Case Report

Multiple Chemical Sensitivity as A Variant of Idiopathic Intracranial Hypertension: A Case Report

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Abstract

Introduction: There is currently no recognized association between intracranial hypertension and multiple chemical sensitivity, despite nearly identical symptomatology and similar findings.

Case Report: This case report details the complex case of a woman who has multiple chemical sensitivity and idiopathic intracranial hypertension, as well as obstructive sleep apnea. Upon exposure to inhaled common air deodorizer products, her intracranial pressure increased significantly by 7%, during a lumbar puncture.

Conclusions: This paper discusses the similarity between the neurological symptoms and the illness model of multiple chemical sensitivity as it compares to intracranial hypertension, specifically the model of this condition as triggered by medications such as retinoids or tetracyclines. This suggests that multiple chemical sensitivity is actually a variant of idiopathic intracranial hypertension, and argues for further investigation of intracranial pressure in patients with chemical sensitivity. The hypothesis is thus proposed that the chemical exposure mediates the production of increased intracranial pressure by way of an effect on brain edema as mediated by a stimulation of glutamate neuro-excitotoxicity, possibly via neural sensitization. Fragranced consumer products have been demonstrated to contain multiple volatile organic compounds that are registered as hazardous. These findings demonstrate that multiple chemical sensitivity is undoubtedly a neurobiological illness. New discoveries in this arena may lead to further understanding of the etiology of not only chemical sensitivities and idiopathic intracranial hypertension, but also of autism.

Keywords: Idiopathic Intracranial Hypertension; Multiple Chemical Sensitivity; Environmental Intolerance; Maxillomandibular Advancement; Obstructive Sleep Apnea; Fragrance; Autism; Sensory Disorders
**Introduction**

This paper will discuss a case report of a complex patient who has both Multiple Chemical Sensitivity (MCS) and idiopathic intracranial hypertension (IIH). This case points out the similarities between these conditions and provides a link between them which suggests that MCS may be a variant of IIH. See Table 1 for a list of abbreviations used in this paper.

**Idiopathic Intracranial Hypertension**

Idiopathic intracranial hypertension has also been called pseudotumor cerebri and benign intracranial hypertension. [1] IIH is defined by the modified Dandy Criteria: 1) signs and symptoms of increased intracranial pressure; 2) no localizing signs except abducens nerve palsy; 3) CSF (cerebrospinal fluid) opening pressure ≥25cm of water with normal CSF composition; and 4) normal neuroimaging (ruling out venous sinus thrombosis). [2]

The ICHD-2 (International Classification of Headache Disorders) criteria for IIH are:

1. Progressive headache with at least one of the following characteristics and fulfilling criteria C and D:
   a. Daily occurrence
   b. Diffuse and/or constant (non-pulsating) pain
   c. Aggravated by coughing or straining

2. Intracranial hypertension fulfilling the following criteria:
   a. Alert patient with neurological examination that either is normal or demonstrates any of the following abnormalities:
      i. Papilledema
      ii. Enlarged blind spot
      iii. Visual field defect (progressive if untreated)
      iv. Sixth nerve palsy
   b. Increased CSF pressure (>200mmH2O in the non-obese, >250mmH2O in the obese) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring
   c. Normal CSF chemistry (low CSF protein is acceptable)

<table>
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<th>Abbreviations</th>
<th>Description</th>
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<tr>
<td>AHI</td>
<td>Apnea-Hypopnea Index</td>
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<tr>
<td>CC-MMA</td>
<td>Counterclockwise Maxillo-mandibular Advancement</td>
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<td>CFS</td>
<td>Chronic Fatigue Syndrome</td>
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<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
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<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>MRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<td>GSTM1</td>
<td>Glutathione S Transferase M1</td>
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<tr>
<td>GSTT1</td>
<td>Glutathione S Transferase T1</td>
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<td>ICP</td>
<td>Intracranial Pressure</td>
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<td>IIH</td>
<td>Idiopathic Intracranial Hypertension</td>
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<td>AHI</td>
<td>Apnea-Hypopnea Index</td>
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<td>LP</td>
<td>Lumbar Puncture</td>
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<td>MCS</td>
<td>Multiple Chemical Sensitivity</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>MRV</td>
<td>Magnetic Resonance Venogram</td>
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<td>NAT2</td>
<td>N-acetyltransferase</td>
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<tr>
<td>NMDA</td>
<td>N-Methyl-D-Aspartate</td>
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<tr>
<td>OSA</td>
<td>Obstructive Sleep Apnea</td>
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<tr>
<td>REM</td>
<td>Rapid Eye Movement</td>
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<td>SPECT</td>
<td>Single-Photon Emission Computed Tomography</td>
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<tr>
<td>SOD2</td>
<td>Superoxide Dismutase 2</td>
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<tr>
<td>TSS</td>
<td>Transverse Sinus Stenosis</td>
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<tr>
<td>VOC</td>
<td>Volatile Organic Compound</td>
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<tr>
<td>TILT</td>
<td>Toxicant-Induced Loss of Tolerance</td>
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and cellularity
(d) Intracranial diseases (including venous sinus thrombosis) ruled out by appropriate investigations
(e) No metabolic, toxic or hormonal cause of intracranial hypertension

(3) Headache develops in close temporal relation to increased intracranial pressure

(4) Headache improves after withdrawal of CSF to reduce pressure to 120-170mmH2O and resolves within 72 h of persistent normalization of intracranial pressure. [3]

The more recent ICHD-3 criteria published in 2013 state that the opening pressure must be greater than 25 cm H2O. [4] However, a study by Higgins, et al. suggests that disorders of raised intracranial pressure may begin at CSF pressures much lower than previously recognized, as will be discussed later. [5] In 2017, Gerstl et al. published a study looking at pediatric patients who had been diagnosed with IIH based on older criteria, and found that only 33% of these would have fulfilled the revised diagnostic criteria published in 2013. Among the patients who would not have fulfilled the new criteria were patients with papilledema and headache who had obvious improvement upon draining CSF. The authors comment on other similar studies, and suggest that there should be discussion of replacing the strict LP opening pressure cut-off value with a range of 20-30 cmH2O, because of the unspecific and various clinical presentations in children and adolescents. [6]

The underlying cause of IIH is still largely unknown. Several pathophysiological mechanisms that may lead to altered cerebrospinal fluid hydrodynamics have been proposed. Clinical evidence suggests that obesity, delayed CSF absorption and venous outflow problems with increased cerebral venous pressure contribute to the elevation of intracranial pressure (ICP). [3] One hypothesis that has been considered since the 20th century is that decreased conductance to CSF outflow may be due to dysfunction of the absorptive mechanism of the arachnoid granulations or possibly through the extracranial lymphatics. [7] The more recent discoveries about the glymphatic system may shed some light on our understanding of this condition. Lenck et al. recently hypothesized that an initial impairment of the transport of interstitial fluid from the glymphatic system to the venous blood of the dural sinuses may trigger the hydrodynamic cascade of IIH. [8]

Lorberboym et al. demonstrated that in IIH there are regional cerebral hypoperfusion abnormalities seen on SPECT scans, the degree of which correlate with disease severity. [9] Alperin et al. has shown that in a group of obese women with IIH, they manifested both increased interstitial fluid volume in the grey matter of the brain, and decreased internal jugular venous drainage. [10] Rothwell et al. performed a CT study which suggested that cerebral swelling is present in benign intracranial hypertension. [11] A recent publication by Lenck et al. discusses MRI diffusion studies that have demonstrated the presence of increased extra- and intracellular water content in the brains of patients with IIH, and how this indicates an increased resistance to CSF outflow leading to interstitial edema, suggesting a congestion of the glymphatic system which would result in increased ICP. Lenck et al. propose that in IIH there is a primary restriction of the venous outflow pathway (either via intrinsic or extrinsic venous sinus stenoses), then a secondary congestion of the glymphatic system, and finally a secondary overflow of the lymphatic CSF outflow pathway. The arachnoid villi and granulations are commonly considered the resorptive mechanism for CSF; however CSF is also removed from the skull via traveling through the lymphatics which run along the cranial nerves. One of the cardinal radiological signs of IIH is the excess of CSF seen along these cranial nerve sheaths. This can be seen not only along the optic nerve, but also along the olfactory, facial, trigeminal, acoustic, oculomotor and abducens nerves, and erosion of surrounding bone can lead to CSF leaks. Lenck et al. discuss the variability of ICP in different patients with IIH, and how this may be a result of variations in the efficiency of this lymphatic outflow pathway. They suggest that patients with an effective lymphatic outflow pathway may have lower ICPs and more problems with cranial nerve edema. Lenck et al. also hypothesize that a
primary problem with the aquaporin channel may be at the root of the venous CSF outflow restriction in IIH. [8]

The headache in IIH can mimic migraine or tension-type headache patterns and IIH can exist in the absence of papilledema, therefore proper diagnosis can be hindered without a high index of suspicion. IIH is found more often in obese women, however it can occur in males and in those who are thin.[3] Other symptoms may include severe fatigue, dizziness, impaired memory and concentration, depression and joint pains.[5] Also, cranial nerve palsies, radicular pain, transient visual obscurations, photophobia, phonophobia, pulsatile tinnitus, nausea, diplopia, and shoulder, neck and back pain can be seen.[1] Osmophobia has been reported as well. [12]

There are many treatments for IIH but only rare cures. Weight loss is very important if obesity is present. Medications to decrease CSF production, acetazolamide and topiramate are used. Furosemide also can reduce ICP. Steroids can help but are problematic and limited due to side effects. [13] Optic nerve sheath fenestration may relieve papilledema. Occasionally a single lumbar puncture (LP) can abort the disease. Bilateral transverse sinus stenosis (TSS) has been seen in a large majority of patients however it is not known if the intracranial pressure itself can compress the venous sinus, leading to a vicious cycle of elevated ICP which is interrupted upon drainage of CSF at LP. Stenting can be helpful in some with TSS. If visual loss is not controllable through these other means then CSF diversion procedures, ventriculoperitoneal or lumboperitoneal shunting is recommended. [3] Subtemporal decompression can also be utilized. [13] Intracranial hypertension can be caused by secondary factors. These include certain medications (tetracyclines, retinoids, lithium, etc.), hypercoagulable states, hormonal disturbances, obstructive sleep apnea, and cerebral venous abnormalities, and at times the disease can be cured by treating these underlying conditions. [1] Intracranial hypertension which is caused by certain medications can be reversible by stopping the medication. [13] It is known that obstructive sleep apnea (OSA) can cause papilledema, OSA is associated with IIH, and it is also known that apneas can raise ICP. IIH can remit with treatment of the OSA. [14-17] IIH has been demonstrated to be caused in some people by internal jugular venous compression in part by an elongated styloid process; Dashti et al. published a case report of IIH cure by surgically correcting the styloid anomaly. [18]

Multiple Chemical Sensitivity

Multiple chemical sensitivity (MCS) is a chronic condition with multiple symptoms that are reported to flare after exposure to low levels of environmental chemicals, certain foods or medications. 70-80% of sufferers are women. Many patients report an initial exposure event in which they inhaled, absorbed or ingested a toxic level of a chemical agent. [19] The commonly involved chemicals are volatile organic solvents and pesticides, although mold toxins can also be inciting agents. This leads to a hypersensitivity to low levels of multiple different chemicals, most of them in the class of hydrocarbons. MCS sufferers can be up to 1000 times more sensitive to these chemicals than normal people, and generally they do not recover from this illness [20] although they can achieve a relatively normal baseline as long as they avoid further chemical exposure. [19] Most of the symptoms of MCS are neurological in origin, [20] including cognitive difficulties with concentration and memory, fatigue, slowed thinking, and feelings of unreality/spaciness and lightheadedness. Patients can suffer insomnia, depression, anxiety, sleepiness, irritability, panic disorder, migraine headaches [19] and joint pains. MCS can be co-morbid with fibromyalgia and chronic fatigue syndrome in at least 10% of cases. [21] In addition to their odor intolerance [19], it has recently been demonstrated that patients with MCS also show noise sensitivity and decreased sound tolerance. [22] Dr. Claudia Miller has proposed an alternate term for this illness: toxicant-induced loss of tolerance (TILT), which emphasizes that there is an initiating event with subsequent triggers that produce symptoms. Her writings on TILT detail further symptoms these patients describe, which include "head fullness/pressure, brain feels swollen, ringing in ears, headache, feeling groggy, weakness, double
vision."[23]

The response to low levels of environmental chemicals has led to the development of a theory of neural sensitization to explain MCS, [19] which is fairly well accepted in environmental medicine. Neural sensitization is the process by which an organism learns to augment the response to threatening stimuli in order to protect against tissue damage. [24] The presumed mechanism of neural sensitization is long term potentiation (LTP) and involves stimulation of NMDA (N-methyl-D-aspartate) receptors in the brain. The NMDA receptor is the receptor for the neurotransmitter glutamate. [20] Win-Shwe et al. has discussed the finding that low-level formaldehyde exposure increases NMDA mRNA expression in the hippocampus, indicating that the effects of this chemical exposure are mediated by NMDA receptors. [25] Further evidence for this idea that the symptoms of MCS are mediated by glutamate is found in a recent case study. Levetiracetam, an anti-epileptic medication which reduces the release of presynaptic neurotransmitter including glutamate, was shown to improve the recurrent symptoms of a 23-year-old woman with MCS. [26]

The search for biomarkers in MCS has yielded correlations between alterations in catalase, glutathione-transferase and glutathione peroxidase detoxification capacity and clinical manifestations in MCS. [21] Xiaoyi et al. found a high prevalence of upregulated SOD2 mutations in MCS. The NAT2 rapid acetylator genotype has been associated with self reported severe MCS cases. Similarly, the null genotypes for glutathione transferase genes GSTM1 and GSTT1 have been associated with MCS cases. [27] Katoh et al. identified a significant increase in levels of hexanoic acid and pelargonic acid, and a significant decrease in the level of acetylcarnitine in patients with MCS. [28] A SPECT study of MCS patients revealed significant brain hypoperfusion, [29] similar to what is seen in IIH. This was seen at baseline, with a significant change upon chemical exposure that produced symptoms. [29] Later studies using near-infrared spectroscopy imaging demonstrated an increase in cerebral blood flow upon exposure to odorants, specifically in the prefrontal cortex and the orbitofrontal cortex. [30] Utilizing positron emission tomography, abnormal activation of the amygdala, piriform and anterior cingulate cortex during odor processing in MCS has also been shown. Other imaging studies investigating differences in brain glucose consumption have also demonstrated alterations from the norm in MCS patients, implying that brain metabolism in MCS subjects during olfactory stimulation is different from healthy individuals. [31]

Many researchers and clinicians have concluded that MCS is evidence of a disordered psychology and fits into the category of somatic symptoms disorder, even now when there is a great deal of evidence that MCS is a pathophysiologic condition. [32] Certainly if there is an association with abnormalities in detoxification enzyme production, related to the specific chemicals that MCS patients have problems with, this does not support a somatoform origin for MCS. This bias has likely limited the quantity and funding of quality research into the biology of MCS. Currently there is still no better treatment for this condition other than avoidance of exposure. [21]

What is striking is that the model of illness for MCS is: exposure to triggering substance leads to illness, removal of substance leads to improvement or resolution of symptoms, and the patient relapses upon re-exposure. This is identical to the medication induced intracranial hypertension model of illness. Furthermore, the neurological symptoms described in MCS are nearly identical to those described in IIH, and SPECT scans in both groups show baseline cerebral hypoperfusion. There is a female preponderance in both illnesses. (See Table 2)

There does not appear to have ever been an investigation into intracranial pressure in MCS. There is one case report in the literature showing an association of MCS in a woman who had intracranial hypertension, presumably from a meningioma. There is no documentation in this report that her ICP was measured upon removal of the meningioma, however her MCS symptoms did not resolve after removal. [33] The current case study presented here
demonstrates that at least in this patient, her MCS symptoms are identical to her IIH symptoms, chemical exposure triggers her IIH symptoms and this is shown to correlate with a measurable and significant increase in her ICP. Her IIH was put into remission with jaw surgery, and while her odor hypersensitivity is unchanged afterwards, the degree of her neurological response to chemical exposure, while still present, is significantly reduced. Therefore, there is the suggestion that the neurological symptoms in MCS are a result of chemical exposure leading to an increase in intracranial pressure. The discussion of this case study explores this possibility and hypothesizes that the increase in ICP may be mediated by a change in blood flow and/or the development of cerebral edema initiated by the chemical exposure.

**Case Report**

The woman in this case report developed Graves disease at age 35, and about 6 months after diagnosis began having symptoms that in retrospect may have been the onset of idiopathic intracranial hypertension (daily headaches, intermittent pulsatile tinnitus). At about a year after Graves diagnosis, she noted the onset of headache and “brain fog” triggered by certain indoor environments, in conjunction with the beginning of Graves ophthalmopathy. She developed proptosis as well as vertical phoria and had a total thyroidectomy, after which point all of her symptoms improved for quite some time and the eye disease became quiescent. She had had a large goiter that required extension of the original incision at surgery and a complex dissection. She has persistence of diplopia on right lateral gaze.

At age 38 she began to notice that perfume was bothering her a lot, and that it was triggering her “migraines”. After complaining about it at work, she was told that no one else was smelling what she was, and that she had a “bionic nose”. She routinely had a great deal of trouble whenever someone used the Lysol spray in the bathroom. Over several years she began carrying an N95

| Symptoms and Findings in MCS and IIH |
|-----------------|-----------------|
| MCS             | IIH             |
| Fatigue         | Fatigue         |
| Memory problems | Memory problems |
| Concentration problems | Concentration problems |
| Lightheadedness | Dizziness       |
| Depression      | Depression      |
| Headaches       | Headaches       |
| Tinnitus        | Tinnitus/pulsatile tinnitus |
| Diplopia        | Diplopia        |
| Joint pains     | Joint pains     |
| Co-morbid fibromyalgia | Neck, back, shoulder pain |
| Triggered by toxin exposure | Triggered by drug exposure |
| Helped by toxin removal | Helped by drug removal |
| Baseline brain hypoperfusion | Brain hypoperfusion |
| Female preponderance | Female preponderance |
| Phonophobia     | Phonophobia     |
| Osmophobia      | Osmophobia      |
mask in her work bag so she could use it if needed to protect herself from chemical scent. By the time she was 44, she was having to use it so much that it was interfering with work relationships. A particularly bad Lysol exposure (however not notable as unusual by others present) triggered her into steroid dependent asthma. This led to her having to claim disability because of her inability to tolerate indoor work environments due to the chemical exposures which were causing both respiratory and neurological symptoms. After eye surgery that seemed to precipitate a Graves ophthalmopathy flare, she took a taper course of steroids, and while on this her asthma was quiescent, however so were her headaches. About 6 weeks after stopping the steroids, and immediately after dieting and losing 10-15 pounds, she developed the sudden onset of near daily “brain fog”. It was disabling, and described as beyond fatigue, but a feeling like one is deep underwater, like having the flu or a hangover. She was barely able to function with this extreme alteration in her sensorium, which would come and go and appear to be aggravated by chemical exposure. She described episodes of brain fog that felt like trying to wake up from general anesthesia. Chemical exposures could cause episodes of brain fog and headache that would take up to 24 hours to clear. Hence she was initially diagnosed with multiple chemical sensitivity (MCS), given her history of poor odor tolerance of chemical scent and symptoms triggered by the exposure. This patient carries several genetic polymorphisms associated with MCS. She carries the null genotype for GSTM1 (Glutathione-S-transferase M1), as well as a heterozygous polymorphism of GSTP1, (Glutathione-S-transferase P1), the gene products of which are required for detoxification of hydrocarbons by glutathione conjugation. [21] Indeed, all of the substances which cause her trouble are hydrocarbons, or VOCs (volatile organic compounds). She also carries the fast acetylator NAT2 polymorphism, which plays a role in the metabolism of heterocyclic and aromatic amines. [27] Interestingly, the GSTs are highly expressed in the olfactory epithelium, [21] which may explain the severe olfactory symptoms in this patient who harbors two genetic anomalies involving GSTs. Shortly after the onset of the brain fog, she developed chronic nausea that lasted 6 months, and during this time she lost 40 pounds. Despite being thin, she continued to have severe symptoms which were ultimately diagnosed later, at age 47, as idiopathic intracranial hypertension.

Regarding her headache history, these were accompanied by brain fog and occasionally nausea, but no increase in photophobia or phonophobia. She had intermittent headaches going back to childhood, prior to the worsening described above. Phonophobia developed slowly after age 45 and became disabling, however this auditory hypersensitivity did not fluctuate. Photophobia developed at age 36 concurrent with Graves ophthalmopathy and did not fluctuate. The headaches were usually unilateral and pounding, were moderate and occasionally severe, and could be triggered by altitude changes, food sensitivities and inhaled chemicals, as well as severe stress. While she did have odor hypersensitivity, her symptoms could occur from chemical exposures in the absence of odor perception, and neurological changes from chemical exposure below odor threshold was confirmed on functional MRI testing.

At age 45 she was diagnosed with OSA at Stanford University. Her AHI was 10.2 with a minimum oxygen desaturation to 91%. This was after two prior sleep studies in her home city failed to detect the OSA. An ophthalmology exam was normal. By this point she was having daytime airway symptoms that at times led her to gasp for air and become lightheaded, triggered by eating, only to resolve these symptoms with a tongue thrust out of the mouth. Now age 46, these daytime airway symptoms resolved completely after a midline glossectomy, however her AHI on another sleep study at Stanford was 17 after the tongue surgery. She tried multiple different methods to treat the OSA, including auto-CPAP, CPAP, a tongue retaining device and a mandibular advancement device. The tongue retaining device, when it stayed on without fail, worked well to prevent the brain fog and headaches, leading to the conclusion that the OSA was causing these symptoms. Auto-CPAP was poorly tolerated, and a CPAP of 8 helped somewhat but not completely, however it was more reliable than the tongue-retaining device. The mandibular advancement device (MAD) did not resolve the apnea; her AHI was 6.7
using it, and while using it she had a near syncopal episode that required TIA (transient ischemic attack) workup. This episode was triggered by a Valsalva maneuver, and in the aftermath it was determined that a LP should be performed.

She had two LPs a month apart, showing opening pressures of 22 and 23 cm H2O. These were considered positive because her brain fog symptom improved after CSF was removed. The neuro-radiologist who performed the LPs noted that her speech became more rapid after the ICP was reduced. Her brain MRI was normal. Hence she was diagnosed with idiopathic intracranial hypertension which explained most of her neurological symptoms which included the brain fog, headache, tinnitus, pulsatile tinnitus, and vestibular problems.

While the sleep apnea appeared to be the greatest ICP trigger and required aggressive management, her other ICP triggers clearly included a prominent Valsalva trigger, as well as chemical exposures. The Valsalva trigger inhibited her speech and made her dizzy with singing or shouting. Crying would trigger an immediate ice-pick type headache and lead to her being ill for 24 hours afterwards. Consistent with her initial diagnosis of MCS, chemical odor was a very strong trigger for the ICP symptoms and an exposure could ruin her day, render her unsafe to drive, or put her in bed with severe pain. It generally took close to 24 hours to recover from such an exposure. At times she habituated to the scent, yet if the exposure persisted despite her no longer smelling it, she would still react.

A CPAP titration was performed at Stanford, and she was titrated to a pressure of 12-13. However, at that pressure, she experienced the expiratory pressure as a Valsalva and after one night she developed an episode of severe ICP symptoms including sudden weakness and inability to stand or walk. She changed to a Bi-level machine that allowed her to increase the inspiratory pressure without developing severe ICP symptoms but still did not feel normal. She concluded that she was failing all OSA treatments despite having only mild OSA that was triggering her IIH, and that she had failed medical management of the IIH, as she was unable to tolerate acetazolamide or topiramate, and found furosemide inadequate. Prednisone worked to abort the symptoms triggered by OSA, however this is not acceptable as a long term solution.

At age 47, this patient underwent a counter-clockwise maxillomandibular advancement (CC-MMA) by the procedure of Dr. Larry Wolford. [34] By 6-8 weeks after the procedure, she began to feel much better and was able to exercise again after years of feeling lightheaded and weak with exercise. She was no longer using anything for sleep apnea other than a nasal decongestant at bedtime, and while she continued to have symptoms of sleep apnea such as waking with a sore throat, her IIH symptoms were markedly improved. If it seemed that sleep apnea triggered her ICP symptom of brain fog, it was mild and responded to furosemide or exercise. In terms of the MCS, she continued to have severe odor hypersensitivity. However, upon exposure, her headaches were rare and the brain fog was milder overall and could go away on its own within an hour or with furosemide or exercise. There were times the brain fog could become deep enough to cause her to feel she was unsafe to drive, if she allowed a longer exposure, however these events would still usually clear rapidly once removed to fresh air. As noted above, prior to the CC-MMA, she had a very prominent Valsalva trigger for ICP, such that just starting to cry could precipitate an ice-pick type headache with persistent symptoms for 24 hours afterward. After the CC-MMA, she was able to cry without any ICP symptoms developing. Any headaches were mild and infrequent. Prior to the CC-MMA, she could feel dizzy just from shouting, while post surgery she could speak, shout, laugh and cry with no consequences. Her personality appeared to change because she could now speak animatedly and rapidly, whereas prior to the CC-MMA she was soft spoken and moved slowly, with a logy feeling in the head similar to vertigo.

11 months after the CC-MMA, the patient had a repeat sleep study at Stanford which showed an AHI of 8.5 and minimum oxygen desaturation to 91%, consistent with her perception of subtle symptoms of persistent OSA. 14 months after the CC-MMA, at age 48, she had a repeat
LP, which showed an opening pressure of 14 cm H2O. Upon chemical exposure during the LP, her ICP increased to 15 cm H2O, over the course of 25 minutes, concurrent with the development of mild brain fog. She was exposed to a hanging car air deodorizer, and a common room air deodorizer sprayed onto paper towels. Pertinent to the discussion which follows, it should be noted that the woman in this case report has a son with autism, who is also chemically sensitive, and who has also been diagnosed with intracranial hypertension as well as OSA.

Discussion

This is the case report of a very complex patient who carries the diagnoses of obstructive sleep apnea, idiopathic intracranial hypertension, and multiple chemical sensitivity. In this patient, these three conditions appear to interact so intimately that at times it is as if they are one condition with these different clinical manifestations. Her presentation of IIH was atypical, with her opening pressures being in the borderline range for ICP and with her headaches not being persistent. She did not have papilledema. Her strong Valsalva triggers for symptoms did suggest that intracranial pressure was involved in these symptoms. She matched the definition of IIHWOP = idiopathic intracranial hypertension without papilledema, which can be associated with a headache pattern indistinguishable from migraine. [35] Even if her IIH diagnosis prior to CC-MMA might be arguable, depending on which ICHD criteria were in use at the time, her clinical improvement afterwards coincident with a significant decrease of ICP and an insignificant decrease in AHI, is not. This is clearly a disorder of raised ICP which has been ameliorated by CC-MMA. As detailed in a companion case report, the CC-MMA appeared to eliminate her IIH, as evidenced by the opening pressure on LP dropping from 23 to 14 cm H2O. In the companion report the case is made that this cure was effected by the mandibular advancement, independent of the effect on sleep apnea, given that the AHI in this patient did not change considerably after surgery. In that report authored by Wardly, Wolford, and Veerappan, it was proposed that the mandibular advancement led to increased jugular venous flow, allowing normalization of the baseline CSF pressure. This conclusion is supported by the fact that prior to CC-MMA the tongue retaining device helped more than any other sleep apnea treatment, and by the fact that total thyroidectomy led to initial remission of IIH symptoms (these may have decompressed the internal jugular veins). [36]

The discussion here will focus on this patient’s very prominent chemical trigger for her ICP symptoms, and the demonstration in her last LP of her ICP increasing in response to chemical exposure. Despite the fact that her IIH appears to be eliminated, and her ICP after chemical exposure is still in what is considered to be the normal range of ICP, she does develop symptoms of brain fog coincident with the increase, and there is no valid reason other than the chemical exposure to explain the increase in ICP observed during the LP described. In fact, after the first opening pressure is measured, a small amount of CSF is lost after use of the manometer, and the hole in the dura from the spinal needle even though it was left in place can allow leakage of pressure and fluid. This will produce the expectation that an opening pressure measured just 25 minutes later might be lower than what was obtained initially [37] certainly one would not expect it to be 7% higher. These findings strongly suggest that this patient’s MCS has been a manifestation of her IIH.

As per Alperin et al.’s findings of decreased jugular venous drainage and increased interstitial fluid in grey matter in obese women with IIH, [10] it is argued here that the CC-MMA in this patient corrected her jugular venous flow problem, however did not correct her tendency to develop brain edema. Incorporating the finding that 77% of people with IIH have peripheral edema, [38] it is implied that there may be a system wide problem with the endothelial barrier in IIH that predisposes to edema not just in the brain but throughout the body. It is proposed here that this patient may experience brain edema triggered by chemical exposure, to effect the 7% increase in ICP documented to occur after exposure. It is also proposed that the brain fog symptom is caused in large part by this brain edema, regardless of whether ICP rises to the abnormal range. With current radiological procedures, it is unlikely that this small amount of brain edema can be measured. As
an aside but related to the above, if in IIH/MCS there is a basic systemic problem with the endothelial barrier, this may explain the gastrointestinal and pulmonary symptoms seen in MCS. As Lenck et al. suggest, future research in IIH may be best directed at this interface, and there is evidence that aquaporins may be involved. [8] To further complicate matters, it has been shown that intermittent hypoxia can decrease aquaporin 1 and increase brain water content in mice brains. [39] The contribution of OSA to the production of these illnesses has likely been under-recognized.

Alternatively, it has been recently demonstrated that patients with MCS can experience a regional increase in cerebral blood flow upon exposure to odorants. [40] According to the Monro-Kellie doctrine this would lead to an increase in intracranial pressure. [11] This increase in regional cerebral blood flow during odor stimulation in MCS has been shown in multiple studies using near-infrared spectroscopy imaging. [40] If these MCS patients actually have IIH, then per Lenck et al.’s discussion any increase in cerebral blood flow would compound the glymphatic congestion in these patients. Given that SPECT studies show baseline hypoperfusion, it is likely that our understanding of vascular flow in MCS has yet to be fully illuminated.

The functional MRI results obtained on this patient indicate that very low levels of chemical are capable of triggering an abnormal brain response in this patient. This is clearly a pure neurological reaction to the chemical exposure itself, and not a psychological response to the odor perception, because the patient did not perceive the odor during the study. This work proposes the hypothesis that this brain activation may be mediated by glutamate, based on the neural sensitization theory put forth by Dr. Iris Bell. [19,20] It is known that glutamate stimulation of the brain may cause brain edema, [40,41] and Win-Shwe et al. has demonstrated that the VOC formaldehyde likely exerts its effects via NMDA receptors. [25] This idea provides a biologically plausible connection between (typically VOC) chemical exposure and the production of brain edema which may then cause neurological symptoms in MCS and may raise intracranial pressure to abnormal levels such that it then becomes IIH. It may be that a venous drainage anomaly must be present to allow the ICP to build to abnormal levels and plateau, regardless of whether the ICP increases initially due to edema or to increased cerebral blood flow after chemical exposure.

It is also known that obstructive sleep apnea can produce glutamate neuro-excitotoxicity, [43] and several studies suggest that brain edema occurs in OSA. [39,44] OSA causing brain edema could explain the fact that prednisone was able to abort this patient’s symptoms which resulted from sleeping without airway support. Dr. Avram Gold has discussed a concept whereby he hypothesizes that somatic syndromes (like MCS) are linked to sleep disordered breathing via neural sensitization to pharyngeal collapse. The nerve which senses pharyngeal collapse is the olfactory nerve, [45] and again, neural sensitization is mediated by glutamate. [20] Bell's theory is that the chemical exposure triggers the neural sensitization, however it may be that OSA plays into the development of the neural sensitization specifically as it relates to the sense of olfaction. The knowledge that patients with MCS have been found to have increased nasal resistance compared to controls [46] suggests that MCS patients are more prone to airway obstruction. Patients with MCS have been found to have higher blood pressures upon waking, compared to normals, and also show decreased total sleep times, increased awakenings, and decreased REM sleep. [19] These are all signs seen in patients with sleep disordered breathing. [47] A recent study published by Nordin et al. showed that patients who were environmentally intolerant to chemicals showed higher levels of obstructive breathing than controls. [48] A type of neural sensitization called TDS (time dependent sensitization) has been associated with post traumatic stress disorder and attention-deficit hyperactivity disorder, [19] both of which have been linked to OSA; both will improve with treatment of OSA. [49,50] A recent hypothesis involving atrial natriuretic peptide (shown to be elevated in OSA) also suggests that neural sensitization may be involved in the symptoms of upper airway resistance syndrome. [51] Thus it may be that given sufficient neural sensitization and narrow jaw anatomy,
glutamate then becomes the final common mediator in a pathway that is triggered by seemingly disparate events.

These correlations between MCS and OSA, and those previously mentioned between IIH and OSA, combined with the data here suggesting that MCS may be a form of IIH, intersect with the clinical presentation of the patient in this case study to suggest that these three conditions are interdependent on one another in the patient to produce the phenotype observed.

It would be important for this case study to be followed by further investigation into whether a group of known MCS patients have elevated ICP and if their ICP can be triggered to increase above baseline by exposure to volatile organic compounds. Comparing them to a control group would be important for determining if people who do not carry a diagnosis of MCS also show an increase of their ICP with exposure, which would more broadly implicate this class of chemicals as significantly neurotoxic. It is critical to choose substances for study which are xenobiotics and known chemical triggers for MCS symptoms. Some of the studies evaluating odor response in MCS patients employ odors that are naturally occurring, [40] which may not be likely to provide a proper test of this illness. Using such substances is evidence of an assumption about this illness which may be mistaken: that the odor sensitivity in MCS is primary to the illness, rather than being simply downstream from the primary pathology. In published discussions of the existing research on neuro-physiological findings in MCS, there seems to be a bias towards the idea that these are manifestations of a psychological reaction to odor. The discussion here is attempting to demonstrate that these neuro-physiological findings may simply be downstream from a biological response to the specific chemicals in question, regardless of their odor, which occurs due to individual perturbations in detoxification capacity, anatomy and barrier function. Also important to note is the fact that if MCS is determined to be due to a form of intracranial hypertension which is triggered by an idiosyncratic reaction to chemical exposure and exacerbated acutely by chemical exposure, then it may be an illness characterized by acute or chronic neurological injury worsened by acute toxic reactions, rather than one produced by a total toxic body burden of chemicals. It would be a great service to these patients to move them into the sphere of neurologists who can address what may be the primary physiological problem causing the most disabling symptoms of MCS.

A study by Higgins, et al. has been performed looking at ICP in a group of chronic fatigue syndrome (CFS) patients. Out of a group of 20 CFS patients, 5 had elevated ICP, and 4 met the criteria for IIH. 85% of the 20 patients had improvement in their symptoms with removal of CSF, despite the fact that most of them had what are considered normal opening pressures. The authors point out that the development of the "normal" ranges for CSF pressure utilized patients who were not completely normal neurologically, and they suggest that we may not know what true normal ICP is, and that disorders of raised intracranial pressure may begin at CSF pressures much lower than previously recognized.[5] Therefore in the proposed MCS study, the patients should have their ICP reduced by CSF removal to observe whether symptoms remit with CSF removal, even if their initial opening pressures are "normal". It is also important to note that the lack of recognition up to this point that intracranial pressure may be abnormal in CFS and MCS patients, is due in part to misperceptions about papilledema being required for the diagnosis of intracranial hypertension. Again, intracranial hypertension can exist in the absence of papilledema. The findings of Higgins, et al. throw into question some of what we believe is fact regarding the range and frequency of pathology in intracranial hypertension as well as our definitions in disorders of raised ICP.

It would be important to look at this problem from the other direction, also. A group of IIH patients should be investigated for signs of previously unrecognized chemical sensitivity. Informal reports do suggest that odor hypersensitivity and chemical sensitivity exist in IIH patients, [52] but this should be formally evaluated because it is not generally recognized that these are regular features of IIH. Given that the symptoms of chemical
sensitivity and odor hypersensitivity are frequently mistaken for somatoform disorder manifestations; it would be important to document that these are actually common symptoms of a confirmed neurobiological disease process. Patients with invisible illnesses are subject to a great deal of discrimination, such that proving that they have a legitimate disease will go far in protecting the basic human rights of neurologically disabled people.

It might also be productive to investigate the frequency in IIH of the gene polymorphisms found to be common in MCS. However, the improvement after jaw surgery of this patient's chemically triggered neurological symptoms suggests that it takes more than just a gene polymorphism to produce a severe case of MCS. It is likely a case of needing multiple strikes for the full syndrome to manifest. This case report suggests that MCS patients should be evaluated in multiple steps, including not only with LP, but brain MRI/MRV, neck MRV, sleep study, airway imaging, and genetic testing.

Chemical analysis of fragranced air “freshener” products have revealed the presence of multiple VOCs which are registered as hazardous carcinogens and/or neurotoxicants. [53] This patient’s glutathione transferase deletion and polymorphism would indicate that she would have difficulty detoxifying these chemicals by glutathione conjugation, and this may be the reason why these type of chemicals in particular cause her so much trouble. This detoxification problem may allow these chemicals to contribute to neural sensitization and also to IIH in this patient. (It may be that other genetic polymorphisms account for why some patients develop IIH from retinoids or from tetracyclines, for example.) In contrast to IIH being considered a rare disease, there are many who complain of fragrances causing headaches. A recent study on the prevalence of fragrance sensitivity in the American population found that almost 26% of the general US population reports being “chemically sensitive” and of this group, 42% reported having “migraine” headaches in response to fragrance exposure. [54] The present case study calls into question the etiology of these headaches, and demands further study into the full spectrum of illness caused by fragrances which have become so ubiquitous in indoor environments.

A Piece of the Autism Puzzle?

A very recent study of women with MCS by Heilbrun et al. showed that chemically intolerant mothers were 3 times more likely to report having a child with autism. These chemically sensitive mothers reported that their children had a greater sensitivity to noxious odors more often than controls. [55] There are other studies which have linked autism to chemical sensitivity. There is a rate of about 40% of autistic children manifesting odor hypersensitivity, [56] as well as one study suggesting that exposure to volatile organic compounds can cause autistic behavior. [57] In vitro experiments demonstrating increased mutagenicity and cytotoxicity caused by common perfumes, has led to the proposal of an hypothesis that these fragrances are involved in the autism epidemic. [58] Reflecting on this data, it is notable that the patient in the present case study has a child with autism who is also chemically sensitive. More notable is the fact that this child also has intracranial hypertension, as well as OSA. Heilbrun et al. suggest that there is a genetic component involving detoxification genes to account for the autism and chemical sensitivity in children of mothers with MCS. [55] However, given the discussion here, one must consider that the genetic component may involve anatomy and/or barrier physiology at least as much as specific detoxification issues. For example, aquaporin-4 is significantly decreased in the cerebellum of postmortem subjects with autism. [59] Autism surely has a very complex etiology given how difficult it has been to elucidate it.

Perhaps the closest any current research has come to discovering the etiology of autism is found in some recent publications by Shen et al. Three papers by Shen et al. since 2013 have demonstrated that not only did increased extra-axial cerebrospinal fluid at 6 months predict autism later, but that children with autism had significantly higher extra-axial CSF volume than typically developing children, at ages 2-4 years. [60-62] There is further data demonstrating probable brain edema in autism [63] although studies showing the range of intracranial pressure in autism have
not yet been conducted. These extra-axial fluid collections have also been seen in children with pseudotumor cerebri, consistent with the idea that this extra-axial space is where the pressure in intracranial hypertension begins, as opposed to in hydrocephalus. Hellbusch reviewed extra-cerebral fluid collections in infancy and states that it is commonly accepted that a transient disturbance of CSF circulation, possibly due to delayed maturation of the arachnoid villi, is responsible. [65]

Shen et al. in their 2017 paper discuss the idea that their findings may suggest that there is a role for abnormal CSF circulation in the pathogenesis of autism. They raise the idea that without proper function of the glymphatic system to clear metabolic byproducts from the brain, there may be a pathological effect on normal brain development. [61] They have suggested the possibility that this CSF dysfunction they have identified in autistic children may be present at birth. [62] Most certainly, if intracranial hypertension exists during early neurodevelopment, the clinical syndrome will undoubtedly present differently than it does in adults. In Shen’s papers there is no mention of the idea that intracranial pressure may be elevated in these autistic children, but hopefully future studies will address this question. It is more likely that pressure is the culprit, rather than an isolated build up of toxins due to glymphatic dysfunction, because of the anterior fontanelle. The anterior fontanelle provides increased cranial compliance during infancy, but when it closes at about 18 months, that compliance is lost and pressure will rise if there is a problem with CSF drainage or brain edema. This is the typical age of the autistic regression. [66]

Given the recent information about the need for accepting a range of pressure between 20-30 cm H₂O for diagnosis of pediatric IIH, it should be anticipated that a study of ICP in autism will need to consider that it may be associated with more borderline elevated pressures. The Higgins study results imply that any research done should investigate autistic behaviors before and after removal of CSF, rather than relying on established norms for CSF opening pressure. In light of the present case study suggesting that MCS is IIH, if autism is determined to be related to elevated intracranial pressure then there is suggestion for further research as to the cause of these intracranial pressure problems. Certainly anatomy and other genetic factors may play a role, however the knowledge that MCS is triggered by pesticides implies that research on how pesticides affect the blood brain barrier and molecules involved in water transport is indicated.

In their 2018 publication, Shen et al. noted that their autism high CSF subgroup had more sleep problems than the typically developing group. The authors discuss the fact that normal sleep is necessary to allow clearing of toxic substances from the brain, and suggest that disrupted sleep may have contributed to the impaired circulation of CSF. [62] Many studies in autism demonstrate that these children manifest multiple symptoms of OSA. [66] Hirata et al. discusses the fact that between 40-80% of children with autism have sleep problems, more so than neurotypical children, and that autistic children with sleep problems show daytime behavioral improvement with interventions for sleep. Their study demonstrated that children with autism had evidence of a greater prevalence of OSA based on a questionnaire of OSA symptoms, than did neurotypical children. [67] Still, a formal study looking at OSA prevalence in autism based on sleep study evidence has yet to be performed. As seen in the present case study, OSA clearly disrupted sleep but also contributed to the symptoms of increased ICP, and the physiological mechanisms for how apnea increases ICP are known [14]. If this hypothesis regarding ICP in autism is correct, it may be so in autism as in the present case study, that the neuropathological effects of OSA and elevated ICP cannot be easily separated and have a synergistic negative effect on the brain. Again, the clinical manifestations will be different when this occurs during critical periods of neurodevelopment.

A further topic for discussion is the frequency of sensory problems seen in MCS, IIH, as well as in autism. As previously discussed, these are known to occur in MCS and IIH as well as autism, [56] but actual frequency of the different types of sensory disorders in these conditions is uncommonly measured, and not well recognized in IIH. It would be useful to conduct studies examining the
frequency of the different types of sensory problems in each condition, and then compare these. As previously discussed, Lenck et al. go into great detail regarding the lymphatic drainage pathway for CSF, which travels along the cranial nerves which sub-serve our senses of sight, hearing, smell, and vestibular function. [8] It is known that IIH can result in blindness, hearing loss, and olfactory dysfunction. [7, 68] It is known that the vision loss in IIH is generally due to optic nerve edema. [7] One of the cardinal radiological signs of IIH is the swelling of the optic nerve sheaths from this lymphatic congestion, but there is MRI evidence of edema in other cranial nerves as well. [8] Therefore, is it not conceivable that prior to complete sensory loss, lesser congestion of the cranial nerves might result in a hypersensitivity or distortion of some of the senses, producing hyperacusis, osmophobia, and vertigo? Furthermore, if this is the case, might the presence of these sensory disorders in any individual by definition require an investigation into the presence of a disorder of elevated ICP? Perhaps the presence of sensory disorders in MCS, IIH, and autism suggests that these conditions may be more related to each other than has previously been considered.

Summary

This case report discusses a very complex patient with obstructive sleep apnea, idiopathic intracranial hypertension, and multiple chemical sensitivity. Her IIH was eliminated by jaw surgery with CC-MMA, and her symptoms of MCS were ameliorated significantly upon IIH remission, despite residual severe odor hypersensitivity. Her ICP was shown to increase significantly upon chemical exposure, suggesting that her IIH and her MCS are one and the same. The hypothesis is proposed that the chemical exposure may be causing brain edema, via glutamate neuro-excitotoxicity. The greater implication from this case study is the suggestion that MCS is a variant of IIH, or that MCS is a feature of IIH, and further study is required to elucidate this. IIH caused by chemical exposure may technically be considered a secondarily caused intracranial hypertension and not idiopathic, however we may find that the relationship is less clear. Perhaps chemical exposure is the missing link in determining the actual cause of “idiopathic” intracranial hypertension. Finally, it is apparent from this case and the summarized research, that MCS is a neurobiological illness, such that all claims of this condition being evidence of psychopathology should be currently dismissed. Certainly, a lumbar puncture in addition to an extensive medical workup should ensue upon presentation of chemical sensitivity symptoms which resemble IIH, and psychopathology should always be a diagnosis of exclusion. Additionally, new research showing correlations between MCS and autism and signs of possible elevated ICP in autism are discussed with implication for future study. Recent recognition of the importance of the lymphatic drainage pathway in IIH suggests a new avenue into investigation of the etiology of sensory disorders.

Acknowledgments

A case report entitled: “Idiopathic intracranial hypertension eliminated by counter-clockwise maxillomandibular advancement: a case report” by the same author has been published in Cranio and contains some word for word similarities in the case presentation only. [36]

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