

## Intractable Headaches in a Patient with Alport Syndrome with No Evidence of Brain Lesions-A Case Report

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### Abstract

Alport Syndrome results in a genetic mutation in type IV collagen; one place of major significance is the glomerular basement membrane of nephrons. These patients are at high risk for glomerulonephritis and renal failure in addition to inner ear and eye pathology. This patient is a 25 year old Caucasian female with non-deaf Alport Syndrome who was hospitalized for intractable headaches with pain scale measuring 8-10 out of 10 of severity. This patient received a CT of the head, MRI, MRA and MRV of the brain that demonstrated no evidence of chronic or acute hemorrhage, acute intracranial process, chronic or acute infarction, vasculitis, brain lesions or emboli. This patient's headaches were refractory to oral Fioricet, Aspirin, Tylenol and NSAIDS. The patient initially refused oral and intravenous analgesics including morphine, oxycodone due to the side effects of nausea, lethargy and drowsiness. The patient's pain was moderately relieved by small doses of oral oxycodone and intravenous morphine. The patient experienced mild nausea and drowsiness from these medications; however her pain reduced over 60% in severity to a final rating of 3-4 out of 10 from an initial 8-10 out of 10 in severity. This patient was the first patient reported with Alport Syndrome and intractable headaches without evidence of acute or chronic brain lesions on brain MRV, MRI, MRA and CT imaging whose headache pain was reduced by over 60% in severity by oral and intravenous analgesics in the inpatient setting.

**Keywords:** Alport syndrome; Intractable headaches

### Introduction

Alport Syndrome [1,2] is a congenital genetic mutation in type IV collagen [3]; one place of major significance is the glomerular basement membrane of nephrons [4] in addition to the lens of the eye, skin, alveolar lining and the cochlea of the inner ear. Around 85% of cases are inherited via a sex linked recessive pattern, whereby females are less likely to have the disease in comparison with males; there are mutations in medical literature that result in Alport Syndrome with an autosomal recessive pattern and rarely an autosomal dominant pattern [5,6]. Around 1 in 50,000 children are affected by the disease [4]. Characteristics of this disease include glomerulonephritis [7,8], end stage renal disease (ESRD), difficulty in vision and hearing loss.

Patients commonly experience proteinuria and hematuria [9] due to the leaky basement membrane in the glomerulus, whereby the filtration process of the blood by the kidneys does not tightly filter out protein and cells. These patients also must be watched to maintain adequate hemoconcentration, protein and albumin levels, and subsequently their intravascular volume.

These patients frequently require hearing aids in their teenage and young adult years and are at risk for tracheobronchial leiomyomas, which are benign smooth muscle tumors in the esophagus and tracheal tracts. Furthermore, aortic dissection is described in some patients with this disease [10].

Treatment consists of Angiotensin Converting Enzyme (ACE) inhibitors that slow down the progression of ESRD and prolong the need for dialysis in these patients [10]. Additional research has

involved cyclosporine [11], immune modulating agents and gene therapy as potential candidates for treating this disease.

Headaches are a common symptom of the general population [12], yet in Alport Syndrome is more worrisome for vascular abnormalities and concerns with cochlear pathology. Generally, headaches can be monitored in the outpatient setting and do not frequently require hospitalization for acute management.

### Case Report

This patient is a 25 year old Caucasian female with congenital Alport Syndrome who was repeatedly hospitalized for intractable headaches with pain scale measuring 8-10 out of 10 of severity. This patient had mild intensity hearing aids bilaterally and was born to parents both carriers and non-affected by Alport Syndrome. This patient was admitted to the inpatient service by her nephrologist for definitive workup of the etiology of her headaches and to reach tolerable pain control. This patient was seen frequently in the outpatient setting without success in the control of her headaches while attempting to control her progression of ESRD.

The patient reported consistent headache pain of 8-10 out of 10 in severity with no particular precipitating event. The pain was bilateral band like in distribution with no focal tenderness on the scalp. The patient denied nausea, vomiting, visual changes, balance changes or loss of consciousness. The patient reported having these headaches for several months and denied any visual or auditory aura, tinnitus or worsening symptoms when exposed to light. The patient reported intermittent throbbing like pain that had mild relief from over the counter acetaminophen and Non-Steroidal Anti-inflammatory Drugs (NSAIDS).

On physical exam the patient had normal range vital signs. She had severe headaches 8-10/10 in severity without pain on palpation to the entire cranium; the remainder of the physical exam was non-focal.

The patient was worked up in the outpatient setting was negative for infectious causes of headache pain, worsening kidney disease and autoimmune etiologies causing the pain. The patient's labs were consistent with chronic kidney disease, normal ESR, hepatic enzymes, electrolytes and coagulation studies. The patient's chest x-ray and ECG were unremarkable.

At this stage, the nephrologists desired a CT of the head, MRI, MRA and MRV of the brain that demonstrated no evidence of chronic or acute hemorrhage, infarction, acute intracranial process, vasculitis, brain mass lesions, demyelinating lesions or emboli.

The patient was given Intravenous Morphine for acute pain and titrated with oral oxycodone to an overall pain scale of 1-3 out of 10 in severity. Initially the patient required 1 mg intravenous morphine regularly every 3 hours for the first 20 hours of hospitalization. The patient was then converted to 5 mg of oral oxycodone every 4 hours with 1 mg intravenous morphine pushes as needed every 4 hours. Fioricet was added and quickly discontinued after a few doses because no pain reduction was appreciated. The patient was able to suffice with controlled headache pain towards the end of her hospitalization only requiring 5-10 mg total of oxycodone daily with oral acetaminophen as needed. She experienced some nausea and drowsiness due to the oxycodone and preferred not to take it. Upon discharge the patient was taking only 2.5 mg of oxycodone or none daily and sufficing her headache pain with mild use of oral acetaminophen and NSAIDS. This patient was the first patient reported with Alport Syndrome and intractable headaches without evidence of acute or chronic brain lesions on brain MRV, MRI, MRA and CT imaging whose headache pain was reduced by over 60% in severity by oral and intravenous analgesics in the inpatient setting. The patient was scheduled for regular follow up with her Nephrologist to resume managing her Alport Syndrome and delaying the progression of ESRD.

## Discussion

Headache pain is often refractory and multifactorial with a wide spectrum of characteristics, exacerbating factors and treatment combinations. Patients in the inpatient setting often experience worsening in their headaches likely due to a combination of acute and or chronic illness and systemic complications thereof.

The use of opiates in the inpatient setting is very common and it is used to treat a wide spectrum of acute and chronic pain [13,14]. Typically intravenous opiates are used in the acute setting until a stable oral regimen can be used and titrated. The ultimate goal is to wean patients off opiates to tolerate only oral acetaminophen, NSAIDS or no pharmacological treatment all for their acute and/or chronic medical conditions [15]. Opiates and other pain medications are a symptomatic approach to aiding pain and do not provide a definitive cure [16]. Furthermore, opiates may cause many side effects including nausea and constipation and may create additional medical complications. It is imperative to monitor the patient frequently in the inpatient setting when introducing potent medications to ensure no acute reactions or worsening of symptoms occur. Further, drug to drug interactions must be kept in mind in addition to the synergistic effect of opiates when combined in the same patient.

In this patient with Alport Syndrome, treatment with NSAIDS may seem counterintuitive as it can potentiate glomerular damage and opposes the actions of ACE inhibitors on the efferent arterioles of nephrons. However, NSAIDS may be used in conjunction with ACE inhibitors and in patients with chronic kidney disease under guidance of an experienced Nephrologist. The risks and benefits of such drug combinations must be balanced to ensure the maximum anti-inflammatory and analgesic effects are reached using NSAIDS, and at the same time ensuring to prevent or minimize the progression of glomerular disease and glomerulonephritic pathology [17].

The differential diagnosis for acute headache pain in a young patient is extensive, consequently it is imperative to rule out potentially life threatening and treatable causes initially before engaging in symptomatic relief with oral analgesics [18]; treating such a life threatening condition is both therapeutic for headache pain and lifesaving. This case was particularly worrisome for acute brain pathology; hence the CT, MRI, MRA and MRV were performed to rule out acute or chronic brain pathology. Acute subarachnoid hemorrhage, other intracranial hemorrhages and acute stroke must be ruled out initially as in this case due to the time sensitive and potentially lifesaving interventions that need to be implored in such pathology. Furthermore, such conditions can typically present with severe throbbing head pain. Additionally, cochlear [18], inner ear or brain masses need to be ruled out as potential causes of refractory headache pain in young adults. Acute venous brain thrombosis and cerebral vasculitis are other life threatening and treatable cause of severe intractable headache pain. Of particular note, acute demyelinating lesions, as seen in multiple sclerosis, must be kept in mind in a young adult with severe headache pain, especially one with the cultural demographics and gender of this case. In this case all the imaging and labs were not diagnostic of acute or chronic brain pathology as the source of her headache pain. Furthermore, improvement in such symptoms with weaning of opiates doses to one small dose of oxycodone and the control of pain using oral acetaminophen and NSAIDS was reassuring. If the pain was due to one of the above conditions or a serious medical complication, the pain would likely not improve with such an approach and would continue to worsen in addition to causing further systemic manifestations of disease.

This patient was the first patient reported with Alport Syndrome and intractable headaches without evidence of acute or chronic brain lesions on brain MRV (Magnetic Resonance Venography), MRI (Magnetic Resonance Imaging), MRA (Magnetic Resonance Angiography) and CT (Computed Tomography) imaging whose headache pain was reduced by over 60% in severity by oral and intravenous analgesics in the inpatient setting. No Cortical Spreading Depression or Spreading Depolarization was commented on within these imaging reports. This patient will need close attention under her Nephrologist to ensure adequate maintenance of her disease and prevention and delayed progression of ESRD. Additionally, it is important to recognize that if further pain or headaches ensues, it should be approached and worked up individually. Although this patient had a negative inpatient workup for acute or chronic etiology of headache, she could develop such conditions on the future and they must not be disregarded if severe headache pain occurs again. Furthermore, treatment of such acute pain episodes should start with oral acetaminophen and/or NSAIDS without an immediate jump to opiates; opiates can be added and uptitrated as necessary. This approach ensures the maximum safety of the patient with the lowest risk of abuse, overdose and side effects of medications.

## Conclusion

New onset severe headaches in a young adult must be approached with a full diagnostic workup to rule out potentially fatal and treatable causes of such symptoms including acute hemorrhage, stroke, cerebral thrombosis, vasculitis, malignancy and acute autoimmune demyelinating disease. The treatment approach of an acute pain crisis in the inpatient setting should be approached conservatively with the goal of weaning patients off highly dosed, highly potent, long acting medications to low dose and infrequent oral-over-the-counter-analgesics. Also, caution must be taken not to combine medications that can potentiate certain disease processes in each patient, such as the use NSAIDs in chronic kidney disease; such use of medications should be under the strict guidance of a professional experienced specialist.

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