# OCCURRENCE OF ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS IN CLUSTERS

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## SYNOPSIS

**From 11 index cases of acute post-streptococcal glomerulonephritis (APSGN), 8 families consisting of 48 members were studied. Two additional cases of overt nephritis, and 17 cases that were suggestive of subclinical nephritis were discovered. The latter included microscopic haematuria and proteinuria, abnormal complement profile or both. Multiple cases of overt and subclinical nephritis within the same family were common, and was usually due to streptococcal skin infection with scabies infestation. There are at least 3 different strains of nephritogenic streptococci in Singapore by T-typing, and one of them is M55. The anti-deoxyribonuclease B was found to be superior than the anti-streptolysin 0 as an index of streptococcal infection. Low total serum complement and C3 were found in overt nephritis, whilst $C_{1q}$ and $C_4$ could be depressed in the subclinical cases. This clustering of abnormalities was attributed to large families and adverse socio-economic conditions. In APSGN, it is important to treat family members for streptococcal infections and scabies infestation, and to screen for subclinical nephritis. For the latter, the use of urine analysis and serum complement profile are advocated.**

## INTRODUCTION

Acute post-streptococcal glomerulonephritis (APSGN) is known to affect several members in the same household occasionally (Goldsmith, Cowan and Gooder, 1958). The disease could also reach epidemic proportions within closed communities (Earle, 1973; Anthony, Perlman and Wannamaker, 1967). However,

the extent to which it can affect the rest of the household in a non-epidemic setting is seldom investigated. We set forth to study this and to determine the pattern of involvement of the family members.

## PATIENTS AND METHODS

Over an 18 month period from July 1975 to January 1977, the family members of 11 patients, who were hospitalised for APSGN, were investigated for the same disease. The diagnostic criteria for overt APSGN were: (1) Presence of haematuria, proteinuria, hypertension and signs of fluid overload. (2) B-haemolytic streptococcal Group A were isolated from throat and/or skin swabs. (3) Hypocomplementaemia (low total complement and/or $C_3$). (4) Complete recovery on follow-up. All these were seen in the 11 index cases coming from 8 different families. Six of these were Chinese and the rest Indian in origin. The index cases were mainly children. From these we managed to study 48 family members, consisting of 14 parents and 34 siblings. The sex and age distributions of the index cases and family members are shown in Table 1.

The family members were screened as outpatients within 1 week of hospitalisation of the index cases. Apart from clinical assessment, they had the following tests: (1) Urine for microscopic examination and protenuria on 2 occasions at intervals of 1 to 2 weeks apart. (2) Serum complement profile (total complement activity, $C_{1q}$, $C_4$, $C_3$). (3) Anti-streptolysin 0 (ASO) and anti-deoxyribonuclease B (ADNase B) titres, and (4) Throat and/or skin swabs. These and other routine tests had already been carried out in the index cases.

Total complement activity was measured by the haemolytic activity at 50% lysis. Serum $C_{1q}$, $C_4$ and $C_3$ were measured by single radial immunodiffusion. Normal values were obtained from 38 adult normal controls.

ASO titre was determined by the sphectrophotometer method, with end-point at 50% lysis. ADNase B was based on the method by Kleen et al (1969). Normal values for ASO and ADNase B were obtained from 71 adult normal controls.

B-haemolytic streptococci were isolated and group identification was carried out based on Lancefield's method (1933). T-typing of group A streptococci was done according to Griffith's method (1934) using commercially available rabbit hyperimmune sera. M-typing was carried out by courtesy of the WHO International Collaborating Centre for Reference and Research in Prague, Czechoslovakia, using precipitation reactions.

## RESULTS

Two additional cases of overt APSGN were discovered amongst the siblings. Subclinical abnormalities were observed in 17 cases: 5 had microscopic haematuria and proteinuria, 11 had abnormal complement profiles and 1 had both (Table 2). The siblings, as well as the parents, were affected.

### Serum complement profile

All the 13 overt cases had both low total complement activity and $C_3$, but $C_{1q}$ and $C_4$ were normal. For the 12 subclinical cases with complement abnormalities, the pattern was different, as hypo-complementaemia could affect any of the 4 components (Figure 1). They consisted of isolated depression of $C_3$ (5 cases), $C_{1q}$ (3 cases), total complement activity (2 cases) and $C_4$ (1 case). In 1 instance, both $C_{1q}$ and $C_3$ were low. In the 6 cases with low serum $C_3$, the mean serum $C_3$ was 41 ± 13.8 mg% (± S.D.). This was significantly higher than the mean $C_3$ of 14.9 ± 9.2 mg% (± S.D.) in all the overt cases ($p < 0.005$).

### Bacteriological studies

The results were for all the index cases and the affected family members. About 70% of the skin swabs were positive for B-haemolytic streptococci (Table 3). All except 1 grew the group A organisms. Of the throat swabs, 26.5% were positive. More than half were group

**TABLE 1: APSGN — FAMILY STUDY**

| | | | | |
|---|---|---|---|---|
| **Families** (8) Chinese 6 Indian 2 | | | | |
| **Index Cases** (11) | **Male** | **Female** | **Total** | **Mean Age (yrs) (Range)** |
| | 5 | 6 | 11 | 11.7 (5—16) |
| **Family Members** (48) | | | | |
| Parents | 4 | 10 | 14 | 38.1 (29—60) |
| Siblings | 25 | 9 | 34 | 11.9 (3—22) |

**TABLE 2: APSGN — Results of Family Study**

| Findings | Parents | Siblings | Total |
|---|---|---|---|
| | No. of Cases | | |
| I. Overt APSGN | — | 3 | 2 |
| II. Subclinical— | | | |
| A. Mic. haematuria and proteinuria | 2 | 3 | 5 |
| B. Abnormal complement profile | 2 | 9 | 11 |
| C. Both (A) & (B) | — | 1 | 1 |
| Total | 4 | 15 | 19 |

**TABLE 3: APSGN — Bacteriological Study**

| Site | No. Examined | Positive Culture (%) | Organisms (No. of Cases) | |
|---|---|---|---|---|
| Skin | 23 | 16 (69.6%) | B haemolytic strept. | Group A (15) |
| | | | B haemolytic strept. | Group C (1) |
| Throat | 49 | 13 (26.5%) | B haemolytic strept. | Group A (7) |
| | | | B haemolytic strept. | Group G (4) |
| | | | B haemolytic strept. | Group C (2) |

A and the rest group G and C streptococci. The 22 cases of group A infection accounted for either overt APSGN or subclinical abnormalities in 21 instances (Table 4). Skin infection was responsible for 71.4% of these cases. The remaining case was also due to skin sepsis. The clinical consequence was unknown, as blood tests could not be carried out.

Streptococcal sero-typings were preformed in 14 cases. Three patterns of T-typing were obtained: (1) 8/25/IMP/9 (8 cases), (2) 3/13/B3264 (4 cases) and (3) 5/12/27 (2 cases). For M-typing, most of the cases were not typable. In 3 instances, M55 was identified, corresponding to the T-typing of 8/25/IMP/9.

The nature of the nephritogenic streptococcal infection is best illustrated by some of the affected members in 2 families (Table 5). In the J. family, 2 members (M.J. and I.J.) had overt APSGN. In the other member, the consequence of infection was unknown, as referred to above. All of them had streptococcal skin infections of the same T-type. The overt cases were due to M55. In the C. family, streptococci of the same T-type caused both skin and throat infections in an overt case (C.K.O.), and also skin infection in a subclinical case (C.K.W.). Another subclinical case (C.K.S.) had throat infection due to streptococci of a different T-type.

### ASO and ADNase B titres

Only 3 cases of streptococcal infections had raised ASO titre, whereas for ADNase B, 14 cases were above normal (Figure 2). When the cases were divided into skin or throat infections, the superiority of ADNase B as a index of streptococcal infection remained.

**TABLE 4: B Haemolytic Streptoccoci Group A Infections (22 Cases)**

| Consequences | Site of Infection | | Total (%) |
|---|---|---|---|
| | Skin | Throat* | |
| Overt APSGN | 10 | 3 | 13 (61.9%) |
| Subclinical Abnormalities - | 5 | 3 | 8 (38.1%) |
| Total (%) | 15 (71.4%) | 6 (28.6%) | 21 (100%) |

* 1 case ? Subclinical Abnormalities

### Overall findings

Overt APSGN was present in as many as 4 out of a family of 8 (Figure 3). Subclinical abnormalities affected every family and in 4 families, 3 members were involved. Streptococcal infection was found in 6 out of 8 in 1 instance. Skin infections were often associated with scabies infestation. The overall attack rate for overt APSGN amongst all the family members was 1 in 4.5, and 1 in 3.5 for the subclinical group. The combined abnormalities affected 1 in 2. B-haemolytic streptococcal infections had the same attack rate.

### Progress

Both streptococcal infections and scabies infestations were actively treated. The overt cases recovered completely within 6 months, whereas the subclinical abnormalities disappeared in 3 months.

## DISCUSSION

The number of abnormalities in the 8 families are quite astonishing. Thus following infections by nephritogenic streptococci, a spectrum of manifestations could occur (Figure 4). This ranged from full-blown APSGN on the

**TABLE 5: Streptococcal Infections**

| Patients | Consequences | Specimen | T Typing | M Typing |
|---|---|---|---|---|
| J.Family | | | | |
| M. F/5 | APSGN | Skin | 8/25/IMP/9 | 55 |
| I. M/12 | APSGN | Skin | 8/25/IMP/9 | 55 |
| S. M/9 | ? | Skin | 8/25/IMP/9 | —ve |
| C. Family | | | | |
| K.O. M/9 | APSGN | Skin | 8/25/IMP/9 | 55 |
| K.O. M/9 | APSGN | Throat | 8/25/IMP/9 | —ve |
| K.S. M/10 | Subclinical | Throat | 3/13/B3264 | —ve |
| K.W. M/15 | Subclinical | Skin | 8/25/IMP/9 | —ve |

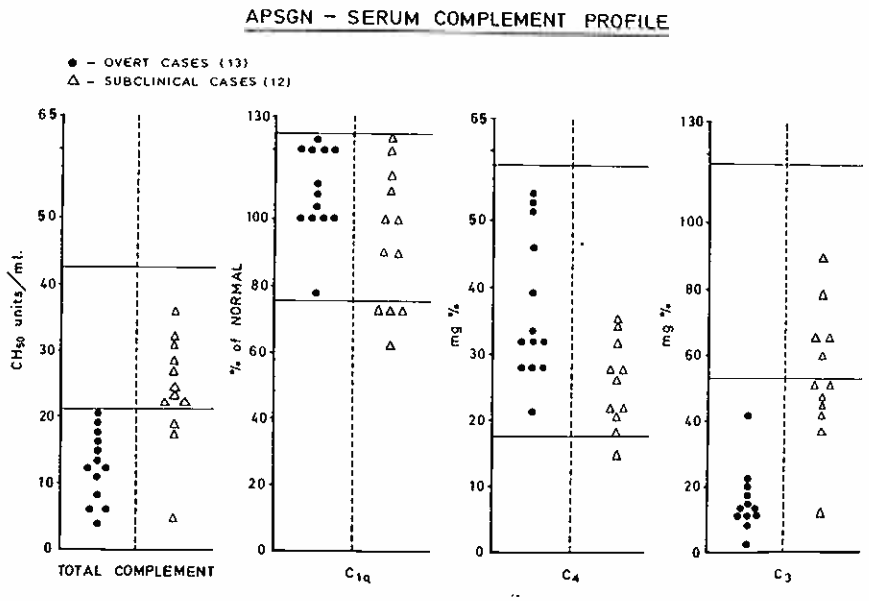


**Fig. 1.** Serum complement profile in overt APSGN (13 cases) and subclinical group (12 cases).

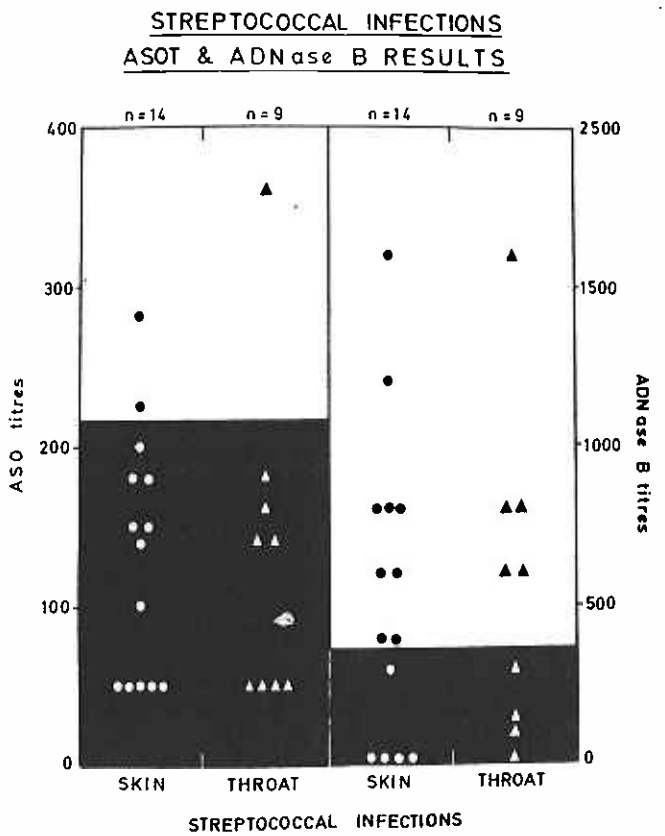


**Fig. 2.** Correlation of ASO and ADNase B titres with group A B-haemolytic streptococcal skin and throat infections.

one hand to just asymptomatic transient urine abnormalities on the other. In between, there were overt cases with milder clinical manifestations, and subclinical cases with complement abnormalities, or both urine and complement abnormalities. Similar asymptomatic findings were observed by Derrick et al (1970) in a study of 7 families, and postulated that these denote subclinical nephritis. The combined attack rate for overt and subclinical nephritis in his series was also 1 in 2, an equal number of clinical and subclinical cases being seen. In a familial outbreak of APSGN studied by Lange (1973), histological evidence of nephritis was obtained in 2 siblings who had asymptomatic microscopic haematuria and low total complement. For subclinical cases with isolated urine or complement abnormalities, histological proof has not yet been forthcoming.

The occurrence of multiple cases of overt and subclinical nephritis in the same family is not unusual in an epidemic. As many as 4 could be found within the family (Anthony, Perlman and Wannamaker, 1967). This is, however, uncommon in a sporadic setting, although Goldsmith et al (1958) reported 4 overt cases in a family of 10. In this study of selected families based on sporadic index cases, subclinical cases were seen in all 8 families (Figure 3). In a family of 8, there were 4 overt cases. A fifth member had subclinical abnormalities. In another family of 12, there were 3 overt and 3 subclinical cases.

In overt APSGN, the complement profile is known to consist of low serum $C_3$, $C_4$ may be transiently low, but $C_1$ and $C_{1q}$ are normal. In the subclinical cases, although low $C_3$ is a recognised feature, the other complement components have never been studied. Our findings indicate that $C_{1q}$ or $C_4$ could also be depressed in the early and thus subclinical cases, and that by the time the disease becomes clinically overt, these early components would return to normal. An alternative, but less likely, explanation is that different complement pathways are pursued—the overt cases follow the alternate but the subclinical cases the classical pathway. Low $C_3$ occurred in only 6 out of 12 subclinical

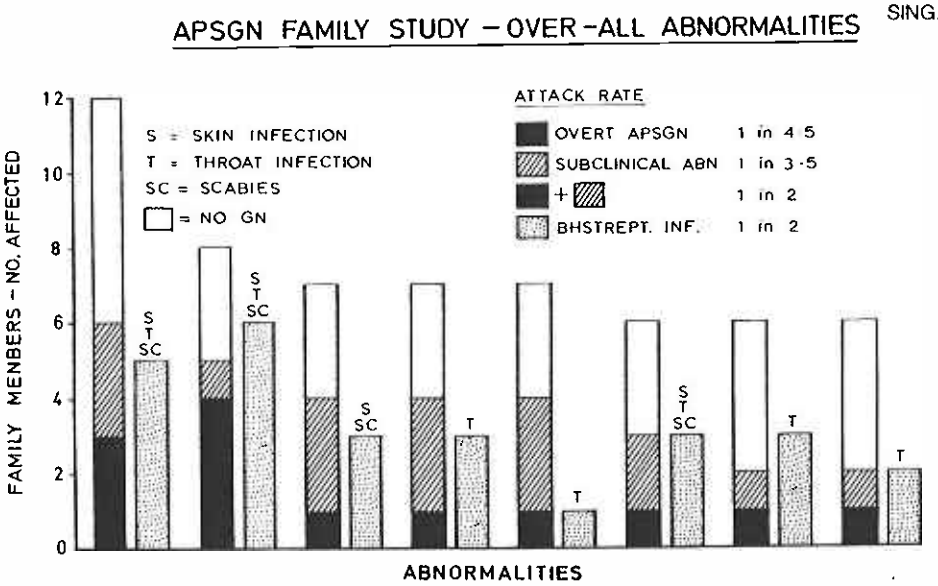


**Fig. 3.** Overall findings in 8 families of patients with APSGN.

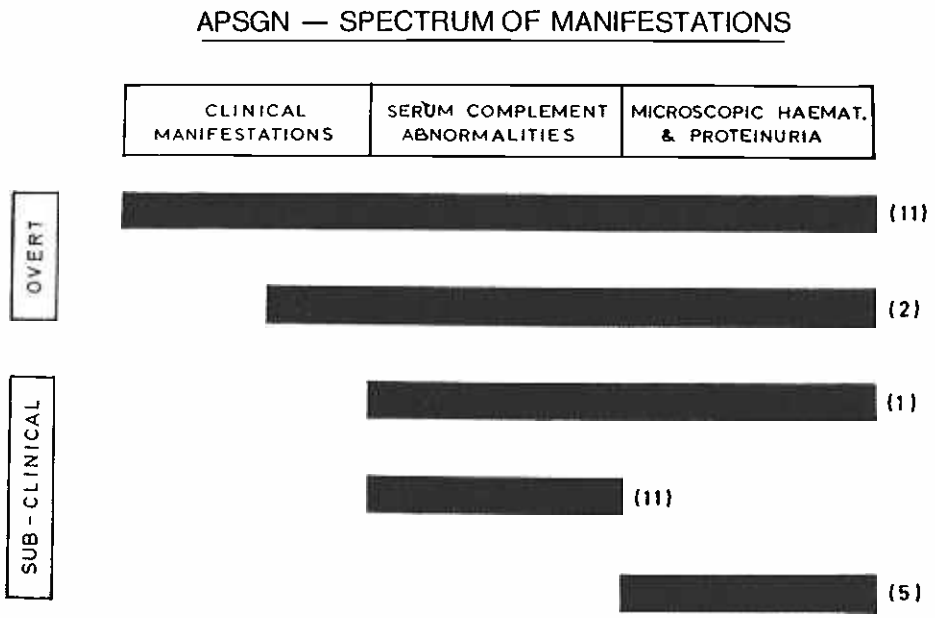


**Fig. 4.** Spectrum of manifestations following infections by nephritogenic streptococci.

cases with abnormal complement profiles, and the depressions were significantly less than the overt cases. We therefore advocate that to detect this subclinical group, all 4 complement components must be determined and not $C_3$ alone. For the overt cases, measurement of either $C_3$ or total complement activity would suffice.

There are at least 3 different strains of nephritogenic streptococci in Singapore as identified by T-typing. One of these is M55. In this study, only 3 out of 14 strains of group A streptococci were M-typable. This is not surprising as only 30-50% of all group A organisms are M-typable (Rotta, 1972). The failure of typing is due to insufficient quantity of M protein in the bacteria, or the presence of new antigenic strains. Skin infection was definitely more important than throat in Singapore. Scabies infestation, by virtue of its multiple and pruritic lesions, played a major part in spreading the disease amongst the family members. Thus, in the J. family, the same strain of nephritogenic streptococci circulated within the family causing different manifestations (Table 5). On the other hand, within the C. family, there was more than 1 strain of streptococci, and that both skin and throat were vulnerable.

In our experience, the ASO response to streptococcal infections was very low (Figure 2). This was also the finding of Earle et al (1973), and could be attributed to the fact that about 15% of the strains do not make streptolysin 0, and therefore, do not induce an ASO response. Another explanation is that in skin infection, the

skin lipids may modify antibody response. In our cases, poor ASO response was seen in both skin and throat infections. We found that irrespective of the site of involvement, the ADNase B was a better index of infection than the ASO (Figure 2). This was also confirmed by other workers (Dillon, 1972).

The occurrence of overt and subclinical nephritis in clusters in these 8 families was mainly attributed to large families, over-crowding, hot climate and other adverse socio-economic factors. Thus, apart from treating streptococcal infections and scabies infestation, socio-economic problems also need to be solved.

Our findings are of epidemiological importance, and points to the need for screening and treatment of family members in APSGN for streptococcal infections, scabies infestation and for possible subclinical nephritis. For the detection of the latter, the use of urine analysis and serum complement profile are advocated. These findings also provide food for thought and pose an obvious problem. What is the outcome if the subclinical group is left alone? The possibilities remain that it may develop into overt nephritis or repeated attacks may cause the more chronic and serious types of glomerulonephritis. The answer may be forthcoming by further studies of this subclinical group.

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