Overview on acute poststreptococcal glomerulonephritis in pediatrics

Abstract: Acute poststreptococcal glomerulonephritis (APSGN) is the most common kind of post-infectious glomerulonephritis and is caused by group A streptococcus (Streptococcus pyogenes). although the prevalence of PSGN has decreased in affluent nations, non-streptococcal species are becoming more common. and it is still the major cause of glomerulonephritis in children. APSGN can manifest itself in epidemic outbreaks or clusters of instances, as well as in single persons. Epidemic outbreaks have previously been documented as a result of upper respiratory or cutaneous streptococcal infections in various parts of the world. In developed nations, APSGN is now mostly a disease of the elderly, who are more likely to have disabling illnesses such as cancer, alcoholism, or diabetes. Children between the ages of 3 and 12 (with a peak incidence between the ages of 5 and 6 years) and seniors over the age of 60 are the most commonly affected. The pathophysiology of APSGN is complicated by inflammation. (APSGN) often occurs one to two weeks after a throat infection and three to five weeks after a skin infection. Hematuria, edoema, azotemia, and hypertension are the most common clinical signs. Loop or thiazide diuretics, are the most effective therapy for hypertension and edoema in PSGN. In this review we'll be looking at the disease causes, epidemiology, presentation and treatment.

Introduction:

Acute poststreptococcal glomerulonephritis (APSGN) is the most common kind of post-infectious glomerulonephritis and is caused by group A streptococcus (Streptococcus pyogenes) or, less commonly, groups C or G streptococcus. The progress of dark and scanty urine was a feared complication of scarlet fever epidemics in the fourteenth century, according to Becker and Murphy (Becker & Murphy, 1968), and clinical descriptions of the "dropsy that follows scarlet fever" have appeared in medical literature since at least 1812. APSGN was most likely the cause of Wolfgang Amadeus Mozart's death in 1791. [1,2,3,4]

Though the prevalence of PSGN has decreased in affluent nations, non-streptococcal species are becoming more common. The two most common antigens linked to the pathophysiology of PSGN are nephritis-associated plasmin receptor (NAPlr) and streptococcal pyrogenic exotoxin B (SPeB). They have an

affinity for plasmin and glomerular proteins, as well as activating the alternative complement pathway, resulting in hypocomplementemia. The clinical manifestations of PIGN might range from minimal symptoms to renal failure needing dialysis . [5]

Poststreptococcal glomerulonephritis (PSGN) is the most prevalent kind of acute glomerulonephritis in children, which mainly develops between the ages of 3 and 12. In around 15% of cases, PSGN develops after infection with a nephrotogenic strain of group A Streptococcus (GAS). PSGN is currently recognised as a nonsupporative, immunologically induced complication of GAS. Gross hematuria affects 30–70% of patients, but microscopic hematuria affects all patients, and hypertension affects 70% of patients who require hospitalisation. In 10% to 1% of children hospitalised for PSGN, severe PSGN problems, hypertensive encephalopathy, and fast progressive glomerulonephritis occur. When hypocomplementemia is evident during acute glomerulonephritis and recovers spontaneously within a few months, the diagnosis is likely. Over the course of a year, we saw a case series of severe PSGN patients at a paediatric tertiary care institution. [6]

The prevalence of poststreptococcal glomerulonephritis (PSGN) is decreasing globally, despite the fact that it is still the major cause of glomerulonephritis in children, according to substantial study data. The overall drop in PSGN prevalence has been mostly attributed to a major decrease in pyoderma during the previous half-century, with postpharyngitic PSGN being more frequent in industrialised countries. The latency interval between streptococcal infection and the development of nephritis is a characteristic of PSGN, with this time lasting 1 to 2 weeks with pharyngeal infections or 2 to 6 weeks with cutaneous infections, based on mostly agreement due to a paucity of relevant clinical research. [7]

Epidemiology:

APSGN can manifest itself in epidemic outbreaks or clusters of instances, as well as in single persons. Epidemic outbreaks have previously been documented as a result of upper respiratory or cutaneous streptococcal infections in various parts of the world, including the Red Lake Indian Reservation in Minnesota, Port of Spain, Venezuela, and Australia's Northern Territory. The most recent epidemics were in the Northern Territory of Australia, where pyoderma developed after

infection with emm55 group A streptococcus, and in the rural region of Nova Serrana, Brazil, where unpasteurized milk obtained from cows with mastitis caused by Streptococcus zooepidemicus was consumed. [1]

PSGN incidence has decreased dramatically in industrialised nations such as the United States, the United Kingdom, Central Europe, and Japan during the last three decades. The use of antibiotic prophylaxis and the enhancement of sanitary conditions are the reasons for this progress. PSGN has grown more common in adult patients suffering from chronic disabling disorders in these industrialised countries. [5] Streptococcus zooepidemicus has been linked to clusters of infections (5–15 patients) in disadvantaged communities in developed nations over the previous two decades. [1] PSGN is more common in underdeveloped nations, owing to a rise in skin diseases (pyoderma). Though the frequency of glomerulonephritis (GN) in children in the United States has decreased in industrialised nations, it is still the most prevalent cause of GN in children in the United States. [5]

In developed nations, APSGN is now mostly a disease of the elderly, who are more likely to have disabling illnesses such as cancer, alcoholism, or diabetes. APSGN, however, continues to be a substantial health issue in developing countries. The most prevalent glomerulonephritis among children in underdeveloped nations and aboriginal cultures is endocapillary glomerulonephritis, which is thought to be caused by a post-streptococcal infection. [1] PSGN is also the leading cause of kidney damage in children in the Middle East, Africa, Australia, and the rest of the world. In underdeveloped nations, the yearly incidence of new cases of PSGN varies from 8.5 to 28.5 per 100,000 people. Around 97 percent of PSGN cases are recorded in low-income countries. [5] The incidence of APSGN in poor nations has been assessed by two independent investigations. According to Carapetis et al., the yearly burden of APSGN in poor nations is 9.3 cases per 100,000 persons, based on an analysis of 11 population studies. Using reports of paediatric acute renal failure related to glomerulonephritis, the incidence of APSGN in developing countries was assessed. thus it was presumed that the instances of acute glomerulonephritis were APSGN, which was mentioned explicitly in most but not all of the series. Because they were examined at a referral hospital and admitted to the critical care unit, if one was available, and then dialyzed, these individuals had severe renal failure. [1,8,9]

PSGN clinical symptoms are more prevalent in males than females, with a 2:1 ratio. The incidence of subclinical PSGN, on the other hand, is about equal in both sexes. There is no evidence that racial characteristics plays an effect. Children between the ages of 3 and 12 (with a peak incidence between the ages of 5 and 6 years) and seniors over the age of 60 are the most commonly affected. [5]

In the modern age, no epidemiologic research on M types in PSGN have been reported. More severe illness may have been caused by other strains and virulence factors in the past. It's unclear if the elevated prevalence of severe PSGN will be limited to the year in question. Thrombocytopenia may also be linked to PSGN, albeit it is unclear if PSGN is the sole cause. Future patients with PSGN and low platelets may benefit from testing for thrombotic microangiopathies. Furthermore, knowing the M serotype of organisms that cause severe PSGN can assist determine whether a severe clinical course is caused by the infecting organism or underlying patient features. [6]

Etiology and pathogenesis:

Streptococcus pyogenes, a Lancefield serogroup A beta-hemolytic bacterium, is also known as group A streptococci. Surface M proteins, which serve as virulence factors, are used to classify Group A streptococci. M types 1, 4, and 25, as well as several M12 strains, are typical pharyngitis-associated nephritogenic strains. The near extinction of streptococcal pyoderma owing to increased hygiene and/or lower prevalence of skin infection related nephritogenic M serotypes is thought to be the cause of an apparent fall in the incidence of PSGN in the United States during the last 40 years. Since the near abolition of pyoderma-associated PSGN in industrialised nations, hardly little epidemiologic data on the M serotypes has been published. Prior reports of the emm 44 subtype reported in Patient D were not found. [6,10,11]

The pathophysiology of APSGN is complicated by inflammation. Immune complexes generated against nephrotic streptococcal antigen may circulate and deposit in the glomeruli, and APSGN is characterised by a decrease in circulating complement. Although immunoglobulin (Ig)-binding proteins on the streptococcal surface partially inhibit the traditional complement pathway, the alternative complement pathway is frequently active. As a result, C3 levels in blood tests are

often low, while traditional pathway activation and lowered C1 and C4 levels are only seen in 15–30% of individuals. [12,13,14,15]

In APSGN, the lectin–complement pathway may also be activated. In 10% of instances, despite considerable complement activation, normal complement levels can be found. The development of APSGN is also influenced by cell-mediated processes. Infiltration of lymphocytes and macrophages into the glomerulus, as well as cytokine production, are significant factors in renal damage. [12,16,17]

Clinical Presentation and diagnosis:

(APSGN) often occurs one to two weeks after a throat infection and three to five weeks after a skin infection. Hematuria, edoema, azotemia, and hypertension are the most common clinical signs, whether macroscopic or microscopic. It mainly affects youngsters between the ages of 4 and 14. Acute nephritic syndrome, nephrotic syndrome, rapidly progressive glomerulonephritis (RPGN), or subclinical nephrotic syndrome are all possible presentations. Hypervolemia can cause congestive heart failure, pulmonary edoema, and severe hypertension-induced encephalopathy in the acute phase. [12]

Other causes of glomerulonephritis should be examined if there are concurrent infection and nephritis symptoms. PSGN is one of a small number of nephritic illnesses associated with hypocomplementemia, according to experts (low C3 level). C3 deficiency is detected in more than 90% of PSGN cases, and it usually occurs before a rise in antistreptolysin O titers. C3 and C4 measurements can also be used to rule out other causes of acute nephritis. The primary consequences of PSGN (hypertension, edoema, gross hematuria, and reduced renal function) are highest in the first 7 to 10 days of illness, based on mostly agreement due to a paucity of relevantclinical trials. As a result, extreme caution is required at this time to avoid negative consequences. [7]

APSGN is still one of the leading causes of acute renal failure and hospitalisation in children, despite the favourable short-term prognosis. Furthermore, after 15–18 years of follow-up, 15% of children have abnormal urinalysis and 1% have azotemia, and the incidence of long-term decreased glomerular filtration

rate (GFR; 60 mL/min/1.73 m2) is also elevated in APSGN. According to the current evidence, the degree of renal involvement is the most important factor of long-term prognosis in APSGN. [12]

Research Data and Discussion:

Research was conducted to determine the prevalence of APSGN among children in Hawai'i, to identify individuals at higher risk for APSGN, and to identify risk variables associated with the length of hospitalisation by APSGN subtype. The incidence of APSGN in Hawai'i was found to be greater than 4 per 100,000 children, which is much higher than the 0.3 per 100,000 children seen in high-income nations. This elevated frequency might be attributed to Hawai'i's distinct ethnic group makeup, and hence the unusual immunologic response of Hawai'i's children (especially Pacific Islanders, who make up 62 percent of APSGN patients in this research but only make up 10% of the overall population). In addition, nephropathogenic Streptococcus pyogenes strains may be more prevalent in Hawai'i. Children with greater serum creatinine levels and lower bicarbonate levels spent considerably more time in the hospital. [18]

In a study that was done to find the probable risk factor(s) for lower glomerular filtration rate (GFR) in people with APSGN. In this study children with an average age of 8.20 years was presented. Edema (86.7%), macroscopic hematuria (82.7%), and hypertension are the most prevalent symptoms (73.3 percent). On laboratory evaluation, (37.3%) had hypoalbuminemia, (77.3%) had proteinuria, (26.7%) had elevated C-reactive protein (CRP), There were 22 children having a GFR of less than 90 mL/min/1.73 m2 (29.3 percent). Patients with elevated CRP, hypoalbuminemia, and low C4 had a considerably greater risk of reduced GFR. In addition, individuals with low GFR had considerably higher WBC counts, neutrophil counts, and neutrophil/lymphocyte ratios (NLR). [12]

Loop or thiazide diuretics, which may also address hyperkalemia, are the most effective therapy for hypertension and edoema in PSGN, according to some study data and agreement. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may reduce blood pressure, however they can cause hyperkalemia and slow the recovery of renal function. The prognosis for PSGN, even in the long run, is positive, according to some study data and agreement. Despite being the most common of the paediatric glomerulonephritides, it

seldom leads to chronic kidney disease; nonetheless, in less than 10% of individuals, persistent microscopic hematuria and proteinuria may be detected. [7]

Infection should be treated if it is present at the time of diagnosis. The delivery of preventative antibiotic therapy to household members of index cases has been found to reduce the number of cases in epidemic scenarios and high-risk areas. The consumption of salt and liquids must be restricted in patients with acute nephritic syndrome. Aldosterone antagonists can cause hyperkalemia, and thiazide diuretics are ineffective. Nifedipine may be beneficial in situations of severe hypertension. Hyperkalemia is a side effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. In rare circumstances, nitroprusside may be required to treat hypertensive encephalopathy. [1]

Several streptococcal antigens that may have a pathogenic role in acute poststreptococcal glomerulonephritis have recently been identified. Streptococcal plasmin receptor and streptococcal pyrogenic exotoxin B, both related with nephritis, are presently regarded important potential nephritogens. A greater frequency of host susceptibility factors, such as HLA-DRB1*03011, has been reported in individuals with acute post-streptococcal glomerulonephritis. New clinical correlations with the condition include reversible posterior leukoencephalopathy and autoimmune hemolytic anaemia. [19]

APSGN in children has a favourable prognosis, although serious systemic complications and renal failure might occur during the follow-up period. Increased inflammatory markers (WBC, CRP, neutrophil count, and NLR) as well as decreased C4 and hypoalbuminemia may be risk factors for the severity of renal involvement. In such children, a drop in C4 may be a risk factor for a decrease in GFR. [12]

In poor countries and among disadvantaged people, severe group A streptococcal illness, especially acute poststreptococcal glomerulonephritis, is still a leading cause of morbidity and mortality.

Conclusion:

There’s no doubt that Acute poststreptococcal glomerulonephritis (APSGN) is one of the most serious cases that can challenge the medical staff. Its real danger

opposed upon children mainly and elder patients with co-morbidities. The disease incidence has decreased recently due to improvement of treatment method and usage of effective antibiotics. However, it's still imposing a challenge, we hope for better treatment options in the future and new more effective and safe antibiotics regiments that will help combat the disease.

References:

1. Rodriguez-Iturbe B, Haas M. Post-Streptococcal Glomerulonephritis. 2016 Feb 10. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes : Basic Biology to Clinical Manifestations [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK333429/
2. Becker C. G., Murphy G. E. The experimental induction of glomerulonephritis like that in man by infection with Group A streptococci. The Journal of Experimental Medicine. 1968;127(1):1–24.
3. Zegers R. H., Weigl A., Steptoe A. The death of Wolfgang Amadeus Mozart: an epidemiologic perspective. Annals of Internal Medicine. 2009;151(4):274–278.
4. Wells, C. (1812). Observations on the dropsy which succeeds scarlet fever. In Transactions Of A Society For The Improvement Of Medical And Chirurgical Knowledge, Volume 3 (pp. 167-186). Ghent: Ghent University
5. Rawla P, Padala SA, Ludhwani D. Poststreptococcal Glomerulonephritis. [Updated 2021 Sep 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538255/
6. Ayoob RM, Schwaderer AL. Acute Kidney Injury and Atypical Features during Pediatric Poststreptococcal Glomerulonephritis. Int J Nephrol. 2016;2016:5163065. doi: 10.1155/2016/5163065. Epub 2016 Aug 23. PMID: 27642522; PMCID: PMC5011525.
7. VanDeVoorde RG 3rd. Acute poststreptococcal glomerulonephritis: the most common acute glomerulonephritis. Pediatr Rev. 2015 Jan;36(1):3-12; quiz 13. doi: 10.1542/pir.36-1-3. PMID: 25554106.

8. Carapetis J. R., Steer A. C., Mulholland E. K., Weber M. The global burden of group A streptococcal diseases. The Lancet Infectious Diseases. 2005;5(11):685–694.
9. Rodríguez-Iturbe B., Musser J. M. The current state of poststreptococcal glomerulonephritis. Journal of the American Society of Nephrology. 2008;19(10):1855–1864.
10. Cunningham M. W. Pathogenesis of group A streptococcal infections. Clinical Microbiology Reviews. 2000;13(3):470–511. doi: 10.1128/cmr.13.3.470-511.2000.
11. Schwartz B., Facklam R. R., Breiman R. F. Changing epidemiology of group A streptococcal infection in the USA. The Lancet. 1990;336(8724):1167–1171. doi: 10.1016/0140-6736(90)92777-f.
12. Demircioglu Kılıc B, Akbalık Kara M, Buyukcelik M, Balat A. Pediatric post-streptococcal glomerulonephritis: Clinical and laboratory data. Pediatr Int. 2018 Jul;60(7):645-650. doi: 10.1111/ped.13587. Epub 2018 Jun 26. PMID: 29729114.
13. Perez-Caballero D, Garcia-Laorden I, Cortes G, Wessels MR, de Córdoba SR, Albertí S. Interaction between complement regulators and Streptococcus pyogenes: Binding of C4b-binding protein and factor H/factor H-like protein 1 to M18 strains involve two different cell surface molecules. J. Immunol. 2004; 173: 6899–904.
14. Berge A, Kihlberg BM, Sjöholm AG, Björck L. Streptococcal protein H forms soluble complement-activating complexes with IgG but inhibits complement activation by IgG-coated targets. J. Biol. Chem. 1997; 272: 20774–81.
15. Levy M, Sich M, Pirotzky E, Habib R. Complement activation in acute glomerulonephritis in children. Int. J. Pediatr. Nephrol. 1985; 6: 17–24.
16. Hisano S, Matsushita M, Fujita T, Takeshita M, Iwasaki H. Activation of the lectin complement pathway in poststreptococcal acute glomerulonephritis. Pathol. Int. 2007; 57: 351–7.
17. Strife CF, McAdams AJ, McEnery PT, Bove KE, West CD. Hypocomplementemic and normocomplementemic acute nephritis in children: A comparison with respect to etiology, clinical manifestations, and glomerular morphology. J. Pediatr. 1974; 84: 29–38.

18. Limm-Chan B, Musgrave J, Lau R, Ahn HJ, Nguyen L, Kurahara D. Incidence of Acute Post-Streptococcal Glomerulonephritis in Hawai'i and Factors Affecting Length of Hospitalization. Hawaii J Health Soc Welf. 2020 May 1;79(5):149-152. PMID: 32432220; PMCID: PMC7226310.
19. Ahn SY, Ingulli E. Acute poststreptococcal glomerulonephritis: an update. Curr Opin Pediatr. 2008 Apr;20(2):157-62. doi: 10.1097/MOP.0b013e3282f45bcf. PMID: 18332711.