# Characteristics of Acute Nystagmus in the Pediatric Emergency Department

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abstract

**OBJECTIVES:** Acute nystagmus (AN) is an uncommon neurologic sign in children presenting to pediatric emergency departments. We described the epidemiology, clinical features, and underlying causes of AN in a large cohort of children, aiming at identifying features associated with higher risk of severe underlying urgent conditions (UCs).

**METHODS:** Clinical records of all patients aged 0 to 18 years presenting for AN to the pediatric emergency departments of 9 Italian hospitals in an 8-year period were retrospectively reviewed. Clinical and demographic features and the underlying causes were analyzed. A logistic regression model was applied to detect predictive variables associated with a higher risk of UCs.

**RESULTS:** A total of 206 patients with AN were included (male-to-female ratio: 1.01; mean age: 8 years 11 months). The most frequently associated symptoms were headache (43.2%) and vertigo (42.2%). Ataxia (17.5%) and strabismus (13.1%) were the most common neurologic signs. Migraine (25.7%) and vestibular disorders (14.1%) were the most common causes of AN. Idiopathic infantile nystagmus was the most common cause in infants <1 year of age. UCs accounted for 18.9% of all cases, mostly represented by brain tumors (8.3%). Accordant with the logistic model, cranial nerve deficits, ataxia, or strabismus were strongly associated with an underlying UC. Presence of vertigo or attribution of a nonurgent triage code was associated with a reduced risk of UCs.

**CONCLUSIONS:** AN should be considered an alarming finding in children given the risk of severe UCs. Cranial nerve palsy, ataxia, and strabismus should be considered red flags during the assessment of a child with AN.

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**WHAT'S KNOWN ON THIS SUBJECT:** The diagnostic value of acute-onset nystagmus has been investigated in adults, focusing on the risk of vertebrobasilar strokes. In children and adolescents, possible etiologies have not been investigated, and the diagnostic value of nystagmus in the emergency setting is uncertain.

**WHAT THIS STUDY ADDS:** Migraine is the most common cause of acute nystagmus in the emergency setting. Almost 20% of children with acute nystagmus have an urgent neurologic condition, and the recognition of several red flags conferring a higher risk may help their identification.

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Nystagmus is an abnormal, rhythmic, and repetitive oscillation of the eyes that may impair visual acuity because of movement of images away from the fovea.[1] It is a sign of cerebellar, vestibular, or visual pathways dysfunction. According to age at onset, nystagmus is usually classified as infantile nystagmus, which appears within the first 6 months of life, and acquired nystagmus, which appears later.[2]

In a single retrospective, population-based study on children and adolescents, the annual estimated incidence of nystagmus was 6.72 per 100 000 residents <19 years of age.[3] However, its incidence in the emergency care setting is unknown. Given the broad differential diagnosis of acute nystagmus (AN), its clinical assessment can be challenging.[4] Facing a child with AN, the physician's concern is to exclude that nystagmus could be the sign of a significant neurologic disorder needing immediate intervention.[1] In only few previous studies, limited to the adult population, authors have investigated the clinical features, underlying causes, and management of AN in the emergency department setting.[5,6] Nevertheless, the spectrum of disorders causing acute neurologic dysfunction in children significantly differs from that of adults.[7,8]

To our knowledge, no study has been used to investigate the presentation and management of AN in the pediatric and adolescent population, neither in emergency department nor in outpatient settings.

Through a retrospective analysis of a large multicenter cohort of children presenting to Italian pediatric emergency departments (PEDs), we aimed to describe the epidemiology, clinical features, underlying causes, and management of AN in children. Our secondary aim was to identify clinical features associated with a higher risk of significant underlying neurologic abnormalities in children with AN to contribute to the improvement of its management in the emergency setting.

## METHODS

This retrospective, multicenter cohort study was conducted in the PED of 9 Italian hospitals (Padua, Genoa, Bologna, Florence, Siena, Perugia, L'Aquila, Caltagirone, and Rome) after having obtained approval from the institutional ethics committee of the participating hospitals. Patients' identification was performed through keyword searching of electronic databases of the participating hospitals, including all patients aged <18 years attending the PED from January 2009 to December 2016. Medical charts were selected by searching the keyword "nystagmus" in the fields "history," "clinical examination," and "diagnosis" of the electronic notes. Potential case-patients were manually screened by medical chart review. We included all patients referred to the PED with a history of <30 days of an ocular movement abnormality in whom a diagnosis of nystagmus was confirmed. Exclusion criteria were (1) abnormal eye movements other than nystagmus (such as ocular flutter, opsoclonus, and/or supranuclear gaze disturbances), (2) patients attending the PED because of head injury or (3) epileptic seizures, and (4) patients affected by an already known neurologic condition explaining the nystagmus.

We included both patients attending the PED complaining of the eye movement abnormality and patients complaining about other symptoms whose nystagmus was detected during the clinical examination. In the latter case, nystagmus was considered as new onset when it was reasonably linked with the same pathologic process causing the acutely presenting symptoms (eg, ataxia, vertigo, headache, altered mental status), it had neither been noticed before nor mentioned in medical records, and it was not explained by any of the known preexisting medical problems.

From each medical record, information about demographic features, clinical history, examination findings, investigations performed, hospital admission, and length of stay (as applicable) was extracted. Accordant with Italian National Health Service guidelines, the priority of consultation on PED admission was based on a 4-color triage coding scale:

- red code: critical medical state, vital signs alteration needing immediate life-saving intervention, high-priority access to urgent care;
- yellow code: serious state, risk of evolution into critical conditions, intermediate-priority access and reevaluation needed in 5 to 15 minutes;
- green code: fair state, stable vital signs, medical consultation postponable without risk, low-priority access and reevaluation needed in 30 to 60 minutes; and
- white code: good state, nonurgent consultation.

The triage code has to be assigned by a trained triage nurse at entrance in the emergency department and is periodically reevaluated during the waiting time. This system was enforced during the entire study period, which was conducted after the Italian Ministry of Health agreement with all Italian regions in 2001.[9]

Etiology of nystagmus was classified on the basis of the diagnosis made at the end of the diagnostic workup. Nystagmus causes reflecting significant neurologic abnormality, requiring further investigations and intervention (ie, neoplastic, cerebrovascular, infectious, demyelinating, degenerative, or central nervous system [CNS]

malformations), were considered as urgent conditions (UCs).

The clinical and demographic features were described in the overall cohort and in the 2 subgroups (patients with and without UCs). Each variable was compared between the 2 subgroups to identify significant differences. After reviewing for appropriateness, $\chi^2$ and Student's $t$ tests were used for statistical comparison of categorical and continuous variables, respectively.

To detect predictive variables associated with a higher risk of UCs in patients with AN, a logistic regression analysis model was applied. Clinical features revealing significant differences on $\chi^2$ and $t$ tests were selected as independent variables. Sex and age were included a priori to adjust the effect of each independent variable for the demographic characteristics of the cohort. Variables with extremely unbalanced distribution in the 2 groups (frequency 0% in 1 group) were excluded.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were used as measures of effect. The statistical significance was set at $P < .05$ for all analyses. SPSS Statistics software package (IBM SPSS Statistics, IBM Corporation) was used to perform all statistical analyses.

## RESULTS

A total of 206 patients meeting the inclusion criteria were identified (108 male patients; male-to-female ratio: 1.01). Demographic and clinical features of the whole cohort and the 2 subgroups with and without severe UCs are summarized in Table 1. The mean age at PED attendance was 8 years 11 months. Thirty-seven patients (18%) were <2 years of age (25 of 37 were <6 months), 87 children (42%) were aged between 2 and 12 years, and 82 (40%) were >12 years. In 77 cases (37%), patients attended the PED complaining of abnormal eye movements. In the remaining cases, nystagmus was detected during clinical examination in patients with other complaints. The mean time from symptoms onset to admission to the PED was 5 days, with 68% of the whole cohort reporting the onset of symptoms within 3 days before admission (median: 2 days). Nystagmus plane was horizontal in the vast majority of cases (71.4%). Less frequently, vertical (6.8%), torsional (1%), or combined (3.4%) nystagmus was reported. Nevertheless, in a significant proportion of patients, the oscillation plane was not reported in clinical records (17.4%). The symptoms most commonly referred during PED consultation were headache (43.2%) and vertigo and/or dizziness (42.2%), followed by nausea and vomiting (25.7%) and visual disturbances (16.02%). Many patients presented with a constellation of associated symptoms (Supplemental Fig 3). Clinical findings most commonly reported during examination included ataxia (18.45%), strabismus (13.1%), or a decreased level of consciousness (6.3%). Sixteen patients (7.8%) were febrile at PED admission (Table 2). In 54.9% of the cases, nystagmus was the only neurologic abnormality reported.

Specialist consultations were requested for 83.5% of the patients, mainly neurologic (61.2%) or ophthalmologic (35.4%) consultations. Approximately one-half of the patients underwent neuroimaging tests (53.9%); 60.4% of them performed the test directly in the PED (Table 3).

A total of 118 patients (57.3%) were hospitalized after PED consultation.

Migraine was the most common cause of AN (accounting for 25.7% of all cases), followed by vestibular disorders (14.1%) (Fig 1A). Transient, not otherwise identified vertigo accounted for 12.6% of the cases. Idiopathic infantile nystagmus (IIN) was responsible for 6.8% of the AN cases, representing the first cause of PED consultation for nystagmus in the first year of life (Fig 1B). Other rarer causes of AN included toxic ingestion, postinfectious cerebellar ataxia, and periodic syndromes (Fig 1A).

Thirty-nine patients were diagnosed with a UC (18.9%). Brain tumors were the first UC causing AN (17 cases; 8.3% of the whole cohort). Other causes included idiopathic intracranial hypertension, demyelinating disorders, degenerative conditions, and CNS infections or malformations (Fig 1C).

Patients with UCs were found to be significantly younger than non-UC patients (mean age: 6 years and 11 months versus 12 years and 4 months), with the highest frequency of UC cases occurring in children between 1 and 6 years of age (Fig 1D). Time delay from symptoms onset to PED presentation was significantly longer in UC compared with non-UC patients (Table 1). Diplopia, blurred vision, strabismus, cranial nerve palsy, ataxic gait, dysmetria, pyramidal weakness, and papilledema, as well as the absence of accompanying symptoms, were significantly more frequent in patients with UCs (Table 2). In contrast, vertigo and the absence of any neurologic sign were more commonly found in non-UC patients (Table 2), as well as the attribution of a nonurgent (green or white) triage code.

On this basis, 14 variables were selected for the logistic regression model (Table 4), including 199 patients (96.6%). According to our model, the presence of cranial nerve deficits, ataxia, or strabismus was strongly associated with an underlying UC, increasing its risk by 46.82-, 9.29-, and 9.17-fold, respectively ($P < .02$) (Table 4). Though not reaching statistical

**TABLE 1** Demographic and Clinical Features of the Whole Cohort and the 2 Subgroups With and Without Severe UCs

| | Non-UC ($n$ = 167) | UC ($n$ = 39) | Whole Cohort ($n$ = 206) | $P$ |
|---|---|---|---|---|
| Sex, $n$ (%) | | | | .6 |
| Male | 86 (51.50) | 22 (56.40) | 108 (52.43) | — |
| Female | 81 (48.50) | 17 (43.60) | 98 (47.60) | — |
| Triage code,[a] $n$ (%) | | | | .02 |
| Red | 1 (0.60) | 1 (2.60) | 2 (1.00) | — |
| Yellow | 43 (26.90) | 20 (51.30) | 63 (31.70) | — |
| Green | 115 (71.90) | 18 (46.20) | 133 (66.80) | — |
| White | 1 (0.60) | 0 (0.00) | 1 (0.50) | |
| Main reason for consultation, $n$ (%) | | | | .27 |
| Nystagmus | 59 (35.30) | 18 (46.20) | 77 (37.40) | — |
| Other symptom | 108 (64.70) | 21 (53.80) | 129 (62.60) | — |
| Hospitalization after PED consultation, $n$ (%) | 79 (47.30) | 39 (100.00) | 118 (57.30) | <.01[b] |
| Age at admission, mo, mean (±SD); median | 112.74 (±62.70); 130.00 | 83.46 (±66.35); 68.00 | 107.20 (±64.28); 120.00 | .01[b] |
| Time from symptoms onset, d, mean (±SD); median | 4.17 (±6.02); 1.00 | 8.10 (±8.98); 3.00 | 4.91 (±6.83); 2.00 | <.01[b] |
| Length of hospitalization ($n$ = 114), mean (±SD); median | 4.91 (±4.14); 4.00 | 15.86 (±28.50); 10.00 | 8.46 (±17.23); 5.00 | <.01[b] |

Percent values refer to the respective column. $P$ values reflect $\chi^2$ and Student's $t$ test for categorical and continuous variables, respectively. —, not applicable.
[a] The triage code was available for 199 patients; in the remaining 7 cases (all belonging to the non-UC group), the triage code was missing from clinical records.
[b] Indicates significant differences.

significance, the presence of pyramidal weakness and abnormal head postures were also associated with an increased risk of UC (with an OR of 8.59 and 7.18, respectively). A longer time from symptoms onset to PED referral was found to raise the odds of an underlying UC, with a 9% increase of the risk by each day from nystagmus onset (OR = 1.09; $P < .01$). Despite the younger age at admission of patients with UCs, this variable was not associated with a greater risk of UC when adjusted for other variables in the logistic regression model (Table 4).

On the other hand, the occurrence of vertigo was found to reduce the odds of an underlying UC (OR = 0.17; $P <$ .01), as well as the attribution of a green or white triage code (OR = 0.30; $P$ = .01).

**TABLE 2** Frequency of Signs and Symptoms Associated to Nystagmus in the Whole Cohort and in the 2 Subgroups

| | Non-UC ($n$ = 167), $n$ (%) | UC ($n$ = 39), $n$ (%) | Whole Cohort ($n$ = 206), $n$ (%) | $P$ |
|---|---|---|---|---|
| Diplopia | 14 (8.40) | 8 (23.10) | 23 (11.20) | .01[a] |
| Blurred vision | 7 (4.20) | 5 (12.80) | 12 (5.80) | .04[a] |
| Photophobia | 6 (3.60) | 1 (2.60) | 7 (3.40) | .75 |
| Headache | 73 (43.70) | 16 (41.00) | 89 (43.20) | .76 |
| Vertigo | 79 (47.30) | 8 (20.50) | 87 (42.20) | <.01[a] |
| Hearing loss | 4 (2.40) | 2 (5.10) | 6 (2.90) | .36 |
| Tinnitus | 5 (3.00) | 1 (2.60) | 6 (2.90) | .89 |
| Vomiting | 41 (24.60) | 12 (30.80) | 53 (25.70) | .42 |
| No associated symptom | 148 (11.4) | 28 (28.2) | 176 (14.6) | .01[a] |
| Abnormal head posture | 3 (1.80) | 3 (7.70) | 6 (2.90) | .049[a] |
| Strabismus | 13 (7.80) | 14 (35.90) | 27 (13.10) | <.01[a] |
| Ptosis | 2 (1.20) | 0 (0.00) | 2 (1.00) | .492 |
| Pupillary defects | 6 (3.60) | 3 (7.70) | 9 (4.40) | .26 |
| Cranial nerve palsy | 1 (0.60) | 5 (12.80) | 6 (2.90) | <.01[a] |
| Hypotonia | 10 (6.00) | 2 (5.10) | 12 (5.80) | .84 |
| Hypertonia | 3 (1.80) | 0 (0.00) | 3 (1.50) | .4 |
| Ataxic gait | 24 (14.40) | 12 (30.80) | 36 (17.50) | .02[a] |
| Tremor | 5 (3.00) | 3 (7.70) | 8 (3.90) | .17 |
| Dysarthric speech | 2 (1.20) | 1 (2.60) | 3 (1.50) | .52 |
| Dysmetria | 3 (1.80) | 4 (10.30) | 7 (3.40) | .01[a] |
| Paresthesia | 5 (3.00) | 1 (2.60) | 6 (2.90) | .89 |
| Consciousness impairment | 10 (6.00) | 3 (7.70) | 13 (6.30) | .69 |
| Pyramidal weakness | 3 (1.80) | 4 (10.30) | 7 (3.40) | .01[a] |
| Sensory loss | 1 (0.60) | 1 (2.60) | 2 (1.00) | .26 |
| Papilledema | 0 (0.00) | 2 (5.10) | 2 (1.00) | <.01[a] |
| No associated neurologic abnormality | 101 (60.5) | 12 (30.8) | 113 (54.9) | <.01[a] |
| Fever | 11 (6.60) | 5 (12.80) | 16 (7.80) | .19 |

Percent values refer to the respective column. $P$ values apply to $\chi^2$ test.
[a] Indicates significant differences.

## DISCUSSION

To the best of our knowledge, this is the first study in which the epidemiology of AN in children is investigated. The most striking finding of our study is that UCs account for nearly 20% of AN in the PED, confirming that nystagmus is an alarming sign. It may be argued that the strict inclusion criteria may have led to an overestimation of the UCs, determining the exclusion of several transient causes of gaze control abnormalities, such as postictal and posttraumatic states. Nevertheless, the large size of the cohort and its multicentric recruiting are in favor of a good external validity of our findings.

The abrupt or subacute appearance of abnormal eye movements represents the main cause for PED admission especially in infants and young

**TABLE 3** Investigations Performed in the Whole Cohort and the 2 Subgroups

| | Non-UC ($n$ = 167), $n$ (%) | UC ($n$ = 39), $n$ (%) | Whole Cohort ($n$ = 206), $n$ (%) | $P$ |
|---|---|---|---|---|
| Blood test | 70 (41.90) | 20 (51.30) | 90 (43.70) | .288 |
| Neuroimaging | | | | <.001[a] |
| No imaging | 94 (56.3) | 1 (2.6) | 95 (46.1) | — |
| CT | 33 (19.8) | 3 (7.7) | 36 (17.5) | — |
| MRI | 28 (16.8) | 16 (41.0) | 44 (21.4) | — |
| CT + MRI | 12 (7.2) | 19 (48.7) | 31 (15.0) | — |
| Specialist consultation | | | | |
| Neurologist | 105 (62.90) | 21 (53.80) | 126 (61.20) | .3 |
| Neurosurgeon | 5 (3.00) | 15 (38.50) | 20 (9.70) | <.01[a] |
| Ophthalmologist | 59 (35.30) | 14 (35.90) | 73 (35.40) | .95 |
| Otorhinolaryngologist | 32 (19.20) | 2 (5.10) | 34 (16.50) | .03 |
| Toxicology screen | 8 (4.80) | 1 (2.60) | 9 (4.40) | .5 |
| EEG | 20 (25.10) | 5 (12.80) | 25 (20.30) | .27 |
| SSEP and/or MEP | 2 (2.50) | 5 (12.90) | 7 (5.90) | .07 |
| VEP | 20 (25.10) | 9 (23.10) | 29 (24.40) | .82 |
| ERG | 13 (16.30) | 3 (7.70) | 16 (13.40) | .2 |
| BAEP | 4 (5.10) | 3 (7.70) | 7 (5.90) | .57 |
| OCT | 2 (2.80) | 2 (5.70) | 4 (3.70) | .45 |
| Fundus oculi | 23 (29.10) | 11 (28.90) | 34 (29.10) | .99 |
| Vestibular tests | 8 (10.30) | 2 (5.40) | 10 (8.70) | .62 |
| CSF sampling | 3 (3.80) | 10 (25.60) | 13 (11.00) | <.01[a] |

Percent values refer to the respective column. $P$ values reflect $\chi^2$ test. BAEP, brainstem auditory evoked potential; CSF, cerebrospinal fluid; CT, computed tomography; ERG, electroretinogram; MEP, motor evoked potential; OCT, optical coherence tomography; SSEP, somatosensory evoked potential; VEP, visual evoked potentials; —, not applicable.
[a] Indicates significant differences.

children (Fig 1 A and B), whereas in older patients, the AN is usually part of a more complex clinical picture and infrequently represents the main complaint of the patient.

Infantile nystagmus has been described as the leading cause of nystagmus in children and adolescents, representing up to 87.3% of the cases in a population-based study.[3] In most cases, infantile nystagmus has a gradual onset and usually does not require urgent evaluation. As expected, in the emergency setting, infantile nystagmus accounts for a considerably smaller proportion of cases (12.08% in our cohort). Despite the lower frequency in the emergency setting, this finding reveals that infantile nystagmus, including IIN and ocular diseases, may have an abrupt presentation, raising the concern of an underlying brain lesion. Indeed, an underlying UC was diagnosed in 6 of 25 infants <6 months (24%) of age, largely exceeding the proportion previously reported in a community-based setting (2.8%)[3] and suggesting that an underlying intracranial lesion is actually more likely when infantile nystagmus has an abrupt onset leading to PED consultation. Even if it has been suggested that acquired nystagmus should be suspected when onset is after 4 months of age,[10] in our series, brain lesions were responsible for 3 of 15 cases of nystagmus in infants <4 months of age, including early-onset leukodystrophies and complex cerebral malformations. Taken together, our data reveal that, at least in the emergency setting, the proportion of young infants with congenital or early-onset brain lesions is not negligible, and a high level of suspicion is required to detect these cases. Although not supported by strong evidence, it is widely reported that direction and waveform are useful indicators of nystagmus origin, with IIN most frequently appearing as bilateral, conjugate, or occurring on the horizontal plane, with either a pendular or a jerk waveform.[1,2] Unfortunately, most medical records lacked this information, preventing the inclusion of these variables in our analysis. Nevertheless, when facing a child with infantile nystagmus, it seems reasonable to consider these characteristics as arguments in favor of IIN, whereas nystagmus with atypical features should be worth further investigation.

In older, otherwise healthy children, acutely or subacutely acquired nystagmus raises the obvious concern of an underlying intracranial lesion.[1]

In our experience, AN is usually detected during PED consultations for acute vertigo or dizziness, severe headache, or acute visual disturbances. Nevertheless, these symptoms often occurred at the same time, confounding the clinical picture (Supplemental Fig 3). Ataxic signs (reported in 18.45% of the cases, including both gait ataxia and/or dysmetria) were the most helpful clinical clues for locating the injury to the cerebellar, brainstem, or vestibular pathways. By contrast, other examination findings were more rarely detected (Table 2). Of note, nystagmus was the only abnormal finding on neurologic examination in 54.9% of the patients at PED admission. Even in the UC group, in 12 of 39 patients, no other neurologic abnormality was noted on admission, and further signs only emerged in the following hours to days.

In adults, AN is mainly described in the context of acute dizziness or vestibular syndrome.[11,12] In this population, vertebrobasilar strokes occur in 3.2% to 4.9% of all patients with dizziness and nystagmus,[5,6] representing the most frequent UC.[13] In our cohort, despite the high frequency of dizziness and vertigo among the reported symptoms, the occurrence of a true vestibular syndrome (encompassing dizziness,

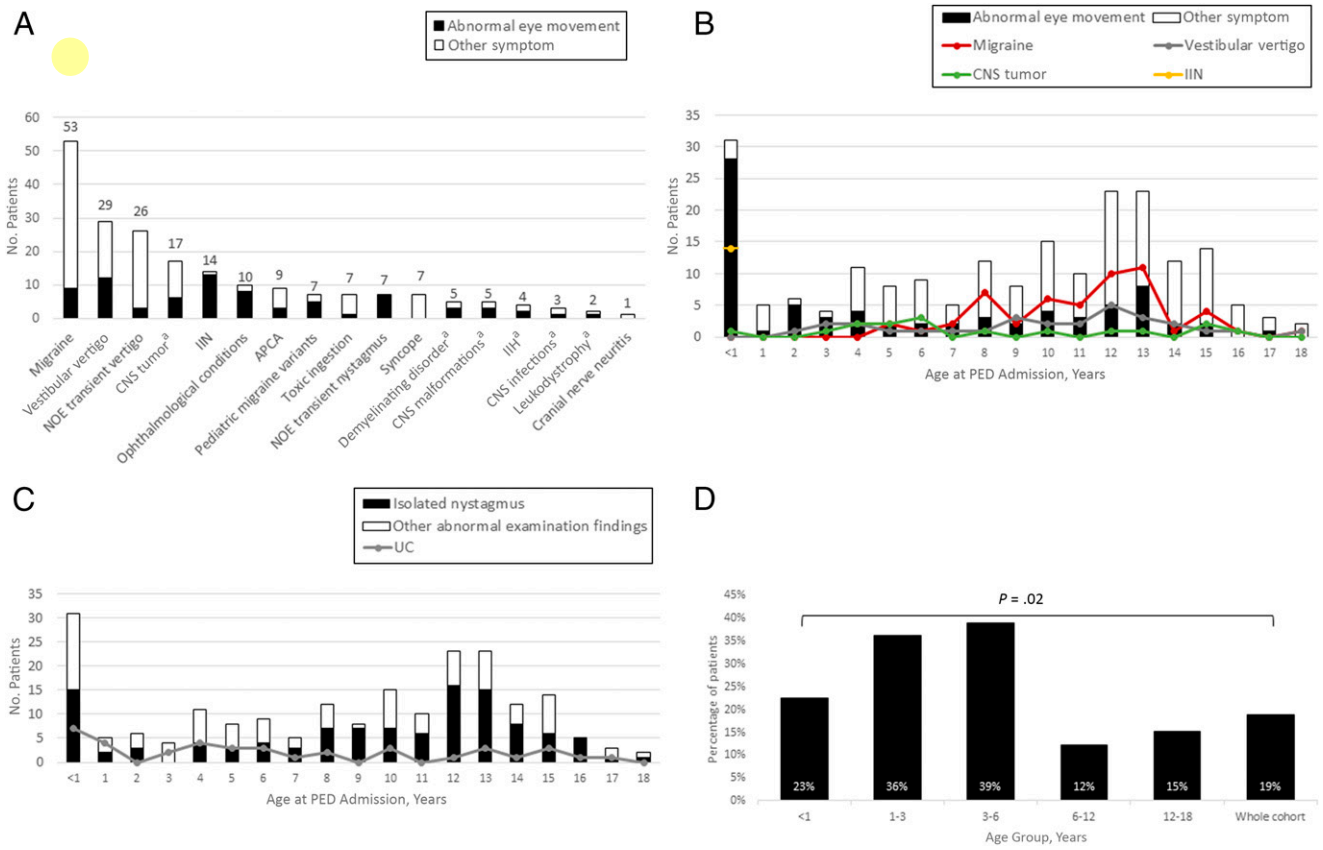


**FIGURE 1**

A, Frequency of AN causes in the whole cohort. Black bars indicate the number of patients attending the emergency department because of the abnormal eye movement, whereas white bars indicate patients complaining about other symptoms, in whom nystagmus was detected during clinical examination. B, Distribution of AN in the whole cohort by age. Black bars indicate the number of patients attendinnt because of the abnormal eye movement, whereas white bars indicate patients complaining about other symptoms, in whom nystagmus was detected during clinical examination. Colored lines show the frequency of selected conditions (migraine, vestibular vertigo, IIN, and CNS tumors) by age. C, Distribution of UCs in the whole cohort by age. Black bars indicate the number of patients with isolated nystagmus, whereas white bars indicate the number of patients showing abnormal findings on neurologic examination. The gray line shows the number of patients with UCs by age. D, Distribution of UCs by class of age. The frequency is expressed as the percentage of patients with an underlying UC on the total number of patients with AN in each age group. The indicated *P* value refers to the probability associated with the Pearson $\chi^2$ test for multiway contingency tables. [a] Indicates UCs. APCA, acute cerebellar postinfectious ataxia; IIH, idiopathic intracranial hypertension; NOE, not otherwise explained.

gait disturbance, and nausea or vomiting[12]) was rare, occurring only in 13 patients, with 10 additional patients presenting with ataxia and dizziness without nausea or vomiting. In addition, CNS tumors accounted for more than one-third of UCs and no case of stroke was identified. In fact, vertebrobasilar infarcts are a rare cause of stroke in children, their frequency ranging from 6% to 13% of all pediatric strokes,[14–18] and nystagmus is rarely cited among the presenting signs.[17] These findings suggest that posterior circulation infarcts are an exceptional cause of acute vestibular syndrome in children,[19] whereas posterior fossa tumors are more frequently associated.

Among benign AN etiologies, migraine was the most common. As previously described, migraine and pediatric migraine variants are the most frequent cause of "brain attacks" in children and adolescents,[7] with vestibular migraine and benign paroxysmal vertigo representing the most common causes of pediatric acute vertigo.[20] In our cohort, migraine frequency reached the highest points between 8 and 14 years of age (Fig 1B). As expected, this peak coincides with the peak of migraine diagnosis in children,[21] with PED attendance being less likely in older patients who already received a migraine diagnosis. Among the differential diagnosis of acute headache and nystagmus, we identified 4 cases of idiopathic intracranial hypertension, confirming that AN is a possible, although atypical, feature of this condition.[22]

As expected, cranial nerve deficits, ataxia, and strabismus resulted to be significantly associated with an underlying UC, their occurrence strongly suggesting a brainstem

**TABLE 4** Results of the Logistic Regression Model

| | OR | CI 95% Lower limit | CI 95% Upper limit | Significance |
|---|---|---|---|---|
| Cranial nerve palsy | 46.82 | 1.868 | 1173.739 | 0.02[a] |
| Ataxic gait | 9.29 | 1.607 | 53.756 | 0.01[a] |
| Strabismus | 9.17 | 2.005 | 41.973 | <0.01[a] |
| Pyramidal weakness | 8.59 | 0.564 | 130.64 | 0.12 |
| Abnormal head posture | 7.18 | 0.735 | 70.076 | 0.09 |
| Dysmetria | 2.01 | 0.082 | 48.982 | 0.67 |
| Male sex | 1.36 | 0.537 | 3.459 | 0.51 |
| Time from symptom onset | 1.09 | 1.027 | 1.148 | <0.01[a] |
| Diplopia | 1.02 | 0.244 | 4.269 | 0.98 |
| Age at onset | 1.00 | 0.99 | 1.006 | 0.60 |
| Nystagmus with no other symptom | 0.48 | 0.14 | 1.635 | 0.24 |
| White or green triage code at admission | 0.30 | 0.117 | 0.78 | 0.01[a] |
| Nystagmus with no associated neurologic abnormality | 0.29 | 0.069 | 1.216 | 0.09 |
| Vertigo | 0.17 | 0.048 | 0.63 | 0.01[a] |

Fourteen variables were selected, and 199 patients were included in the analysis.
[a] Indicates significant associations.

and/or cerebellar lesion. It can be argued that ataxia and strabismus were among the most common findings in the overall cohort, sometimes occurring in absence of any UC. In fact, it is noteworthy that many causes of cerebellar, vestibular, or ocular motility dysfunctions in children are transient and benign, including acute postinfectious cerebellar ataxias or viral vestibular neuritis.[23,24] In some cases, nystagmus occurs as a transient finding during the recovery phase after a peripheral gaze palsy, as in abducens nerve neuritis. These findings lead us to suggest that ataxia and strabismus should be considered as alarming findings in children with nystagmus, justifying the use of neuroimaging to exclude central lesion, unless an obvious benign cause (eg, varicella infection) can be rapidly identified. Somewhat surprisingly, the association between pyramidal weakness or abnormal head postures and an underlying UC did not reach statistical significance in the logistic model (Table 4), despite both these features being significantly more frequent among patients with UCs in the univariate analysis (Table 2) and revealing a strong positive correlation with an underlying UC (Table 4). Pyramidal weakness indicates a corticospinal tract damage; nevertheless, its overall low frequency in our cohort was probably insufficient to reach significance in the multiple regression analysis. Abnormal head postures have been reported as possible presenting signs in pediatric brain tumors[25] but can also be postures adopted by the patient to reduce or

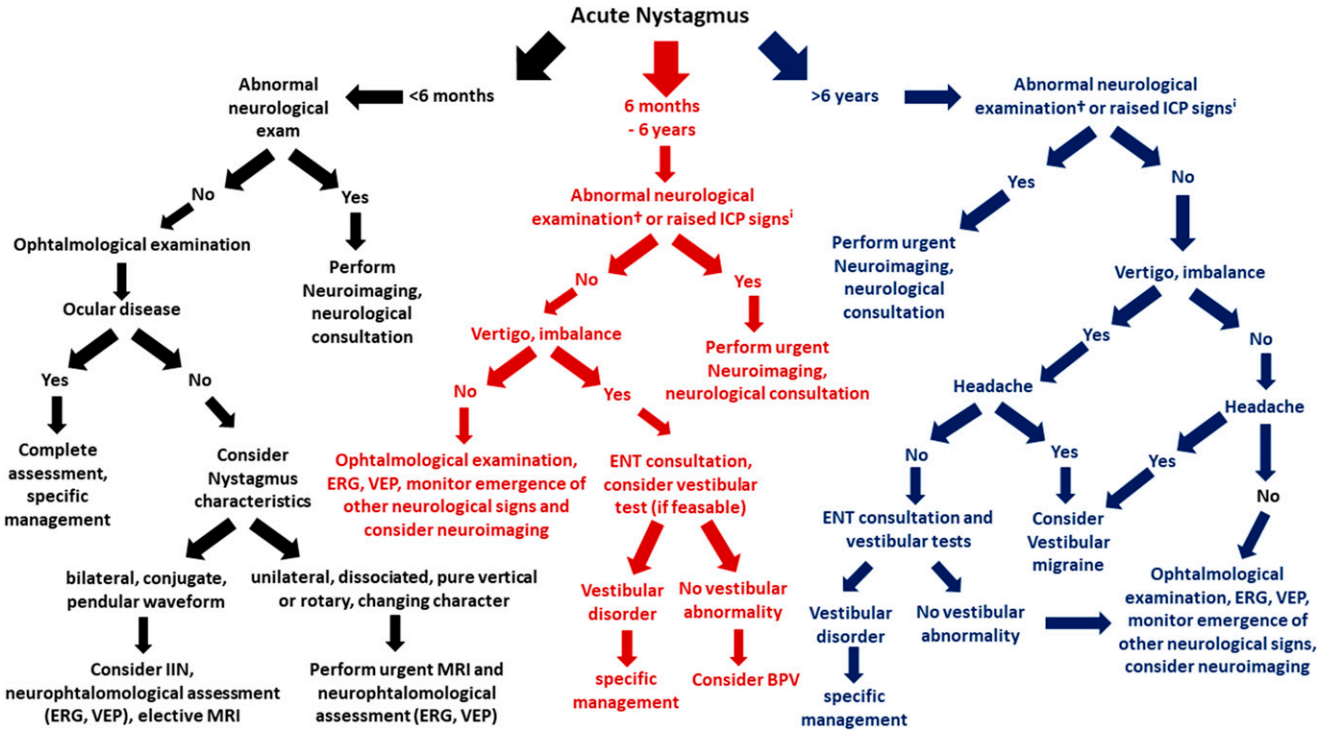


**FIGURE 2**
Proposed clinical approach to AN in the emergency setting. [a] Carefully check for ataxia, strabismus or other cranial nerve deficits, weakness or upper motor neuron signs, and abnormal head postures. [b] Including headache, papilledema or optic atrophy, vomiting, and/or bradycardia. BPV, benign paroxysmal vertigo; ERG, electroretinogram; ICP, intracranial pressure; ENT, ear, nose, throat; VEP, visual evoked potential.

block the nystagmus to attain a better vision. Despite the lack of a significant association, we suggest that any child with these findings should be appropriately investigated and referred to a pediatric neurologist. By contrast, vertigo was significantly associated with non-UCs, reflecting the rare occurrence of central vestibular syndrome in children. Perhaps unexpectedly, patients with underlying UCs attended the PED with a longer delay compared with non-UC patients, resulting in a higher risk of UCs in patients with persistent nystagmus. In fact, with the notable exception of IIN, most non-UCs are paroxysmal disorders (Fig 1), and persistence of nystagmus for several days should be considered an alarming finding. In our series, UCs affected all age groups, but their frequency reached a significant peak between 1 and 6 years ($P = .02$) (Fig 1 C and D). This finding probably reflects the drop in the frequency in this age group of IIN and migraine, the leading benign causes of AN respectively in younger and older children, with a relative increase of UCs. Despite the lack of a significant correlation when adjusted for other variables in the logistic regression model, the higher frequency of UCs in toddlers and preschool-aged children should be considered in the assessment of AN.

In addition, other alarming findings not included in our logistic analysis should be considered. For example, papilledema was not included because of the unbalanced distribution between the 2 subgroups, but it represents an obvious indication for neuroimaging. Similarly, different abnormal eye movements (ie, ocular flutter or opsoclonus) were considered as exclusion criteria, but their co-occurrence with nystagmus suggests a central origin of the gaze control abnormality.

According to our findings, we propose a diagnostic pathway for AN in PED (Fig 2).

Mostly because of its retrospective design, this study suffers from some limitations that could affect our conclusion. First, during the study period, no routine protocol for AN was applied, making assessment and management of our cohort highly heterogenous. In addition, in a significant proportion of patients with transient symptoms, a definite etiology was not identified. This is mainly attributable to the lack of detailed information about the diagnostic workup of nonhospitalized patients. Accordingly, few patients received detailed vestibular function tests. Finally, our logistic regression model was designed to identify patients with significant neurologic abnormalities requiring urgent interventions, but a high risk of an underlying UC is not informative per se of a specific disorder.

## CONCLUSIONS

Our cohort reveals that AN should be considered an alarming finding in children presenting to PEDs given the high prevalence of UCs in this population. Young age or absence of other neurologic signs at presentation do not totally exclude the presence of intracranial lesions. Cranial nerve palsy, ataxia, strabismus, upper motor neuron signs, and abnormal head postures should be considered red flags during the assessment of a child with AN. By contrast, acute dizziness and nystagmus, in the absence of other neurologic signs, are rarely associated with intracranial lesions.


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## ABBREVIATIONS

AN: acute nystagmus
CI: confidence interval
CNS: central nervous system
IIN: idiopathic infantile nystagmus
OR: odds ratio
PED: pediatric emergency department
UC: urgent condition


Dr Garone conceptualized and designed the study, collected data, and drafted the initial manuscript; Dr Raucci conceptualized and designed the study, coordinated and supervised data collection, and reviewed and revised the manuscript; Prof Suppiej conceptualized and designed the study and reviewed and revised the manuscript; Dr Vanacore performed all statistical analyses and critically reviewed the manuscript for important intellectual content; Profs Parisi, Verrotti, Grosso, and Da Dalt critically reviewed and revised the manuscript for important intellectual content; Drs La Penna, Palmieri, Calistri, Poletto, Rossetti, Cordelli, Velardita, d'Alonzo, Bellelli, Gioè, Marin, Zagaroli, Bonfatti, Mencaroni, Masi, and De Liso collected data and critically revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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## REFERENCES

1. Hussain N. Diagnosis, assessment and management of nystagmus in childhood. *Paediatr Child Health*. 2016; 26(1):31–36
2. Papageorgiou E, McLean RJ, Gottlob I. Nystagmus in childhood. *Pediatr Neonatol*. 2014;55(5):341–351
3. Nash DL, Diehl NN, Mohney BG. Incidence and types of pediatric nystagmus. *Am J Ophthalmol*. 2017;182: 31–34
4. Tarnutzer AA, Straumann D. Nystagmus. *Curr Opin Neurol*. 2018;31(1):74–80
5. Kerber KA, Brown DL, Lisabeth LD, Smith MA, Morgenstern LB. Stroke among patients with dizziness, vertigo, and imbalance in the emergency department: a population-based study. *Stroke*. 2006;37(10):2484–2487
6. Kim M-B, Boo SH, Ban JH. Nystagmus-based approach to vertebrobasilar stroke presenting as vertigo without initial neurologic signs. *Eur Neurol*. 2013;70(5–6):322–328
7. Mackay MT, Chua ZK, Lee M, et al. Stroke and nonstroke brain attacks in children. *Neurology*. 2014;82(16):1434–1440
8. Mackay MT, Yock-Corrales A, Churilov L, Monagle P, Donnan GA, Babl FE. Differentiating childhood stroke from mimics in the emergency department. *Stroke*. 2016;47(10):2476–2481
9. Gazzetta Ufficiale. Permanent conference for relations between the state regions and autonomous provinces of Trento and Bolzano. 2001. Available at: https://www.gazzettaufficiale.it/eli/id/2001/12/07/01A12203/sg. Accessed March 20, 2020
10. Ehrt O. Infantile and acquired nystagmus in childhood. *Eur J Paediatr Neurol*. 2012;16(6):567–572
11. Newman-Toker DE, Hsieh Y-H, Camargo CA Jr., Pelletier AJ, Butchy GT, Edlow JA. Spectrum of dizziness visits to US emergency departments: cross-sectional analysis from a nationally representative sample. *Mayo Clin Proc*. 2008;83(7):765–775
12. Spiegel R, Kirsch M, Rosin C, et al. Dizziness in the emergency department: an update on diagnosis. *Swiss Med Wkly*. 2017;147:w14565
13. Royl G, Ploner CJ, Leithner C. Dizziness in the emergency room: diagnoses and misdiagnoses. *Eur Neurol*. 2011;66(5): 256–263
14. Chung B, Wong V. Pediatric stroke among Hong Kong Chinese subjects. *Pediatrics*. 2004;114(2):e206–e212
15. Ganesan V, Chong WK, Cox TC, Chawda SJ, Prengler M, Kirkham FJ. Posterior circulation stroke in childhood: risk factors and recurrence. *Neurology*. 2002;59(10):1552–1556
16. Lagman-Bartolome AM, Pontigon A-M, Moharir M, et al. Basilar artery strokes in children: good outcomes with conservative medical treatment. *Dev Med Child Neurol*. 2013;55(5):434–439
17. Rollins N, Pride GL, Plumb PA, Dowling MM. Brainstem strokes in children: an 11-year series from a tertiary pediatric center. *Pediatr Neurol*. 2013;49(6):458–464
18. Goeggel Simonetti B, Ritter B, Gautschi M, et al. Basilar artery stroke in childhood. *Dev Med Child Neurol*. 2013; 55(1):65–70
19. Ehresmann AM, Van HC, Merlini L, Fluss J. Wallenberg syndrome: an exceptional cause of acute vertigo in children. *Neuropediatrics*. 2016;47(1):61–63
20. Langhagen T, Landgraf MN, Huppert D, Heinen F, Jahn K. Vestibular migraine in children and adolescents. *Curr Pain Headache Rep*. 2016;20(12):67
21. Tarasco V, Grasso G, Versace A, et al. Epidemiological and clinical features of migraine in the pediatric population of Northern Italy. *Cephalalgia*. 2016;36(6): 510–517
22. Jones JS, Nevai J, Freeman MP, McNinch DE. Emergency department presentation of idiopathic intracranial hypertension. *Am J Emerg Med*. 1999; 17(6):517–521
23. Garone G, Reale A, Vanacore N, et al. Acute ataxia in paediatric emergency departments: a multicentre Italian study. *Arch Dis Child*. 2019;104(8): 768–774
24. Raucci U, Parisi P, Vanacore N, et al. A cohort study on acute ocular motility disorders in pediatric emergency department. *Ital J Pediatr*. 2018;44(1):62
25. Ansell P, Johnston T, Simpson J, Crouch S, Roman E, Picton S. Brain tumor signs and symptoms: analysis of primary health care records from the UKCCS. *Pediatrics*. 2010;125(1):112–119