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Prevalence, clinical profile, and diagnosis of pediatric dizziness in a tertiary care hospital

G.R. Haripriya^{a,*}, Anjali Lepcha^b, Ann Mary Augustine^b, Mary John^b, Ajay Philip^b, Manju Deena Mammen^b

^a Otorhinolaryngology, MGM Healthcare Hospital, Chennai, Tamil Nadu, 600029, India

^b Department of Otorhinolarynglogy Unit IV, Christian Medical College Vellore, Ida Scudder Road, Vellore, Tamil Nadu, 632004, India

A R T I C L E I N F O	A B S T R A C T					
Keywords: Children Vertigo Dizziness Migraine Benign paroxysmal vertigo of childhood (BPVC)	Introduction: Pediatric dizziness is an uncommon complaint presenting to the Otolaryngology clinic. While the term dizziness may be used to describe any altered sensation of orientation to the environment which includes presyncope, light-headedness and ataxia, vertigo refers to a false sensation of motion of self or surroundings. Although a variety of etiologies are known to cause dizziness and vertigo, evaluation of this symptom becomes challenging in children who are unable to clearly explain what they experience, the provoking factors, associated symptoms and the duration of attacks. Vestibular tests are also difficult to conduct in the pediatric age group leading to apathy from the clinician. <i>Objectives</i> : To ascertain the prevalence of pediatric vertigo in children under 18 years of age, presenting to the Otolaryngology Clinic of a tertiary care hospital, and to describe the clinical profile, investigations and diagnosis in these children. <i>Methods</i> : A prospective cross-sectional, descriptive clinical study was undertaken from January 1, 2018 to April 30, 2019. All children below the age of 18 years presenting to our department with primary complaints of dizziness were included in the study. After a thorough history and physical examination, screening methods and diagnostic tests were conducted to make a diagnosis. Referrals were sought from other specialties when necessary. <i>Results</i> : The number of children visiting the Department for various ENT ailments during the study period was 10,950. Among these 89 children presented with a primary complaint of dizziness. Their ages ranged from 3 to 18 years; mean age was 11.42 years (SD 3.45). A diagnosis was made in all except two children. The most common cause of dizziness in the age group less than 6 years was being paroxysmal vertigo of childhood (BPVC) and in the older children was migraine associated vertigo, which was also the commonest overall diagnosis made (28.1%). This was followed by circulation related dizziness like orthostatic hypotension and vasov					

1. Introduction

The diagnosis and management of vestibular disorders in childhood is difficult for a variety of reasons. Children invariably cannot describe their sense of disequilibrium as how an adult would. Dizziness is defined as the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion [1]. Internal vertigo is a sensation of self-motion when no self-motion is occurring or a sensation of distorted self-motion during an otherwise normal head movement. External vertigo is a false sensation that the visual surround is spinning or flowing [1]. The term dizziness may be used to describe any altered sensation of orientation to the environment and may include presyncope, light-headedness and ataxia, all of which may have a variety of etiologies. Vertigo is an illusion of motion of oneself or his or her

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^{*} Corresponding author. *E-mail address:* itsgrhari@gmail.com (G.R. Haripriya).

environment, whereas dizziness is usually nonspecific. Vertigo is an acute symptom that can be incapacitating to the patient. Dizziness is usually more lingering and may cause disruption in daily activities, inability to attend school, and even social withdrawal.

The prevalence of vestibular disorders in the pediatric population ranges between 0.7% and 15% [2–4]. In another study the prevalence was 5.3% and increased with increasing age which can be explained by better reporting by older children, of whom at least 18% had a significant problem [5]. An epidemiologic study among school children revealed that in 15%, a symptom like dysequilibrium was experienced at least once [6]. A recent review of all ICD-9 codes related to vestibular and balance disorders in more than 560,000 distinct pediatric patients encountered during a 4-year period, revealed a prevalence of only 0.03% for peripheral vestibulopathy, 0.02% for central vestibulopathy and 0.4% for non-specific dizziness [7].

Dizziness is one of the most challenging symptoms in medicine. It is difficult to define, impossible to measure, a challenge to diagnose, and troublesome to treat [8]. Younger children are not able to verbalise what they are experiencing and may present with other behavioural symptoms. Parents or caregivers may report seeing the child suddenly cry out and drop to the floor or cling to the legs of adults. Associated symptoms such as pallor, sweating, vomiting and behavioural attributes such as screaming, lying face down in the cot and showing reluctance to be moved may also be presenting complaints [9]. Head control and the ability to sit, stand, walk and run are normally accompanied by the integration of vestibular inputs with visual, proprioceptive and other somatosensory inputs. Lack of vestibular input has been shown to delay the acquisition of these motor skills [10].

The etiology of dizziness in children is different from that of adults in terms of relative incidences and prevalence. Since vestibular damage can lead to a range of cognitive, psychological and somatic symptoms and can originate from a vast spectrum of medical causes, management should be holistic and multi-disciplinary. Moreover, the differential diagnosis of childhood vertigo differs from that of adults because several etiologies are unique to the pediatric population while the occurrences of common pathologies are rather different in children and adults [11]. The differential diagnostics is extensive in children with dizziness, and correct diagnosis requires thorough otologic examination as well as neurologic and general physical examination [12].

Diagnosing a dizzy child is an art and localising a neurological, cardiological or neurotological cause of a child presenting with dizziness requires experience, knowledge and accurate clinical acumen [13].

The main objectives of our study were to ascertain the prevalence of pediatric dizziness in children up to 18 years of age, presenting to the Otolaryngology Department in our tertiary care hospital and to describe the clinical profile, investigations and diagnoses of these children.

2. Material and methods

A prospective cross-sectional, descriptive clinical study was conducted to assess the prevalence and to evaluate the different causes of pediatric dizziness.

2.1. Study subjects

All children less than 18 years, presenting with primary complaints of dizziness and balance problems during the period between January 1, 2018 to April 30, 2019 (sixteen months), to the Otolaryngology Department were included in the study. The protocol of the study was reviewed and approved by the Institutional Review Board and Ethics committee.

Children diagnosed with a middle ear disease like otitis media with effusion and chronic otitis media were excluded from the study.

A written informed consent was obtained from the legal guardian of the child and a written assent was included if the child was more than 12 years old. A questionnaire regarding history and symptoms was filled by the parent or by the child wherever possible. A thorough clinical examination and history was elicited, screening methods and diagnostic tests were carried out to differentiate possible diagnosis. The various differential diagnoses were noted and laboratory tests and referrals to other specialists were made accordingly.

During data analysis, the participants were categorised into different age groups: 0–6 years (preschool), 7–12 years (school age) and 13–18 years (adolescents). This was done since the verbal and expressive skills vary between age groups and also to acquire a better understanding of the pattern of presentation and diagnosis based on age.

2.2. Audiovestibular quantification

History was assessed in detail and both the child and parents or guardians were asked questions regarding the exact onset, timing, duration and severity of symptoms and associated features. Characterizing exactly what the child meant by "dizzy" was the most important step in the process of evaluation. The child's description about the type of vertigo was noted as to whether it was a sensation of room spinning, head spinning or syncopal attacks. Information on the nature of the symptoms (acute or chronic, paroxysmal or continuous, attack severity, number and duration of attacks), provocative factors, ear symptoms (aural fullness, tinnitus, pain and hearing loss), other associated symptoms, past history of head trauma and other systemic diseases were recorded. Details of family history, developmental history and scholastic performance were noted.

Clinical examination included detailed physical and neurotological assessment. The vestibulospinal and vestibulo-ocular pathways were also assessed. Audiological investigations like pure tone audiometry (PTA) and tympanometry were carried out. Vestibular laboratory studies such as electrocochleogram (ECOG), vestibular evoked myogenic potential (VEMP), subjective visual vertical (SVV) or electronystagmogram (ENG) were performed where indicated.

2.3. Other investigations

Biochemical blood profiles, imaging studies like High Resolution Computed Tomography (HRCT) of the temporal bone and Magnetic Resonance Imaging (MRI) of the brain with contrast to rule out anatomical abnormalities and space occupying lesions were performed wherever necessary.

In suspected neurogenic, cardiogenic or psychiatric causes, the patient was referred to the respective specialists and evaluated. A clinical algorithm was created according to the findings and diagnosis that were obtained.

The diagnoses of vertigo such as vestibular migraine, benign paroxysmal vertigo of childhood (BPVC), Meniere's disease, orthostatic intolerance etc were based on standard published criteria [14–17].

3. Results

The total number of children who visited the Otolaryngology department during the study period was 10,950. Among these 89 children presented with primary complaints of dizziness and their ages ranged from 3 to 18 years, the mean age was 11.42 years (SD 3.45).

The prevalence of pediatric vertigo among children presenting to the ENT department was 0.8%.

There were eight (9%) children in the 0–6 years age group, 48 (53.9%) in the 7–12 years age group and 33(37.1%) in the 13–18 years age group.

Among our study population 53(59.6%) were males and 36(40.4%) were females. In the youngest age group, there were equal males and females, in the middle age group there were more boys than girls and in the older age group there were more girls than boys (Fig. 1).

According to the type of dizziness, 45(50.6%) presented with complaints of surrounding rotatory type vertigo, 26(29.2%) presented with

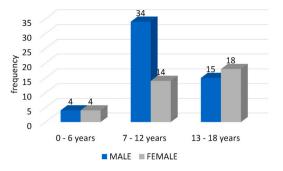


Fig. 1. Graph showing gender distribution in each age group.

head rotatory type of vertigo and 18(20.2%) presented with other symptoms like syncope, linear displacement, imbalance etc.

Co-morbid illnesses like hypothyroidism, seizure disorder and migraine were present in 40(44.9%) children.

Audiological evaluation was done in 70 children, among these 63 were normal and 17 showed hearing loss with 3 children having unilateral profound hearing loss.

ENG test was completed in 59 children, among these 27(30.3%) children showed a normal result. ENG reported bilateral vestibular paresis in 21(23.6%) children, unilateral paresis in 5(5.6%) and unilateral hyperactive response in 2(2.2%). Abnormal smooth pursuit test and optokinetic test were seen in 4(4.5%).

Imaging studies were performed in 45 patients and among these 39 (43.8%) had a normal study and 6(6.7%) revealed abnormalities. Among these six patients, one child was diagnosed with bilateral vestibular schwannoma while one child had an old thalamic bleed. Two children with history of seizures had cortical atrophy while another child with acute vestibulocochlear event had non-specific white matter hyperintensities in the occipital horns bilaterally. Frontal lobe calcified granuloma was detected in a child diagnosed with vestibular migraine.

The most common diagnosis obtained was migraine associated vertigo of childhood 25(28.1%). Circulation related causes like vasovagal syncope and orthostatic hypotension constituted around 14(15.7%), benign paroxysmal vertigo of childhood (BPVC) was seen in seven (7.9%) and vestibular epilepsy in eight (9%). Acute vestibulocochlear event was found to be the cause of vertigo in five (5.6%) and factitious dizziness in five (5.6%) children. Other diagnosis made included bilateral vestibulopathy (3.3%), post traumatic vertigo (2.2%), Meniere's disease (2.2%), drug induced vertigo (1.1%), bilateral vestibular schwannoma (1.1%), refractive error (1.1%), metabolic causes (Pendred syndrome-1.1%), thalamic infarct (1.1%) and vestibular neuritis (1.1%). In two cases the diagnosis could not be ascertained (2.2%).

In the age group less than 6 years, the most common cause for dizziness was BPVC (87.5%). Among the 48 children in the age group between 7 and 12 years, migraine associated vertigo, either definite or probable, was the most common diagnosis (33.3%) followed by circulation related disorders like orthostatic hypotension and vasovagal syncope in 12(25%)children. In the age group between 13 and 18 years, the most common cause for vertigo was migraine associated vertigo (27.5%) (Fig. 2). The various diagnosis made according to the age group is summarised in Table 1.

There were no significant associations (P value > 0.05) between specific age group or gender with diagnosis of dizziness.

4. Discussion

In our study we found the prevalence of pediatric dizziness to be 0.8% among children presenting to the Otolaryngology clinic. The prevalence of vestibular disorders in the pediatric population ranges between 0.7% and 15% according to previous studies [2–4].

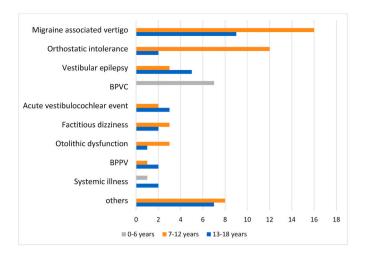


Fig. 2. Diagnosis of dizziness according to age distribution. *BPVC – Benign Paroxysmal Vertigo of Childhood, BPPV – Benign Paroxysmal Positional Vertigo.

Table 1

Diagnosis of dizziness according to age group.

Sl No	Diagnosis	0–6 years	7–12 years	13–18 years	Total
1	Migraine associated vertigo	0	16	9	25(28%)
2	Orthostatic intolerance	0	12	2	14 (15.7%)
3	Vestibular epilepsy	0	3	5	8(9%)
4	BPVC	7	0	0	7(7.9%)
5	Acute vestibulocochlear event	0	2	3	5(5.6%)
6	Factitious dizziness	0	3	2	5(5.6%)
7	Otolithic dysfunction	0	3	1	4(4.5%)
8	Bilateral vestibulopathy	0	2	1	3(4%)
9	BPPV	0	1	2	3(4%)
10	Systemic illness	1	0	2	3(4%)
11	Post traumatic dizziness	0	2	0	2(2.2%)
12	Meniere's disease	0	1	1	2(2.2%)
13	Drug induced dizziness	0	0	1	1(1.1%)
14	Vestibular schwannoma	0	0	1	1(1.1%)
15	Refractive errors	0	0	1	1(1.1%)
16	Pendred syndrome	0	0	1	1(1.1%)
17	Thalamic infarct	0	1	0	1(1.1%)
18	Vestibular neuritis	0	1	0	1(1.1%)
19	Unspecified	0	1	1	2(2.2%)
	Total	8 (9%)	48 (54%)	33 (37%)	89

*BPVC – Benign Paroxysmal Vertigo of Childhood, BPPV – Benign Paroxysmal Positional Vertigo.

4.1. Migraine associated vertigo

Children with migraine associated vertigo presented mainly between 7 and 18 years of age and most of them had both headache and dizziness. This was the most common diagnosis made (28.1%) and is consistent with previously published studies [6,18,19]. These children met the International Headache Society (IHS) criteria for migraine associated vertigo [14].

According to the study by Pe'rez-Plasencia et al. [20] it was hypothesized that vertigo may be related to transitory vasospasm producing labyrinthine or central vestibular pathway ischemia. In another study by Cutrer and Baloh [21], it was suggested that vertigo could be caused by a unilateral, reversible neurochemical derangement in the vestibular periphery. Migraine presents differently in children when compared to adults, with shorter headaches that are more likely to be bilateral [15]. The headache was commonly accompanied by symptoms

like nausea, photophobia and phonophobia and most had episodes of rotatory vertigo lasting minutes to hours followed or accompanied by headache and sensitivity to light and noise [22,23].

4.2. BPVC

The most common cause for dizziness was BPVC in children less than 6 years; 7 out of 8 cases (87.5%), similar to that reported by other studies [24].

Basser [25] defined BPVC in 1964 as a very frequent cause of pediatric dizziness. It was diagnosed in 35% of children with dizziness in one series [26]. The cause of BPVC is thought to be due to an interruption of blood supply to the brain [27]. According to the "vascular hypothesis" [28], classic migraine attack and BPVC follow similar phenomenon. It can begin between the ages of 1 and 4 years but can occur up to the age of 10 years [27]. Recurrent, spontaneous episodes of true vertigo, nystagmus, ataxia and disequilibrium occur for a duration usually less than 10 min, although they can last for hours. There is generally no headache in BPVC in contrast to migraine associated vertigo. BPVC is regarded as a variant of migraine. It has been included in the recent International classification of Headache Disorders-3 (ICHD-3) [15]. Many children with BPVC will go on to develop migraine in later life [29]. In one study the condition had resolved by about 8 years of age, and on long-term follow-up, 21% had developed migraine but none had any vertigo or balance disorders [30]. A detailed physical examination may reveal abnormal eye movements suggestive of nystagmus but no alterations in consciousness, signs of audio-vestibular impairment or neurological changes are seen during the entire attack. Several studies have reported that children with BPVC commonly present with significant bithermal caloric asymmetry [31,32]. Timely counseling of parents regarding the benign nature of the disorder helps to relieve their anxiety.

4.3. Orthostatic intolerance

Our second most common diagnosis was systemic circulation related dizziness like orthostatic intolerance (OI), vasovagal syncope and postural tachycardia syndrome. OI is common in children and is defined as having difficulty tolerating an upright posture as symptoms and signs abate when returned to supine. In one case series [33] it was reported that as many as 40% of people faint during their lives, half of whom faint during adolescence and the peak age for the first faint is 15 years. The onset is near puberty and mostly in girls because of reduced body mass index and onset of menstrual cycles.

Pediatric OI has been mentioned in recent publications [34,35]. The typical symptoms include a sense of impending loss of consciousness, cognitive deficits (memory loss and decreased reasoning and concentration), visual difficulties, lightheadedness, headache, fatigue, weakness, nausea, abdominal discomfort, tremulousness, exercise intolerance and reported signs such as pallor, diaphoresis, tachycardia, bradycardia or hypotension. Postural vasovagal syncope is defined as a transient loss of consciousness and postural tone because of global cerebral hypoperfusion characterized by rapid onset and short duration of symptoms [16].

We diagnosed 14 children with OI and among them 12 were in the age group 7–12 years and 2 were in 13–18 years age group. All were referred to cardiac electrophysiology clinics where the evaluation included Electrocardiography (ECG), Echocardiography (ECHO), Holter and Head up tilt table (HUTT) test.

4.4. Acute cochleovestibular events

In our study we had 5 (5.5%) children who presented with imbalance along with sudden hearing loss. This cohort were classified under the group with acute cochleovestibular events. Among the 5, all had unilateral hearing loss, with 3 of them having profound hearing loss, one having unilateral severe hearing loss and one child having unilateral moderate sensory neural hearing loss. In four patients, MRI of brain with contrast was normal. In one child there was non-specific white matter hyperintense lesions present in the occipital horns bilaterally. ENG showed canal paresis on the side of hearing loss in all 5 patients.

4.5. Vestibular epilepsy

Vestibular epilepsy was diagnosed in 8 children; of these, 3 children had co-existing migraine (these children were counted in the vestibular epilepsy group). Among the eight, two children's EEG showed abnormal waveforms. These children were referred to the pediatric neurophysician for treatment and antiepileptic medications were initiated in all. Vestibular epilepsy are auras (simple or complex partial sensory seizures) with vertigo as the predominant symptom [36]. The patient experiences sudden disequilibrium with rotational (horizontal or vertical) or linear (rising, falling, tilting) vertigo, accompanied in most cases by body or head and eye rotation (with or without nystagmus). The symptoms may last a few seconds or minutes and may be associated with mild nausea. The limited clinical data that exists consist of patients' descriptions, EEG recordings and correlations of vestibular symptoms with the results of brain imaging techniques. Vestibular seizures respond to antiepileptics. First line drugs are carbamazepine or phenytoin: second line drugs are gabapentin, sodium valproate and lamotrigine [37].

4.6. Factitious dizziness

Anxiety disorders should also be considered, as this is a typical manifestation during adolescence. In our study we came across children feigning dizziness for some secondary gain like avoiding exams/punishment etc. We called this 'factitious dizziness' and this was diagnosed in five (5.6%) of our patient cohort. These five children were above seven years of age. All these children had been extensively evaluated in other centers and were finally brought to our hospital by anxious parents. Upon diagnosis, all parents accepted the diagnosis and all children admitted to feigning dizziness and imbalance for secondary gains. They were sent for counseling. No other previous studies have mentioned this disorder amongst the etiologies for vertigo in children. In other medical literature, the term psychogenic vertigo is described [11,12,38-40] but in our study we did not find any underlying psychiatric illnesses in these children, hence this condition warrants a different terminology. Psychogenic dizziness should be diagnosed only after excluding organic pathology and with the input of a psychiatrist.

4.7. Otolithic dysfunction

Otolithic dysfunction was found to be the cause of dizziness in 4 (4.5%) children. These children had occasional imbalance and clinical evaluation showed an abnormal SVV, other tests being normal.

4.8. Other diagnosis

Drug induced vertigo, BPPV, Meniere's disease, thalamic infarct, bilateral vestibular schwannoma, refractive errors, bilateral vestibulopathy, vestibular neuritis and post traumatic dizziness contributed to the rest of the diagnosis. In two children (2.2%) we could not get any specific cause for dizziness despite extensive evaluation and so we grouped them as 'unspecified'.

The age group between 13 and 18 years most often presented with disorders that were similar to those found in adults. It was in this age range that BPPV was encountered. BPPV is characterised by short duration of attacks of giddiness occurring in a definite head position. These children were treated with canalolith repositioning manoeuvres.

In our study there was one child with amblyopia in whom symptoms resolved after correction of the ophthalmic abnormality. Another child who presented with head rotatory vertigo and hearing loss was diagnosed with Pendred syndrome. On presentation he had high levels of TSH (204mIU/L) and was referred to a pediatric endocrinologist.

We noted that close cooperation and communication between different specialties was essential in establishing a correct diagnosis. Most of our study cohort had initially seen a pediatrician or pediatric neurologist and had already undergone a thorough neurological evaluation. A diagnostic flow chart was made according to the presenting symptoms (Fig. 3) in our patients.

In patients suspected of neurological deficits, chronic headache and asymmetrical hearing loss, MRI brain with contrast study is necessary. Among the 45 children who underwent imaging studies 6.7% were found to have positive findings. One child was diagnosed with bilateral vestibular schwannoma and one child had an old right thalamic bleed. Two children with history of seizure disorder had cortical atrophy, one child with acute vestibulocochlear event had non-specific white matter hyperintensities in the occipital horns bilaterally and a child diagnosed with vestibular migraine had a frontal calcified granuloma. Central neurological disorders can generate imbalance caused by lesions in the brainstem especially the nuclei controlling saccadic eye movements, cerebellum and rarely the thalamus or the cortex and can coexist with peripheral vestibular problems [13].

Variability in the study design, inclusion and exclusion criteria may explain the differences in the reported incidence of various aetiologies between our study and previous studies [3,6,11,12,18,19,38,40–42] (Table 2).

4.9. Strengths and limitations of the study

This study analyses the etiology, characteristics and the approach to diagnosis of a dizzy child. Current data on the prevalence and characteristics of dizziness in the paediatric population is limited. In contrast to most previous studies, our study was a prospective study. All symptomatic children were diagnosed and followed up for 16 months. Besides, we encountered different diagnoses as compared to other studies. This was made possible by means of detailed history taking, examination, appropriate investigations and specialist opinions from other fields. In our study, the children were divided into three age groups, 0–6 years, 7–12 years and 13–18 years in order to differentiate the cause of dizziness in each of these age groups. Some of the previously published studies on pediatric vertigo have included patients with only true vertigo but our study evaluated all types of dizziness including imbalance. However this study is limited by the fact that management of dizziness in children and follow up of patients were not included in this study.

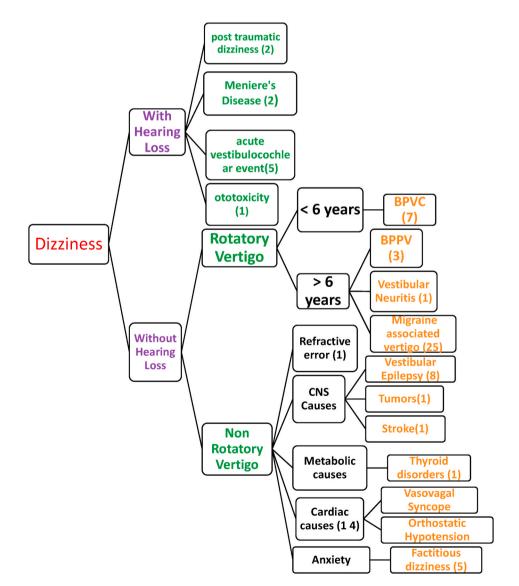


Fig. 3. Algorithm summarizing the distribution of diagnosis of dizziness in children based on symptoms in our study. *BPVC – Benign Paroxysmal Vertigo of Childhood, BPPV – Benign Paroxysmal Positional Vertigo,> - greater than < - less than.

Table 2

Comparison of our study with available studies in the literature.

	n	Study duration (year)	Mean age. (years)	Migraine Associated vertigo	BPVC	Vestibular Neuritis	BPPV	Psychogenic Vertigo	Factitious Dizziness	Middle Ear Effusion	Head Trauma	Meniere's disease	OI
Bower &Cotton [3]	34	R (2 .5)	10.6	12%	7	9%	0	0	x	15%	9%	6%	0
D'Agostino et al. [41]	282	P (4)	n/a	15%	21%	1%	0	0	x	х	30%	0	0
Weiselder and File [40]	31	R (6)	13	25%	19%	0	0	10%	x	0	0	6%	0
Ravid et al. [12]	62	R (2)	11.8	39%	16.5%	14%	0	13%	х	х	3%	0	9%
Choung et al. [42]	55	R (6)	11.8	31%	25%	2%	4%	0	х	х	7%	4%	0
Rine et al. [38]	119	R	10.9	14%	19%	12%	11%	5%	x	10%	5%	2%	3%
Erbek et al. [19]	50	R (3)	11.5	34%	12%	4%	12%	10%	х	х	0	2%	0
Balatsouras et al. [6]	54	R (3)	8.9	20%	17%	28%	7%	0	x	9%	5%	2%	0
Gruber et al. [11]	37	R (7)	14	32%	8%	22%	0	22%	x	х	3%	3%	0
Weiner – Vacher [18]	>2000	R (14)	x	25%	20%	5%	x	x	x	x	10%	x	x
Our Study	89	P (1.3)	11.4	28%	7.9%	1.1%	3.4%	0	5.6%	х	2.2%	2.2%	15.7%

 $R = Retrospective, P = Prospective, x = not assessed, \% = percentage, n = number, BPVC= Benign Paroxysmal Vertigo of Childhood, BPPV = Benign Paroxysmal Positional Vertigo, OI = Orthostatic Intolerance, <math>\geq$ greater than.

5. Conclusion

The prevalence of dizziness as a primary complaint in children presenting to the ENT department was 0.8%. The most common cause of vertigo in children was migraine associated dizziness followed by circulation related dizziness (orthostatic intolerance). In children up to 6 years of age, the most common cause for dizziness was found to be benign paroxysmal vertigo of childhood(BPVC). With a detailed history, neurotological examination, appropriate investigations and specialist referrals it is possible to ascertain the diagnosis in almost all cases of vertigo in childhood.

Declaration of competing interest

The authors declare no conflict of interest.

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