic or restrictive cause; for bilateral: alternating hypertropia characteristic of bilateral fourth nerve palsy), and 2) identify coexistent medical conditions and determine the most likely etiology of the fourth cranial nerve palsy. All presenting features of the documented palsy (made by an ophthalmologist, neurologist or internist) were reviewed. Unilateral fourth nerve palsy with subsequent new onset in the other or same eye was considered as a new episode and etiology was assigned for each occurrence. Most often the diagnosis of presumed fourth nerve palsy is made on the basis of alignment measurements. Because diagnosis is often not confirmed by Magnetic Resonance Imaging of superior oblique muscle morphology, we use the term presumed fourth nerve palsy.

Age at onset of fourth nerve palsy was calculated based on history of onset recorded in the medical record. For all cases of presumed congenital onset, the assigned date of onset was the patient's birthdate. Age at presentation was calculated based on the first examination at which fourth nerve palsy was detected or diagnosed.

Classifying etiology of fourth nerve palsy

Potential etiologies of fourth nerve palsy considered a priori were: presumed congenital, hypertension, diabetes, trauma, post-neurosurgery, post-craniofacial surgery, intracranial neoplasm, demyelination, and other. Presumed congenital fourth nerve palsy was defined as the presence of at least one of the following: history of infantile onset, documented vertical phoria (>2 prism diopters) pre-dating diagnosis of fourth nerve palsy, presence of large vertical fusional amplitudes (5 prism diopters or more, based on previously published data showing normal to be less than 5 prism diopters^{21, 22}), or history of long-standing head tilt. Hypertension was defined using the criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [JNC7]).²³ We considered high blood pressure to be causative if systolic blood pressure was 140 mmHg, or a diastolic blood pressure was 90 mmHg, requiring treatment, and measured within one year of fourth nerve palsy diagnosis. Diabetes Mellitus was defined using the 2010 American Diabetes Association criteria,²⁴ i.e., elevated plasma glucose controlled by diet and/or exercise, and was considered causative if: 1) symptoms of diabetes (hyperglycemia or hyperglycemic crisis) and a random plasma glucose > 200 mg/dL; 2) a fasting plasma glucose of >126 mg/dl; 3) Plasma glucose >200 mg/dl at two hours into an oral glucose tolerance test; or 4) Hemoglobin A1C greater than 6.5% within one year of the fourth nerve palsy. In addition, diabetes was considered causative if the patient was taking medications (insulin or oral agent) for control of elevated plasma glucose at the time of fourth nerve palsy diagnosis. Traumatic etiology was defined as documented onset of fourth nerve palsy following head trauma, with or without loss of consciousness. If the recorded

history, physical examination and ancillary tests revealed no cause or associated medical condition, the etiology was classified as undetermined.

Analysis

The annual age- and sex- adjusted incidence rate was calculated by using the age-specific and sex- specific population figures for Olmsted County, Minnesota, from the 1990/2000 United States census, which states the Olmsted county population in 1990 to be 106,470. Rates were adjusted to the 2010 United States white population. Confidence intervals were constructed for the rates using the Poisson distribution.

For each patient the most likely etiology for the fourth nerve palsy was determined. The proportion of patients with each etiology was calculated, as well as the proportion of patients presenting at each decade of life.

Results

Overall Incidence

We identified 73 patients with fourth nerve palsy over the 15-year study period. Fifty (68%) were male and mean age at presentation was 41.8 (range 3.3 to 81.6) years. The age- and sex-adjusted annual incidence rate for fourth cranial nerve palsy was 5.73 per 100,000 per year (95% Confidence Interval [CI] 4.31–7.14). In females the age adjusted incidence was 3.13 per 100,000 per year (95% CI 1.76–4.50) and in males the age adjusted incidence was 8.55 per 100,000 per year (95% CI 5.96–11.14).

Presenting signs and / or symptoms

Overall, for 43 (58%) of 74 episodes of fourth nerve palsy the predominant presenting sign and / or symptoms was diplopia, 18 (24%) presented with other symptoms (such as problems reading), 7 (9%) were referred from a routine eye exam, 4 (5%) presented with an unspecified type of strabismus, 1 (1%) presented primarily with a head tilt, and 1 (1%) was referred by their school.

Etiology

Of the 73 patients, one patient had two separate episodes of unilateral fourth nerve palsy, yielding a total of 74 included episodes. Seventy (95%) of 74 were unilateral (47% right sided and 53% left sided) and 4 (5%) were bilateral.

The most common cause of fourth nerve palsy was presumed congenital (36, 49%) followed by hypertension (18%), and trauma (18%, Table 1). Other, less frequently observed causes were hypertension with coexistent diabetes (5%), post-neurosurgery (3%), diabetes alone (1%), known intracranial neoplasm (1%) and other (1%) (following Herpes Zoster ophthalmicus infection). For 3 patients (4%) we were unable to determine the likely cause of the fourth nerve palsy. There was no occurrence in our series where isolated fourth nerve palsy was the presenting sign of a neoplasm (95% CI 0% to 4.9%). Of the 4 bilateral cases of fourth nerve palsy, 3 (75%) were caused by trauma and one was presumed congenital. For

the one patient who experienced two separate episodes of fourth nerve palsy, both were caused by hypertension.

Decade of presentation

Overall, most cases of fourth nerve palsy presented in the fourth decade of life (14 [19%]), then the seventh (12 [16%]), third (11 [15%]) or second (10 [14%]) decades of life (Figure 1). For presumed congenital cases, the peak decades for presentation were the 4th decade (9 of 36, 25%) and the 2nd decade (8 of 36, 22%) (Figure 1). For trauma the peak decade for presentation was the 3rd decade (5 of 13, 38%) and for hypertension the peak decade for presentation was the 7th decade (5 of 13, 38%) (Figure 1).

Discussion

In this population-based study, we found the age- and sex-adjusted annual incidence of fourth nerve palsy was 5.73 per 100,000 per year (95% CI 4.31–7.14), with a higher incidence in males than in females. The most common cause was found to be presumed congenital, followed by trauma and hypertension, and across all causes the peak presentation was in the fourth decade of life.

We are unaware of any previous studies reporting the incidence of isolated fourth nerve palsy, across all ages, including congenital onset, in the general population. A previous population-based study²⁵ reported the incidence of fourth nerve palsy, but only for cases with onset in adulthood (documented onset in childhood was excluded). In these adult-onset cases the incidence of fourth nerve palsy was found to be 6.3 per 100,000 (95% CI, 5.0 to 7.6). It should be noted that there is some overlap between cases in the present study and that of Martinez-Thompson et al,²⁵ but Martinez-Thompson et al only studied adult-onset strabismus. Other studies have reported the incidence of fourth nerve palsy in children (2.7 per 100,000 i.e., 36% of 7.6 per 100,000²⁶, and 9.2 per 100,000 i.e., 71% of 12.9 per 100,000²⁷).

We found the incidence of fourth nerve palsy to be higher in males (8.55 per 100,000 per year) than in females (3.14 per 100,000 per year), as noted previously by Ellis and Helveston.¹¹ This finding of a higher incidence of fourth nerve palsy in males than in females was also reported in a previous REP population-based study (of adult-onset strabismus),²⁵ whereas no significant sex differences were observed for sixth and third cranial nerve palsies.²⁵ Other studies have also confirmed this finding of proportionately more males among patients with fourth nerve palsy.^{13, 14} One proposed explanation¹¹ for a higher incidence of fourth nerve palsy in males is that head trauma is more frequent in males.^{28–30} Nevertheless, in a series of closed-head injury patients,³¹ more of those presenting with fourth nerve palsy were male compared with those presenting with third nerve palsy, suggesting that males are particularly prone to fourth nerve palsy. It is possible that males are more susceptible to specific types of head injury, which might be more associated with fourth nerve palsy.³⁰

Several previous studies^{1–17} have reported the etiology of fourth cranial nerve palsy, but we are unaware of previous studies reporting the frequency of different etiologies in a

population-based cohort. Previous reports differ regarding etiological classification, population studied, and whether or not the included fourth nerve palsy was isolated, or present in conjunction with other cranial nerve palsies, making it difficult to compare the frequency of etiological causes. In previous studies which include all ages and possible causes of isolated fourth nerve palsy, some have found the most common cause to be congenital, followed by trauma,^{3, 4, 16} similar to the findings of our present study, whereas others^{11, 12, 17} have found trauma to be a more common cause than congenital. Other studies reporting the etiology of fourth nerve palsy are less comparable to our present study either because they excluded congenital cases,^{1, 2, 5, 7, 9, 10, 14} or included only children,⁶ or reported only surgical patients.^{13, 15} In the present study, applying population-based methods, and including all ages and possible causes, presumed congenital was the most common etiology.

We found that even though presumed congenital was the most commonly encountered etiology of presumed fourth nerve palsy, the majority of cases tend not to present in childhood, but in adulthood, which has also been reported by others.³² In our present study the peak decade of presentation was the fourth decade of life. The reason for such delayed presentation are unclear, but it is likely that control of the deviation decompensates over time,³² possibly exacerbated by factors such as the onset of presbyopia, and the use of downgaze for reading when wearing a presbyopic spectacle correction.

In the present study, as in previous studies,^{1, 3, 4, 11, 12, 16} we found closed head trauma to be a relatively common cause of fourth nerve palsy, with peak presentation in the third decade of life. In addition, hypertension was found to be a relatively common cause, with peak presentation in the seventh decade of life. Most previous studies combine vascular causes,^{2, 7–10, 12, 14, 15} rather than separating into specific diagnoses, and when combining vascular causes (hypertension and diabetes) in the present study we found an overall prevalence of 24%, making vascular disease a more frequently encountered cause of fourth nerve palsy than trauma. One previous study⁴ reported the specific frequency of hypertension and diabetes mellitus and found hypertension was a more frequent cause of fourth nerve palsy than diabetes,⁴ similar to the findings of the present study.

We had no cases where isolated, presumed fourth nerve palsy was the presenting sign of an intracranial mass. The one patient in the present study that had an intracranial mass (metastatic breast cancer), had a known diagnosis prior to the onset of her fourth nerve palsy. In previous studies isolated fourth nerve palsies associated with intracranial tumors are also rare (ranging from no reported cases^{7, 8, 14} to 8%,¹⁰). More typically intracranial tumors affect multiple cranial nerves simultaneously.^{2, 5, 7, 9, 10}

Regarding other causes of fourth nerve palsy, one patient in our study was diagnosed with fourth nerve palsy following a Herpes Zoster ophthalmicus infection. This appears to be a rare cause of fourth nerve palsy and we are aware of only one other case, reported by Ellis and Helveston¹¹ in their series of 130 patients.

We did not have a large proportion of patients for whom it was not possible to determine the etiology of fourth nerve palsy (3 patients, 4%), unlike some previous studies where a large

proportion of patients were classified as having fourth nerve palsy of undetermined cause. 2, 5–7, 10, 11, 14 The low proportion with undetermined cause in the present study is most likely because of increasingly improved identification of vascular risk factors, as well as the fact that we reviewed the entire medical record over a long period of follow-up, in the process of establishing etiology.

There are some limitations to our study. In Olmsted County the population is predominantly Caucasian and the incidence and etiology of fourth nerve palsy may differ in more ethnically or geographically diverse populations. Also, we required alignment criteria for diagnosis of unilateral or bilateral fourth nerve palsy, and therefore we may have missed additional cases that did not have alignment data. There may be some limitation to studying a population who presented between 1978 and 1992, but the strength of this approach is that we had at least 18 years follow-up to capture any later diagnosed, subtle intracranial pathology. Despite evaluation of the entire medical record, it is possible that etiology was incorrectly assigned in some cases, in part because the patient may not always accurately recall etiologies that sometimes rely on patient history, for example previous head trauma. Also, we did not record refractive error data or data on accommodative amplitudes, and therefore cannot confirm our speculation regarding the possible role of presbyopia.

Conclusions

Using population-based methods, this study provides data on the incidence of fourth nerve palsy in the general population, and the frequency of etiologies. Most often fourth nerve palsy is congenital in origin, with trauma and vascular causes also occurring frequently, with most cases of presumed congenital fourth nerve palsy presenting in adulthood.

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Figure 1.
Decade of presentation of fourth nerve palsy in a population-based cohort, showing the number of patients with different etiologies.

Table 1

Etiology of fourth nerve palsy in a population-based cohort of 73 patients (N=74 episodes)

Etiology	N (%)
Presumed Congenital	36 (49%)
Hypertension	13 (18%)
Trauma	13 (18%)
Coexistent Hypertension and Diabetes Mellitus	4 (5%)
Undetermined	3 (4%)
Post-Neurosurgery	2 (3%)
Known Intracranial Neoplasm	1 (1%)
Diabetes Mellitus	1 (1%)
Other (post-viral)	1 (1%)