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Case Study

An Interesting Case of COPD Exacerbation Presenting with Mixed Features of Intracranial Hypertension and Hypercapnic Encephalopathy

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Abstract

Background: Idiopathic intracranial hypertension (IIH or pseudotumor cerebri) has two major morbidities: papilledema with visual loss and disabling headache. Intracranial Venous Hypertension (IVH) is a fundamental mechanism of IIH. Although traditionally considered limiting to the central nervous system, evidence suggests IIH as a systemic disease associated with cardiorespiratory disorders, which has been far less comprehended.

Case Report: A 60-year-old female with Chronic Obstructive Pulmonary Disease (COPD) was admitted for dyspnea and developed a coma with a pH of 7.01 and pCO2 of 158 mmHg. She was intubated and had persistent nuchal rigidity, a brief myoclonus episode with a negative electroencephalogram, and negative CT head studies. A Lumbar Puncture (LP) revealed elevated opening pressure (35 cmH2O) with normal Cerebral Spinal Fluid (CSF) studies. Her nuchal rigidity improved after the removal of 40 mL CSF. The ophthalmology examination the next day after her the large volume LP didn't show visual loss or papilledema. The patient improved clinically and was extubated two days later. Her echocardiogram showed a dilated right ventricle with pulmonary hypertension. The patient was discharged home.

Discussion: IIH is different from hypercapnic encephalopathy and characterized by increased intracranial pressure with papilledema, vision loss, and debilitating headache. Hypercapnia-induced increased intracranial venous flow and pulmonary hypertension-caused elevated central venous pressure with consequent outflow resistance lead to IVH. In hypercapnic encephalopathy, the presentation is mostly cognitive changes. In this case, nuchal rigidity with a negative CT head scan triggered the investigation of IIH.

Conclusion: A deep understanding of the relationship between COPD and IIH is vital. There is insufficient evidence to recommend routine eye examinations in COPD patients for papilledema and to conduct a pulmonary function test for a newly diagnosed IIH patient. However, we highly suggest a timely ophthalmology exam prior to performing an LP in COPD patients with suspecting IIH to avoid unnecessary procedures and meanwhile improve clinical outcomes.

More Information

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Keywords: Hypercapnia; Pulmonary hypertension; Intracranial venous hypertension; Idiopathic intracranial hypertension; Papilledema; Intractable headache

Abbreviations: IIH: Intracranial Hypertension; IVH: Intracranial Venous Hypertension; LP: Lumbar Puncture; Ophthalmology Exam; COPD: Chronic Obstructive Pulmonary Disease; Papilledema

Introduction

Idiopathic Intracranial Hypertension (IIH), previously known as pseudotumor cerebri, is characterized by increased intracranial pressure with papilledema leading to a risk of visual loss and chronic disabling headache [1]. The diagnostic criteria for IIH include (1) a normal neurological exam except for sixth cranial nerve abnormalities; (2) neuroimaging excluding structural lesion, meningeal enhancement, and hydrocephalus; (3) normal Cerebrospinal Fluid (CSF) constituents; and (4) an opening pressure greater than 25 centimeters of water (cmH2O) measured through Lumbar Puncture (LP) [2,3]. The incidence of IIH has a high degree of heterogeneity across different studies and countries. A study showed that the incidence and prevalence of women in 2017 in the UK were 9.3/100,000 and 79/100,000 per year, respectively, with women of productive age and obesity having the highest incidence (16.5/100,000 yearly) [4,5]. The incidence of IIH has been increasing which parallels

the increased prevalence of obesity worldwide. Alongside elevated incidence, IIH-induced hospital admissions and financial burden to our society have been rising.

Traditionally, IIH was considered a disorder limited to the central nervous system and neuro-ophthalmic axis. However, recent studies suggested that certain systemic disorders are associated with Intracranial Venous Hypertension (IVH) leading to IIH [6]. IVH is a primary mechanism and the "final common pathway" for IIH. Based on the pathological drivers, IVH is stratified into 4 groups: (1) Central Venous Pressure (CVP) -mediated elevations in cerebral venous pressures; (2) cerebral venous stenosis- mediated; (3) a combination of both and (4) post-thrombosis syndrome [7]. CVP-mediated IVH is related to cardiorespiratory disease or obesity and accounts for approximately 25% of the total IIH cases [8].

Although the concept of obesity-related elevation in intraabdominal pressure and rising CVP leading to IIH has been widely accepted, however, there is much less awareness of cardiorespiratory disease-associated IVH. Retrospective cohort studies reported Obstructive Sleep Apnea (OSA) as the risk factor for neuro-ophthalmic disorders occurred in 48% to 60% of IIH patients, proposing a strong association between the two conditions [9,10]. Another case series study also reported that 9 out of 16 patients with IIH had asthma or reactive airway diseases (56%) [11]. Currently, no report can be found about acute exacerbation of chronic obstructive pulmonary disease (ECOPD) causing IIH. Here we report a case who presented with mixed features of IIH and hypercapnic encephalopathy (HE) in the setting of ECOPD. Information from this study may provide insight into the link between hypercapnia and Pulmonary Hypertension (PH)-induced CVP causing IVH and IIH, which aids in diagnosing and managing IIH in cardiorespiratory disorders, a typical but far under-recognized entity.

Case

A 60-year-old female presented with exertional dyspnea for one week that worsened on the day of admission. She had a past medical history of emphysema and Rheumatoid Arthritis (RA). She was hospitalized twice over the past 6 months due to ECOPD and discharged with a Trelegy Ellipta (fluticasone-umeclidin-vilanter) inhaler without home oxygen. Her end-stage RA caused symmetrically deformed joints in both hands. She was noticed to have excessive daytime sleepiness for a few weeks by her son. A review of systems showed no fever, headaches, chills, coughs, sputum production, or chest pain. She had no history of pulmonary embolism, deep vein thrombosis, cerebrovascular accident, or heart attack. She reported a history of bilateral otitis media without perforation about a month earlier and received treatment with doxycycline.

On arrival, vital signs were temperature 36.5 °C, heart rate 66, respiratory rate 18, blood pressure 109/59 mmHg, and oxygen saturation of 94% on 3 liters of oxygen. Physical exam showed thin body habitus, mildly increased breathing efforts, positive jugular vein distention (JVD), expiratory wheezing sounds in the posterior lung fields, regular heartbeats without murmurs, and bilateral pitting edema at her ankles. Laboratory work showed elevated bicarbonate (32.3 mEq/L) but otherwise unremarkable (Table 1). She was diagnosed with ECOPD and treated with methylprednisolone, budesonide, and ipratropium bromide/albuterol nebulizers. A Computed Tomography (CT) scan with contrast showed emphysema without pulmonary embolism (Figure 1). An echocardiogram showed a Right Ventricular Systolic Pressure (RVSP) of 45 mmHg with moderate tricuspid valve regurgitation (Figure 2).

On day 2, she became drowsy with intermittent confusion and disorientation but could be easily reoriented. Her vital signs were stable and laboratory workup did not show major changes other than an increase in bicarbonate to 34.8 (Table 1). She was considered to have hospital-induced delirium and no medication changes were made. On that night, a rapid response was called as she had become comatose with

Table 1: Laboratory data.

Laboratory data	Day 1	Day 2	Normal range
White-cell count (per µL)	9.7	6.3	3.5 -10.5
Hemoglobin (g/dL)	15.9	13.9	12 -15.5
Hematocrit (%)	49.6	41.8	35 - 45
Platelet count (per µL)	255	203	150 - 450
Absolute Neutrophils (10^3/µL)	9.0	8.8	1.7 - 7.0
Absolute Eosinophils (10^3/µL)	0.1	0.1	0
Glucose (mg/dL)	126	89	70 -140
Sodium (mmol/liter)	143	144	135 -145
Potassium (mmol/liter)	5.4	3.4	3.5 - 5.3
Chloride (mmol/liter)	108	99	98 - 110
Carbon dioxide (mmol/liter)	**32.3**	**34.8**	**20 - 28**
Angion gap	4.7	4.5	6 -10
Urea nitrogen (mg/dL)	23.0	14	6 - 24
Creatinine (mg/dL)	0.61	0.56	0.5 - 1.0
Aspartate aminotransferase (units/L)	19	18	10 - 36
Alanine transaminase (units/L)	25	20	6 - 29
Alkaline Phosphatase (IU/L)	75	56	33 - 130
Total bilirubin (mg/dL)	0.7	0.5	0.2 - 1.2

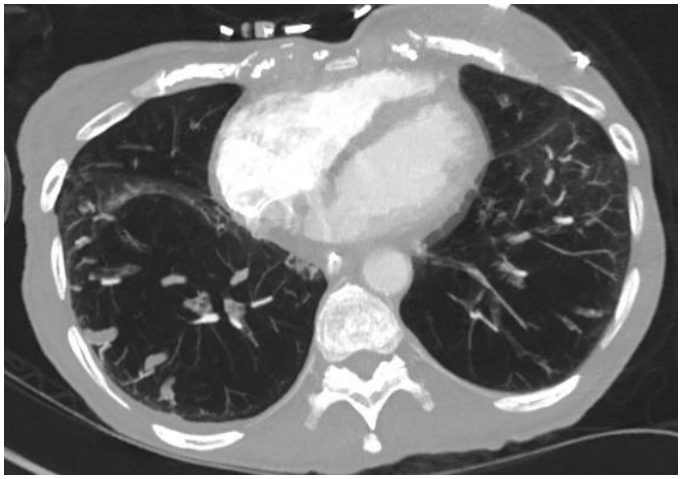

Figure 1: Computed Tomography (CT) scan of the lungs. A CT scan showed diffuse emphysema in the lower lobes of both lungs.

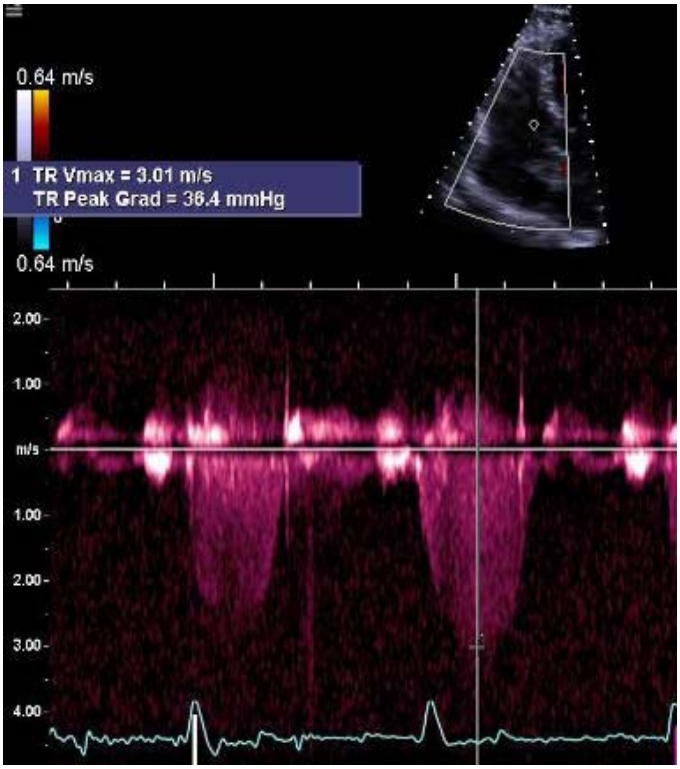

Figure 2: An echocardiogram showed Right ventricular systolic pressure (RVSP) of 45 - 50 mmHg and moderate tricuspid regurgitation with tricuspid valve regurgitation velocity of 3.01 m/s.

Table 2: Cerebral spinal fluid analysis.

CSF	Test	Normal range
Color	Transparent	Transparent
Opening pressure (cmH_2o)	35	< 20
White blood cell count (per mm^3)	2	< 5
Cell differential Mononuclear cells (%)	80%	-
Glucose (mg/dL)	70	40-80
Protein (mg/dL)	24.6	15-60
Bacterial culture	Negative	Negative
West Nile IgM, IgG	Negative	Negative
VDRL	Negative	Negative
Lyme IgM, IgG	Negative	Negative

*The opening pressure was down to 11 cmH2o after tapping 40 mL of CSF.

Table 3: Risk factors for developing idiopathic intracranial hypertension.

Drugs	Systematic disorders
Antibiotics: Tetracycline and derivatives	Respiratory: OSA, COPD
Vitamin A derivatives: isotretinoin, all-trans-retinoic acid	Cardiovascular: Superior vena cava syndrome; pulmonary hypertension
Corticosteroids	Endocrinology: Obesity, POCS, Cushing's disease
Others: Lithium, cimetidine	Hematology: Cerebral venous sinus thrombosis;

Note: OSA: Obstructive Sleep Apnea; COPD: Chronic Obstructive Pulmonary Disease; POCS: Polycystic Ovarian Syndrome

a Glasgow Coma Scale of 8 points and weak cough and gag reflexes. Her vital signs were stable with glucose of 120 mg/dL. An Arterial Blood Gas (ABG) revealed a pH of 7.01, pCO_2 158 mmHg, O_2 87 mmHg, and bicarbonate over 40 mEq/L. She was intubated for respiratory failure and airway protection and received fentanyl for sedation and pain management.

Several hours after her intubation, she had a 20-second episode of right lower leg jerking movement. A neurologic exam revealed nuchal rigidity with no other focal neurological deficit. A ceribell electroencephalogram (EEG) for 24 hours didn't show seizure activities. A CT head scan showed no acute intracranial changes. A spinal tap was performed on day 3 in consideration of meningoencephalitis or subarachnoid hemorrhage. The opening pressure was 35 cmH2O. After removing 40 mL of CSF, the closing pressure reading was 11 cmH2O. The CSF study showed clear fluid with normal cytology, chemistry, and microbiology tests (Table 2).

On day 4 of her admission, the ventilator settings were minimal. An ABG study showed a pH of 7.34, pCO2 59 mmHg, O2 71 mmHg, and bicarbonate 30mEq/L. She was successfully extubated and put on continuous positive airway pressure for 12 hours. Ophthalmology was consulted for papilledema evaluation on day 4. The patient denied any changes in vision or diplopia. Her exam revealed normal visual acuity; no afferent pupillary defect in both eyes; and normal intraocular pressure (IOP: 15 mm Hg OD/right eye and 18 mm Hg OS/left eye). Examination of the optic discs didn't show marked optic nerve swelling or papilledema. The patient was discharged home on day 6 with a diagnosis of ECOPD, respiratory failure, cor pulmonale, hypercapnia, Hypercapnic Encephalopathy (HE), and IIH. The key clinical events and findings are listed in Figure 3.

Discussion

This case had mixed features of IIH and HE as the complications of ECOPD. IIH is characterized by increased intracranial pressure including morbidities of papilledema with increased risk of vision loss and chronic debilitating headache. In contrast, the symptoms of HE are majorly psychomotor agitation, cognitive defects, confusion with asterixis, delirium, and coma [12]. The principal pathological mechanism for IIH is deregulated venous blood flow with resultant IVH. In HE, the predominant mechanism is different, with the presence of brain edema due to cerebral hypoxia and acidosis with deranged neurotransmitters [13,14]. This patient was comatose and had transient myoclonus due to significant hypercapnia (CO2 of 135 mmHg) secondary to ECOPD, indicating the development of HE [15]. After mechanical ventilation support and other treatments, her symptoms of HE improved within two days. However, the patient presented with persistent neck stiffness which was not a usual finding in HE. She was afebrile and had normal white blood cell counts; negative Kernig's and Brudzinski's signs and normal brain CT scan. Nevertheless, her recent history of bilateral otitis media and potential impaired immune function secondary to RA warranted ruling out meningitis or infectious encephalopathy. An LP was therefore performed that revealed an opening pressure of 35 cmH2O with normal CSF analysis. For this, she was diagnosed with IIH in the setting of ECOPD.

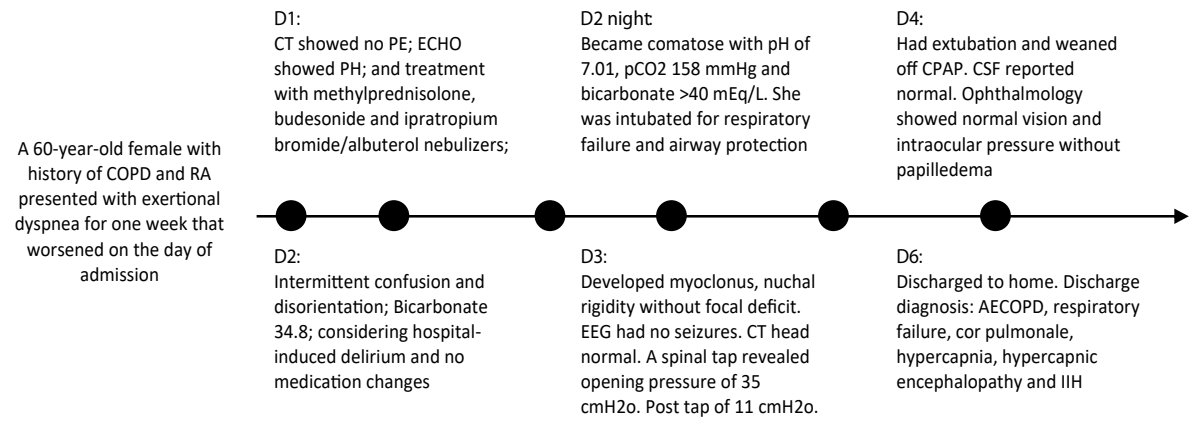

Figure 3: Key Clinical Events and Findings.

In literature, the strong link between OSA, asthma, respiratory reactive disease, and IIH has been suggested [16]. For example, a retrospective cohort study investigated 110 patients with IIH and revealed 48.6% of patients had OSA based on overnight pulse oximetry screening tool [10]. Another two case series studies revealed the occurrence of 60% and 33.3% of OSA in IIH according to the patient's self-reported OSA history [17,18]. Currently, no studies can be found that ECOPD causes IIH. Our article is therefore of great significance to firstly reveal the possible link between ECOPD and IIH.

How does IIH occur in ECOPD? Pathologically, IVH is the fundamental and "final common pathway" for IIH. Based on Monro-Kellie doctrine, an alteration in CSF volume, blood, and brain leads to reciprocal changes in one or the other two to maintain the equilibrium of intracranial pressure (ICP) [19]. Furthermore, the blood volume dynamics weigh much higher than the other two [20]. With ECOPD, hypercapnia($PaCO_2 \geq 45$ mmHg) results in cerebral vasodilation and increased cerebral blood volume (CBV) which eventually causes rising venous flow volume [21,22]. A study showed that $PaCO_2 > 80$ mm Hg increases CBV up to 6 times its baseline [22]. Obstructive sleep apnea (OSA) is also associated with increased ICP secondary to hypercapnia and acidosis due to cerebral vasodilation and increased vascular permeability [23]. On the other hand, hyperventilation therapy lowers CO2 levels with consequently dropped CBV and ICP, and therefore benefits post-traumatic intracranial hypertension [24,25]. Our patient had a CO2 level of 158 mmHg, which constituted one primary pathogenesis in IVH due to venous hyperemia.

Additionally, the venous outflow restriction due to PH-induced CVP elevation could be another critical factor in developing IVH. This patient had JVD, lower leg pitting edema, and elevated RVSP in the ECHO study, which suggested a CVP elevation. It's suggested that CVP and ICP pressures are coupled, which means the alterations in one usually parallel those in the others [26,27]. For example, a study revealed a strong positive linear relationship between CVP and ICP, and further, breathing through inspiratory resistance decreased both CVP and ICP [28]. Accordingly, in our case, the elevated CVP could be retrogradely transmitted to ICP once it prevails over the venous compliance (change in volume relating to the change in pressure, $\Delta V/\Delta P$) [29,30], which could also be described as a Starling resistor of the bridging veins within the skull [31]. Again, although a balanced CSF production and reabsorption is an important determinant of ICP, whether and how ECOPD stimulates the subarachnoid space remodeling involved in CSF deregulation remains unknown.

How is IIH diagnosed? Headache and visual complaints are common symptoms of IIH. Nevertheless, the key finding in our patient was nuchal rigidity. Nuchal rigidity occurs when the rising ICP is transmitted down to the spinal subarachnoid space. There are case reports of nuchal rigidity as a chief complaint in patients with IIH [32-34]. It also provokes the differentials for meningeal inflammation, such as acute bacterial meningitis, subarachnoid hemorrhage, posterior fossa tumor, and multiple sclerosis [35,36]. Brain CT can exclude space-occupying lesions, such as hydrocephalus, subarachnoid hemorrhage, mass, and cerebral venous thrombosis. Magnetic Resonance Imaging (MRI) is not necessary to diagnose IIH, but this may help with diagnosing papilledema with findings of optic disc swelling, optic nerve sheath distention, protrusion or vertical tortuosity, and posterior globe flattening [37]. MRI also helps in the exclusion of transverse sinus stenosis [38]. Spinal tapping is both diagnostic and therapeutic and is particularly helpful through a high-volume tap with the removal of CSF (usually 40 mL - 50 mL). Our patient had a normal CT head scan. 40 mL of CSF removal had an immediate effect on ICP that changed from 35 to 11 cmH2O. Her nuchal rigidity also improved on the next day.

Papilledema is an essential neuro-ophthalmologic finding and emergent morbidity of IIH. Untreated papilledema progressing to irreversible vision loss with optic atrophy occurs in 31% of patients with IIH [39], more likely in a fulminant onset situation [40]. Therefore, a timely ophthalmology exam

is crucial to assess papilledema and identify immediate risk of visual loss. It includes visual acuity, pupil examination, intraocular pressure, and visual field, a dilated fundal examination to assess papilledema severity and disc swelling, and the eye fundus including optic nerve description like hemorrhages or hyperemia. Our patient received an ophthalmology exam the next day after her LP, with normal Ocular Pressure (OP) and normal fundus. The absence of papilledema was most likely due to the large volume tap with transient resolution of IIH. Studies have shown that an OP > 25 cmH2O in the setting of IIH dramatically increases the chance of coexisting intracranial venous sinus stenosis, which may be discovered under venography [41,42]. Accordingly, it's less likely that our patient had concomitant venous sinus stenosis making further neurosurgical evaluation unnecessary.

Another significant morbidity is intractable headache, which can be debilitating if not treated appropriately [43]. The headache phenotype is highly variable mimicking other primary headache disorders, such as migraine. It manifests as a severe, throbbing headache behind both eyes and may also include pulsatile tinnitus, visual blurring, and cognitive disturbance [44]. Actually, patients with IIH may have a 6-fold increased risk of developing migraines [45].

Finally, there are other risk factors for developing IIH (Table 3). As for our patient, she needs polysomnography to evaluate sleep apnea based on her daytime sleepiness and hypercapnia. Her recent use of doxycycline might be another risk factor as tetracycline derivatives, such as doxycycline and minocycline, may cause or worsen IIH [46,47]. Studies have shown that IIH occurs usually after several weeks of continuously using tetracycline antibiotics [47]. Additionally, with an elimination half-life of less than 24 hours, the tetracycline-induced IIH often resolved in a few days to 3 weeks [48]. Our patient took doxycycline 5 weeks prior to her admission and only for 5 days, which made it unlikely to cause her IIH. There are other situations, such as weight gain, obesity, Cushing's disease, chronically using steroids and hypervitaminosis, but none of these fit our patient's situation.

Conclusion

In summary, when COPD patients present with neurological symptoms, one needs to differentiate HE from IIH. Compared to HE, IIH is a far under-recognized complication of ECOPD induced by hypercapnia and elevated CVP. A deep understanding of the relationship between ECOPD and IIH is vital. There is insufficient evidence to recommend routine eye examinations in COPD patients for papilledema and to conduct a pulmonary function test for a newly diagnosed IIH patient. However, we highly suggest a timely ophthalmology exam prior to performing an LP in COPD patients with suspected IIH to avoid unnecessary procedures and meanwhile improve clinical outcomes.

Author's contributions

CW and GM were involved in the conception and design. CW and PA collected pertinent literature and drafted the manuscript. AG, SK, and FS were involved in the literature analysis, manuscript discussion, and revision. RM and PA provided critical revision of the manuscript. All authors read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

This study involves human participants. We declare having received the patient's consent for the case and its publication.

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