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PSEUDOTUMOR CEREBRI SYNDROME (PTCS): CLINICAL ANALYSIS ON A COHORT OF 37 PEDIATRIC SUBJECTS

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Abstract – *Objective:* *Pseudotumor Cerebri Syndrome (PTCS) is defined by the whole of signs and symptoms caused by elevated intracranial pressure of unclear etiology in the setting of normal brain parenchyma and cerebrospinal fluid. The diagnostic workup is important to differentiate this disorder from other conditions including brain tumors. The aim of this study is to emphasize the role of clinical signs as well as ophthalmologic evaluation for an accurate diagnosis, and to present a case-series of 37 children affected by this condition.*

Patients and Methods: *A retrospective study review has been performed using the medical records of the hospitalized children in the Policlinico-Vittorio Emanuele-G. Rodolico, Pediatric Units of Catania (Italy) from October 2005 to February 2020. The study was conducted ethically in accordance with World Medical Association Declaration of Helsinki and was approved by the Ethic Committee of the University of Catania, Italy (Catania 1 Clinical Registration n 138877/PO). We identified 37 children who were diagnosed with PTCS. In all the subjects, diagnosis Intracranial Idiopathic Hypertension has been verified in accordance to the Friedman 2013 criteria. Subjects with secondary intracranial hypertension have been excluded.*

Results: *A total of 37 subjects were included in this study, with a mean age, at the time of the admission, of 10 ± 3.5 years (range 4-18 years). Among these children, 56.7% were female (21 female/16 male) and almost all were overweight and/or obese (35/37, 94.5%). The most frequent symptoms were headache, vomiting and paralysis of the VI cranial nerve. In 16.2% of the cases, headache was not reported, 8.1% were asymptomatic and 5.4% had not manifested papilledema.*

Conclusions: *In this study group, obesity and overweight were the main risk factors of intracranial Idiopathic hypertension, regardless of gender and age of the children. A different gender distribution was observed in the two groups of children based on age and pubertal development: Female gender was a risk factor for children over 10 years old and/or in pubertal stage, while the male gender was predominant in younger and/or prepubertal children. Our data suggest that, even if a minority, there is a number of children that remains under-diagnosed with a greater potential risk of developing long-term complications.*

KEYWORDS: *PTCS, Papilledema, CSF, Headache, MRI.*

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INTRODUCTION

Pseudotumor Cerebri Syndrome (PTCS) is defined by the whole of signs and symptoms caused by elevated intracranial pressure (ICP) of unclear etiology in the setting of normal brain parenchyma and cerebrospinal fluid (CSF)[1]. The term used previously as "benign intracranial hypertension" is out-of-date because of the vision loss and consequent reduction in quality of life are potential complication of this condition[2]. PTCS has been subdivided in primary and secondary[3]. The pathogenesis of IIH remains unclear. Most attention has been focused on dysregulation of CSF dynamics, through hypersecretion of CSF at the choroid plexus or reduction of absorption at the arachnoid granulations and/or lymphatic system[4]. Elevated intracranial venous pressure is considered another possible etiological mechanism of PTCS, in contrast other authors hypothesize that elevated venous pressure could be considered as an effect, rather than a cause of elevated ICP[5].

The exact prevalence of PTCS in the pediatric population is not well established. A recent large study of childhood PTCS from the UK, based on the Friedman criteria[3], reported an annual incidence of 0.71 per 100.000[6]. This rate increases to 12–20 per 100.000 for obese women of reproductive age, suggesting that female gender and obesity are strongly associated with this disorder in adult population[4]. In the pediatric age, Intracranial Idiopathic Hypertension (IIH) is more common among adolescents (12–15 years) compared to young children (2–12 years) [6,7].

The relation between hormonal female gender, obesity and IIH remains a debated topic. An advanced hypothesis is that cytokines and adipokines, such as leptin, released by adipose tissue could act directly or indirectly with effects that modify CSF secretion and absorption[4].

In 1937, Dandy[8] first presented diagnostic criteria for intracranial hypertension without brain tumor. The most recent updated diagnostic criteria for adults and children IIH have been published in 2013 by Friedman et al [3].

To date, a subject with papilledema is considered to have "definite" PTCS if all the following criteria are fulfilled: normal neurologic examination, except for cranial nerve abnormalities; normal brain parenchyma without evidence of hydrocephalus, mass, structural or vascular lesion and abnormal meningeal enhancement on neuroimaging; normal CSF composition; elevated lumbar puncture opening pressure (≥ 250 mm CSF in adults and ≥ 280 mm CSF in children or ≥ 250 mm CSF if the child is not sedated and not obese) in a properly performed lumbar puncture (LP). The diagnosis of PTCS is considered "probable" if all the above criteria are met with bilateral papilledema but the measured CSF pressure is lower than specified for a "definite" diagnosis. In the absence of papilledema, a diagnosis of "definite" PTCS can be made if the above criteria are satisfied provided in addition the subject has unilateral or bilateral sixth nerve palsy. Ultimately, in the absence of both papilledema and sixth nerve palsy, a diagnosis of PTCS can be "suggested", but not made, if the above criteria are fulfilled and in addition at least 3 of the following neuroimaging criteria are satisfied: empty sella, flattening of the posterior aspect of the globe, distention of the perioptic subarachnoid space with or without a tortuous optic nerve, transverse venous sinus stenosis[3].

Herein, we report an observational retrospective cohort study on 37 PTCS subjects reviewing the literature results on epidemiology, clinical presentation and treatment in the pediatric population.

MATERIALS AND METHODS

A retrospective study review has been performed using the medical records of the hospitalized children in the Policlinico-Vittorio Emanuele-G. Rodolico, Pediatric Units of Catania, Italy from October 2005 to February 2020. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethic Committee of the University of Catania, Italy, Ethical Committee Catania 1 (Clinical Registration n 138877/PO).

We identified 37 children who were diagnosed with PTCS. In the subjects diagnosis of IIH has been verified in according to the Friedman 2013 criteria[3]. Subjects with secondary intracranial hypertension have been excluded (e.g. cerebral venous sinus thrombosis, current or previous central nervous system infection, hydrocephalus, cerebral mass) as well as those that were at first admitted on suspicion of papilledema but subsequently diagnosed as pseudopapilledema. Children underwent physical, neurological and ophthalmological examination, brain and orbits Magnetic Resonance Imaging (MRI) and Lumbar Puncture (LP) with measurement of CSF opening pressure (LPOP). Ocular ultrasound, study of visual fields, fluorangiography and Visual Evoked Potentials (VEPs) were performed when necessary. Data of subjects were collected for gender, age, Body Mass Index (BMI) percentile-for-age, secondary sexual characteristics development, clinical presentation and comorbidities. Diagnosis of over-

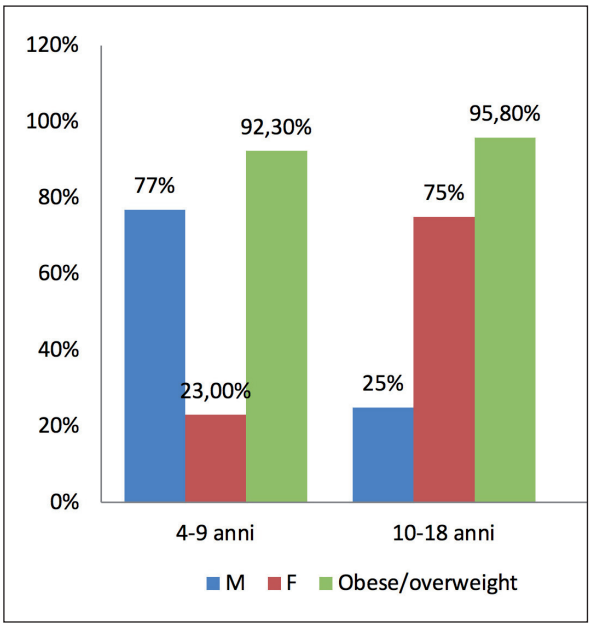

Fig. 1. Epidemiology and gender distribution in this study.

weight and obesity was based on the BMI of the children, and according to the International Child Growth Standards (the 2006 WHO growth chart for children aged 2-5 years[9] and the 2007 WHO growth chart for children aged 5-18 years)[10]. The cut-off points of the BMI-for-age reference for the diagnosis of overweight and obesity were set as the 85th and the 97th percentile, respectively. Our diagnostic clinical pathway is summarized in Supplementary Figure 1.

RESULTS

Epidemiology

A total of 37 children were enrolled in the study, with a mean age, at the time of the admission, of 10 ± 3.5 years (range 4-18 years). Among these children 56.7% were female (21 female/16 male) and almost all were overweight and/or obese (35/37, 94.5%). Sixty-four (24/37) of children were older than 10 years and among them 75% (18/24) were female and 95.8% (23/24) were overweight or obese. Between younger children (13/37, 35%) the majority of patients was male (10/13, 76.9%) and 92.3% (12/13) were overweight or obese. Overall, the median male age was lower than the median female age (8.3 and 12 years, respectively). For more information please refer to Figures 1-4 and Supplementary Table 1.

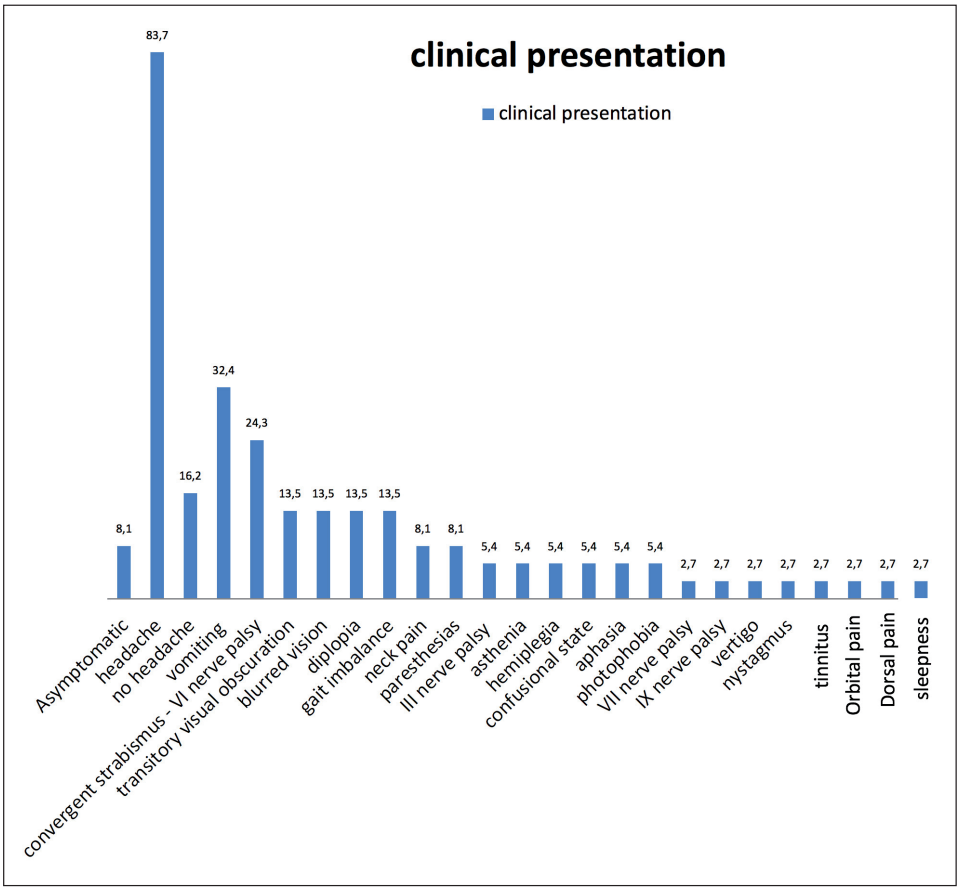

Fig. 2. Clinical presentation in this study.

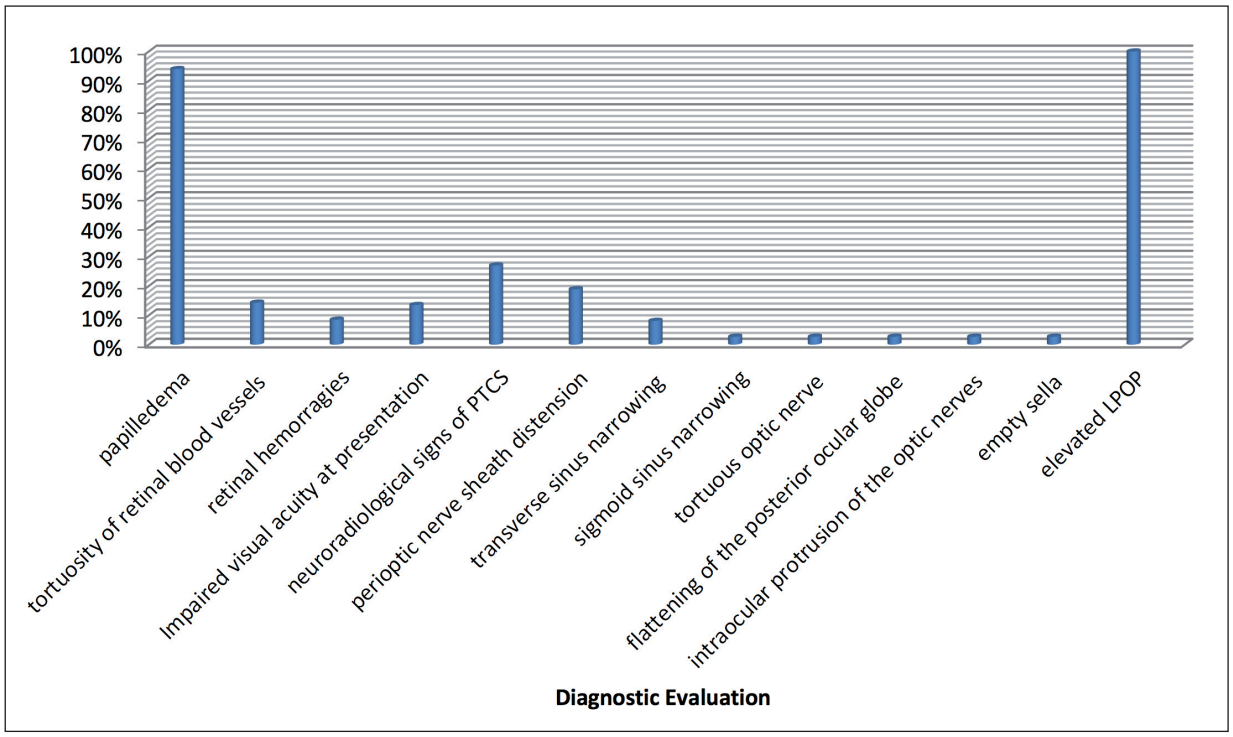

Fig. 3. Diagnostic Evaluation in this study. PTCS: Pseudotumor cerebri syndrome; LPOP: Lumbar Puncture Opening Pressure.

Clinical presentation

The most common symptom of the children was headache (31/37, 83.7%). Thirty-two.25% (10/31) of subjects with headache didn't experience any other disorders, while 67.74% of children (21/31) complained several neurologic symptoms in association with headache. Six subjects didn't have headache (6/37, 16.2%), 3 of them were asymptomatic (3/37, 8.1%) and the diagnostic process for IIH followed the occasional finding of papilledema at a routine ophthalmologic examination. The other 3 children without headache complained other disturbances such as cranial nerve palsy, asthenia, nystagmus, paresthesias, dizziness and gait imbalance; furthermore, 1 of them presented development delay. The second most frequent disorder was vomiting (12/37, 32.4%) and the third one was unilateral or bilateral convergent strabismus due to abducent (VI) nerve palsy, a sign which was reported in 9 children (24.3%). Transitory visual obscuration and blurred vision, diplopia and gait imbalance were described in 13.5% (5/37). Other less common disturbances were: neck pain and paresthesias (3/37, 8.1%), oculomotor nerve palsy (2/37, 5.4%), asthenia (2/37, 5.4%), hemiplegia (2/37, 5.4%), confusional state (2/37, 5.4%), aphasia (2/37, 5.4%), facial (VII) and glossopharyngeal (IX) nerve palsy (1/37, 2.7%), dizziness (1/37, 2.7%), nystagmus (1/37, 2.7%), photophobia (2/37, 5.4%), tinnitus (1/37, 2.7%), orbital and dorsal pain (1/37, 2.7%) and sleepiness (1/37, 2.7%).

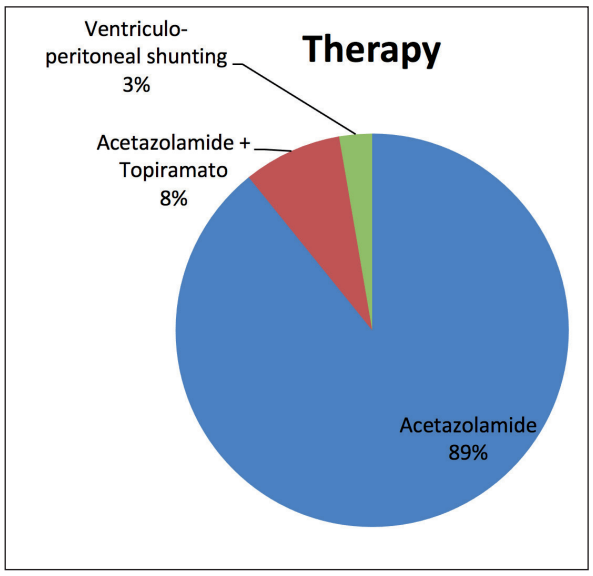

Fig. 4. Therapy in this study.

Diagnostic evaluation

Papilledema was documented in almost all children (35/37, 94.6%), in some cases it was associated with tortuosity of retinal blood vessels (5/35, 14.3%) or retinal hemorrhages (3/35,

8.5%). Two children didn't have papilledema (2/37, 5.4%), among them one had a previous history of IIH, the other one showed only retinal blood vessels tortuosity at the ophthalmoscopic examination.

Impaired visual acuity was reported in 5 children (13.5%) at the time of presentation.

All children performed brain and orbits MRI, 17 children (45.94%) underwent brain Magnetic Resonance Angiography (MRA) and 3 underwent also to spinal cord MRI for the presence of neck pain, dorsal pain or limb paresthesias. Neuroimaging resulted normal in 24 patients (24/37, 64.86%) while neuroradiological findings suggesting of PTCS were observed in 10 children (27%), such as perioptic nerve sheath distension reported in 7 cases (7/37, 18.9%), transverse sinus narrowing (3/37, 8.1%), sigmoid sinus narrowing (1/37, 2.7%), tortuous optic nerve (1/37, 2.7%), flattening of the posterior ocular globe (1/37, 2.7%), intraocular protrusion of the optic nerves (1/37, 2.7%) and empty sella (1/37, 2.7%). As accessory findings, 1 child had slight asymmetry of lateral ventricles (1/37, 2.7%), another had enlargement of spinal subarachnoid space at T5-L2 tract with spinal cord compression, 1 had sphenoid sinus polyp and 3 had an arachnoid cyst (3/37, 8.1%). One of them underwent CSF flow MRI which detected a pulsatile CSF flow within the cystic lesion and an increased CSF flow at the foramen magnum region.

All patients performed a LP. The average value of LPOP was 372.4 mm CSF (range 270-680 mm CSF).

Comorbidities

In the children, some comorbidities emerged both through personal history and through blood chemistry and instrumental tests performed. In addition to obesity (the most common comorbidity found), associated conditions included: hyperinsulinism and insulin resistance (7/37, 18.9%), hypertension (2/37, 5.4%), polycystic ovarian syndrome (2/37, 5.4%), epilepsy treated with valproic acid (2/37, 5.4%), developmental delay (2/37, 5.4%), subclinical hypercortisolism (2/37, 5.4%), celiac disease (1/37, 2.7%), bilateral gynecomastia in a male child (1/37, 2.7%), Legius syndrome (1/37, 2.7%), B19 Parvovirus infection (1/37, 2.7%), Mycoplasma Pneumoniae (1/37, 2.7%) and CMV infections (1/37, 2.7%) documented by serological assay of specific antibodies, polycystic kidney and urinary tract malformation with normal kidney function (1/37, 2.7%), sphenoid sinus polyp (1/37, 2.7%).

Management

All children received medical management with acetazolamide for a period of 3-6 months. Eighty-nine 1% (33/37) of the subjects showed a good response to acetazolamide alone. Three children (8.1%) were initially treated as monotherapy and subsequently in add-on with topiramate with good result. One child underwent ventriculo-peritoneal shunting because of worsening symptomatology and severe visual impairment. Nobody had fenestration of optic nerve sheath.

DISCUSSION

Idiopathic Intracranial Hypertension (IIH), or primary PTCS, is a serious and uncommon neurological disease in children. The term "Idiopathic Intracranial Hypertension" (IIH) is used just for subjects with the primary PTCS, while the secondary PTCS group includes those with recognized causes of intracranial hypertension, such as venous sinus thrombosis, medications and other medical conditions[3] (Table 1).

Most cases may be associated with puberty and hormonal changes. Some studies show that in pediatric population primary PTCS has no association with gender and it is less frequently related with obesity compared with adults[11-13]. However, there is a growing evidence that IIH is different in younger than in older children and that the pubertal development rather than age separates the clinical assessment of younger from the older group. Younger subjects with IIH usually do not demonstrate a propensity towards obesity or a particular gender distinction while in the older age group the majority of subjects is obese and/or female gender[14-16]. Thus, female gender and obesity appear to be the major risk factors in the older, but not younger pediatric subjects[7,16]. These data suggest that in adolescents risk factors for developing IIH might be similar to those in adults[5]. In this study IIH affected girls (21/37, 56.7%) and boys (16/37, 43.3%) almost equally and, in contrast to literature, almost all were overweight or obese regardless of gender and age (35/37, 94.5%). Similarly to Babikian et al [14] report, 64.86% (24/37) of children were older than 10 years. As expected, among older 10 years children, the majority were females (75%), and 95% were obese and/or overweight. On the other hand, an unexpected preponderance of boys (76%) was observed among children under 10 years old with 92.3% of obesity and/or overweight. Since the onset of puberty is an important milestone in IIH and the age of pubertal onset is variable, we also divided the

TABLE 1. Causes of Primary and Secondary Pseudotumor Cerebri.

PRIMARY PSEUDOTUMOR CEREBRI
Idiopathic intracranial hypertension
Includes patients with obesity, recent weight gain, polycystic ovarian syndrome and thin children
SECONDARY PSEUDOTUMOR CEREBRI
Cerebral venous abnormalities
Cerebral venous sinus thrombosis
Bilateral jugular vein thrombosis or surgical ligation
Middle ear or mastoid infection
Increased right heart pressure
Superior vena cava syndrome
Arteriovenous fistulas
Decreased CSF absorption from previous intracranial infection or subarachnoid hemorrhage
Hypercoagulable states
Medications and exposures
Tetracycline, minocycline, doxycycline, nalidixic acid, alfa drugs
Hypervitaminosis A, isotretinoin, all-trans retinoic acid for promyelocytic leukemia, excessive alcohol abuse
Human growth hormone, thyroxine (in children), leuprorelin acetate, levonorgestrel (Norplant system), anabolic steroids, withdrawal from chronic corticosteroids
Lithium
Chlordecone
Medical conditions
Addison disease
Hypoparathyroidism
Sleep apnea
Pickwickian syndrome
Anemia
Renal failure
Turner syndrome
Down syndrome

examined children into a prepubertal and a pubertal group using standard criteria based on secondary sexual characteristics[17,18]. What emerged was comparable with that previously observed: children with pubertal and prepubertal development were almost equally (56.75% and 43.25%, respectively) involved and among pubertal patients 76% were girls while among prepubertal children, the majority were boys (68.75%).

As reported in literature, headache is the most common presenting symptom of IIH in children. Data from a UK study show that headache may be absent in 13% of patients[6]. In this observational study, 16% of children didn't complain headache. Vomiting is another very common symptom of IIH, the second more frequent in this case-study (32.4%), followed by convergent strabismus due to VI cranial nerve palsy (24.3%). Blurred vision, transient visual obscuration and binocular diplopia were reported in 13.5% of this report. Some children complained photophobia (5.4%). In literature, among visual disorders, 'shimmer lights with colored centers' have been described[5]. Palsies of III (5.4%), VII (2.7%), and IX (2.7%) cranial nerves have been seen in this case-study although less commonly than VI nerve palsy that is reported affecting as many as 60% of patients in literature[19,20]. Pediatric subjects with IIH may also experience stiff neck[20], shoulder and arm pain; moreover younger children may present only irritability[21]. Three children (8.1%) in this case-study were asymptomatic, but it has been illustrated in literature that up to 29% of pediatric subjects may be asymptomatic[1].

The mechanism causing the cranial nerve palsy is unclear, it is likely related to the nerve or brainstem traction with increasing ICP[5]. Resolution of cranial nerve palsy with normalization of the ICP is necessary to attribute one of these findings to PTCS[19].

Papilledema is the hallmark of PTCS, and it is almost always present in the acute presentation of PTCS. It ranges from mild blurring of the disc margins to whole disc swelling with hemorrhages and exudates[5] and may be asymmetric, or, uncommonly, unilateral[22]. Absence of papilledema doesn't rule PTCS.

Papilledema was found in 94.6% of the present cohort. Five children had also tortuosity of retinal blood vessels (14.3%) and 3 children had retinal hemorrhages (8.5%). In two patients, papilledema was not found (5.4%); among them, one was a relapse of IIH, while the other one showed only retinal blood vessels tortuosity.

Subjects with previously diagnosed and treated PTCS may relapse years later. Papilledema may be recurrent but sometimes fibrosis of the nerve fiber layer or optic atrophy may preclude the development of disc edema. In these cases, recurrent symptoms and signs and OPLP measurements are helpful to confirm relapse[3]. It is important to distinguish papilledema from pseudopapilledema and this could be particularly difficult in children as optic disc drusen, if present, are often buried and because of the frequent child poor cooperation during the ophthalmologic examination. Kovarik et al[23] and Liu et al[24] showed that among children referred for suspected papilledema/PTCS, the majority actually had pseudopapilledema. Noninvasive test such as B-scan ultrasonography, autofluorescence fundus photography and Optical Coherence Tomography (OCT) may facilitate the distinction of pseudopapilledema from papilledema. B-scan ultrasonography seems to be the most sensitive method for the detection of optic disc drusen in children and adults[19].

Vision loss in pediatric IIH may occur. It is usually mild to moderate and reversible, but in rare cases it can be devastating and permanent leading to total blindness[5]. It is generally accepted that visual acuity remains normal in papilledema except when the condition is long-standing for the onset of optic neuropathy[25]. At presentation, visual acuity loss is reported in 10-16% of children, while visual field defects occurs in up to 85% of cases[26]. Gospe et al[27] in a study of 31 pediatric subjects showed that 19% children developed permanent visual acuity or visual field loss. In another series of pediatric cases, 33% had optic atrophy and 17% had permanent residual visual field deficits[12]. Monitoring of visual function remains one of the challenges in managing children with PTCS. Automated visual field test is the most used method among adults. This type of examination should be obtained in patients above 6-7 years old, however it is not ever feasible due to poor cooperation of many young children. Decreased visual acuity alone cannot distinguish reversible visual impairment due to retinal changes from permanent visual loss due to optic neuropathy. Optical Coherence Tomography (OCT) is a promising, noninvasive test that may facilitate the follow-up and management of children with PTCS[19,25,26]. Normal values for pediatric patients have been published, placing a median Retinal Nerve Fiber Layer (RNFL) thickness of 98.46 mm (SD 10.79)[28].

Diagnosis of IIH is one of exclusion. When evaluating subjects with suspected increased intracranial pressure, secondary causes must be excluded. Parents should be asked whether the child had any recent weight gain, taken medications associated with PTCS or had an underlying medical condition associated with PTCS. Development of secondary sexual characteristics should also be recorded associated with a careful neurologic and ophthalmologic examination. Neuroimaging should be obtained in all subjects and, according to the Friedman diagnostic criteria, must be normal, except for signs of increased ICP[3]. MRI, with and without gadolinium is the method of choice for the diagnosis of PTCS. If MRI is unavailable or contraindicated, contrast-enhanced Computed Tomography (CT) with or without venography may be used. For typical subjects (post-pupertal, female and obese) magnetic resonance venography (MRV) is not routinely necessary while it should be performed to detect cerebral venous sinus thrombosis (CVST) in atypical patients, such as non-obese, prepubertal children, males, children with progressive visual loss despite therapy and children at high risk for CVST[3]. Dedicated orbit imaging with thin cuts acquisition and fat suppressed images ultimately allows identification of subtle findings associated with increased ICP[26].

In this case-study neuroimaging was normal in 64% of cases. Suggesting signs of PTCS were found in 27% of children and the most common were perioptic nerve sheath distension (18.9%) and transverse sinus narrowing (8.1%). Furthermore, one child had asymmetry of lateral ventricles, another had enlargement of spinal subarachnoid space at T5-L2 tract with spinal cord compression and 3 subjects had an arachnoid cyst. One child with arachnoid cyst underwent CSF flow MRI which detected a pulsatile CSF flow within the cystic lesion and an increased CSF flow at the foramen magnum region.

Evaluation of CSF flow dynamics is not a routine investigation in subjects with IIH. In literature, other abnormalities have been reported on neuroimaging in a few cases of PTCS, including tonsillar ectopia[29], narrowing of the Meckel's cave and cavernous sinuses[30], meningoceles[31], and widening of the foramen ovale[32]. No one of these findings were described in this case-study. Moreover, ballooned optic nerve sheath is a phenomenon potentially measured by bedside high-resolution ultrasound[33]. After neuroimaging, lumbar puncture is critical to measure the CSF opening pressure and to exclude abnormal spinal fluid composition or CNS infection[3,26]. Temporary headache relief following a spinal tap is a common occurrence but this doesn't confirm the diagnosis of PTCS[26]. Subjects with "probable" PTC in which clinical presentation is highly suggestive of PTCS but LPOP is not diagnostic, probably as the consequence of diurnal fluctuations of CSF opening pressure, a therapeutic trial should be still considered in order to prevent permanent visual disturbances[21].

In this study several comorbidities have been reported, including, besides obesity, hyperinsulinism, hypertension, epilepsy on valproate treatment, subclinical hypercortisolism and polycystic ovarian syndrome (PCOS) that was diagnosed in two female adolescents.

PCOS is considered a risk factors for IIH by most authors. These association has been frequently reported in female subjects, although more commonly in adult age than in adolescents and only in a few pediatric cases[34,35].

All children in this study received acetazolamide with benefit except for 3 children that needed of topiramate as add-on to acetazolamide and one child that underwent ventriculoperitoneal shunting. Medical treatment was well tolerated by all and almost all children showed asymptomatic metabolic acidosis sometimes associated with hypokalemia as side effects.

However, to date, because of the lack of randomized clinical trials in pediatric population, there are no evidence-based recommendations in the treatment of PTCS in children and most patients are managed based on medications and approaches used in adults.

The primary goals of PTCS treatment are preventing of vision loss and relieve symptoms of elevated ICP. The two cornerstones of therapy are weight loss and medical and/or surgical approach aimed to reduce ICP. Asymptomatic subjects with normal visual function and minimal papilledema could be frequently monitored without management[36]. However, in pediatrics the natural history of untreated PTCS is unknown and so also asymptomatic children are often drug-treated. Most cases respond to medical therapy while surgical intervention is typically reserved if drugs fail or if the visual function is deteriorating. Acetazolamide is the most used first-line medical management in children with IIH. It is a carbonic anhydrase inhibitor, typically used for 3-9 months to reduce the CSF secretion by the choroid plexus[5]. The recommended initial dose for acetazolamide is 15-25 mg/kg/day divided into 2-3 doses daily for children and 1 g/day for adolescents. This dosage may be gradually increased up to 100 mg/kg/day (maximum 2 g/day in children and 4 g/day in adolescents) if needed. Common side effects of acetazolamide include paresthesia, fatigue, metallic taste, gastrointestinal upset, renal calculi, aplastic anemia (rarely), electrolyte imbalance and metabolic acidosis that is typically asymptomatic and well-tolerated enough to not require treatment generally[37], except for high doses of drug that tend not to be tolerated.-

According to some studies, success rate of acetazolamide as monotherapy in pediatric IIH ranged between 47% and 67%. Second-line medical therapy include furosemide, a loop diuretic that has a minor action as a carbonic anhydrase inhibitor, in doses of 1-2 mg/kg/day to 2 mg/kg 3 times daily in children and 20 mg twice daily to 40 mg 3 times daily in adult. It may be used alone, if acetazolamide fails or is not well tolerated, or as an adjunct therapy to acetazolamide to produce additive result [38,39]. Topiramate (1.5–3.0 mg/kg/day in two divided doses, and no more than 200 mg/day), an anti-epileptic drug with weak carbonic anhydrase inhibitor effects, may be also used as a second-line agent in these subjects, particularly when acetazolamide or furosemide are not tolerated. Indeed, topiramate has the added common side effect of appetite suppression and weight loss in many patients. It can be used alone or as an adjunct to acetazolamide to increase the effect of treatment in IIH patients. Zonisamide has been proposed as alternative to topiramate, if topiramate is not tolerated[5,40]. In case of acute and severe visual impairment at the time of presentation, the combination of oral or IV acetazolamide and IV methylprednisolone (15 mg/kg) can be used if surgery is not immediately available. Prednisolone (1–2 mg/kg/day) or dexamethasone (2 mg four times daily or 0.1–0.75 mg/kg/day in 4 divided doses) may be also used. However, the corticosteroids should be avoided or limited to short-time because of the risk of Papillar Thyroid Cancer (PTC) rebound with their rapid withdrawal and the significant side effects related to their prolonged use. Furthermore, there isn't actual evidence of their efficacy in IIH. Thus, after a maximum of two-week course of steroid treatment in IIH a gradual weaning of the dose, over the next two weeks, is recommended [38].

Medical management should be continued until visual function normalizes and papilledema disappears[39,40]. Thus, drugs should be slowly tapered but serial ophthalmological exams are recommended to detect recurrence.

Modern surgical management of IIH includes ventriculoperitoneal and lumboperitoneal shunting. In some centers, optic nerve sheath fenestration (ONSF) is also used. Repeated LPs are not recommended by most experts, due to the painfulness of procedure, necessary of sedation and just partial relief of symptoms.

Instead, endocrinology consult, nutritionist and weight loss program should be instituted for obese children[26].

It's important to remind that up to 20% of affected subjects can relapse and it may occur also when they are still on therapy [21]. Permanent visual loss is the only serious complication of PTCS, and it can develop early or late in the course of the illness. Risk factors associated with irreversible vision impair-

ment are not clear and knowledge are based just on small and a few studies, often over adult age. A correlation was found between worse visual outcome and recent weight gain[41], retinal hemorrhages[42], systemic hypertension[43], high-grade papilledema, early optic nerve atrophy, decreased visual acuity and visual field loss at the time of presentation[26,36]. Instead, other conditions don't seem to influence the visual prognosis, such as age at diagnosis[44], presence or absence of intracranial hypertension sings on neuroimaging[45], value of the LPOP, duration and type of symptoms (transient visual obscurations, double vision, pulsatile intracranial noises, severity of headache)[36]. Although some reports provide conflicting results[46] black subjects, male gender with anemia (itself a cause of secondary PTCS) and fulminant IIH are considered high risk categories for irreversible visual loss[44].

CONCLUSIONS

In this case-report, obesity and overweight were the main risk factors of IIH, regardless of gender and age of the subjects. A different gender distribution was observed in the two groups of children based on age and pubertal development. Female gender was a risk factor for children over 10 years old and/or in pubertal stage, while the male gender was predominant in younger and/or prepubertal children. The most frequent symptoms were headache, vomiting and paralysis of the VI cranial nerve. Sixteen (2%) of children had no headache, 8.1% were asymptomatic and 5.4% had no papilledema. These data suggest that, even if a minority, there is a number of children that remains underdiagnosed with a greater potential risk of developing long-term complications. Five.4% of children had polycystic ovarian syndrome. It should be ever considered in girls with IIH and menstrual irregularities. Although the cornerstone of PTCS diagnostic tests are fundus oculi exam, neuroimaging and measurement of LPOP, ocular ultrasound could facilitate the diagnosis of intracranial hypertension in emergency setting, when the examination of the fundus oculi cannot be performed. Moreover, ocular ultrasound may be useful to distinguish pseudopapilledema from papilledema. The majority of brain MRI gave normal result and the most common reversible neuroimaging findings were perioptic nerve sheath distension and transverse sinus narrowing showing the importance of Gadolinium contrast medium using in the PTCS suspicion. Acetazolamide was the first line drug used with a good clinical response reported in 89.1% in this group of children. Topiramate was the second drug more used. Almost half of the children with impaired visual acuity at presentation had retinal hemorrhages that is considered a prognostic factor of visual function, by most. However, few data are available on the long-term vision outcome of this group of children as limitation of the present study and, of course, more data are needed to understand the factors that influence the unpredictable clinical evolution of visual acuity in this disorder.

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There are no conflicts of interest.

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