ORIGINAL ARTICLE

Immune complex associated complications in the subacute phase of meningococcal disease: incidence and literature review

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Arch Dis Child 2003;88:927-930

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Accepted
3 January 2003

Aim: To determine the incidence of immune complex associated complications (IAC) after severe meningococcal disease (SMD) in a group of Dutch children admitted to a paediatric intensive care unit (PICU).

Methods: Retrospective chart analysis and follow up of 130 survivors of SMD admitted to PICU. Signs of IAC, inflammatory parameters, and temperature profile were reviewed.

Results: Of 130 children with SMD, 20 (15.3%) showed one or more of the three manifestations of IAC: 18 (13.8%) developed arthritis (effusion, with or without erythema/arthritis), 11 (8.4%) vasculitis, and five (3.8%) pleuritis. Eighteen of 20 (90%) patients with IAC had a secondary rise in temperature; in patients with no IAC this was 48 of 110 (43.6%). IAC was associated with leucocytosis in 82.3% versus 47.7% in patients without IAC, and with increased CRP in 86.6% versus 47.2% in patients without IAC. Leucocytes on admission were significantly lower in patients who would later develop IAC (mean 8.6 versus 13.8 $\times 10^9/l$).

Conclusion: IAC is a common complication of SMD, mainly occurring 4-10 days after systemic disease. IAC presents clinically as arthritis or vasculitis, mostly accompanied by secondary fever and raised inflammatory parameters.

Meningococcal disease is one of the most feared infections in children, due to its sometimes rapidly fatal course. Most of the research that has been done in recent years was directed at the pathophysiological mechanisms in the acute phase. Relatively little is known about complications occurring in the subacute phase (4-10 days after initial antibiotic treatment); the so-called type 3 immune complex hypersensitivity reactions, according to the classification of Gell and Coombs. Other examples of type 3 reactions include serum sickness and certain forms of glomerulonephritis. Antigen-antibody (immune) complexes cause an inflammatory reaction in tissue, leading to activation of complement and transmigration of polymorphonuclear leucocytes, resulting in tissue damage.

In meningococcal disease, type 3 reaction, further called immune complex associated complications (IAC), can present as arthritis, vasculitis, episcleritis, or pericarditis.¹ Nephritis is a very rare presentation. It usually takes 4-10 days after the onset of disease for the first symptoms and signs of IAC to develop. Apart from the local manifestations, a recurrence of fever is often observed.¹

A search in PubMed using the keywords reactive arthritis, pericarditis, episcleritis, and pleuritis combined with meningococcal disease revealed only 16 case reports,²⁻¹⁷ and nine articles^{1, 18-25} containing larger patient groups on IAC since 1960. Since 1981 there have been no studies reported on large patient groups. Most of the articles were on adults with meningitis, who were not admitted to intensive care units. Only Schaad,²³ Edwards and Baker,²⁴ and Voss and colleagues²⁵ studied children. In the past 20 years enormous progress has been made in the treatment of meningococcal disease in children, because of better paediatric intensive care unit (PICU) facilities. In our experience the incidence of reactive complications after meningococcal disease did not decline, thus the lack of recent publications is surprising.

The primary aim of this study was to determine the incidence of IAC after severe meningococcal disease in a group

of Dutch children admitted to the PICU; the secondary aim was to determine whether there is any correlation between IAC and fever, leucocytosis, and other infection parameters. We compared our findings to the available literature.

PATIENTS AND METHODS

Between January 1993 and August 2000, 152 children were admitted to the PICU of the Emma children's hospital/AMC for treatment of severe meningococcal disease (SMD).

The records of all children still alive 24 hours after PICU admission were studied retrospectively for history of type 3 reactions. Furthermore, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), maximal temperature, and white blood cell (WBC) count were noted for every day of hospital stay.

The diagnosis IAC was made clinically, according to the criteria summarised in table 1. Other possible causes, such as secondary infection, were sufficiently excluded by additional investigations (synovial fluid aspiration, bone scan, x ray examination).

A total of 133 children were still alive after 24 hours. Three patients were excluded because of lack of data, so the study group consisted of 130 children. All patients had the typical clinical presentation of meningococcal disease. In 70% of patients positive cultures were found. Most patients had systemic disease: sepsis with or without meningitis; some patients had only meningitis.

The following definitions were used:

- Fever: a temperature over 38.5°C. For every 24 hours, maximal temperature was noted.

Abbreviations: CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IAC, immune complex associated complications; PICU, paediatric intensive care unit; SMD, severe meningococcal disease

Table 1 Diagnostic criteria for IAC

Manifestation	Symptoms
Arthritis	Arthralgia, joint swelling and redness, limitation of movement. Synovial fluid shows no bacteria, cultures remain negative.
Vasculitis	Pustular, bullous, nodular lesions or rash.
Pericarditis	Retrosternal pain, pericardial friction rub, ECG abnormalities, cardiac enlargement on x ray/ultrasound.
Pleuritis	Pleural effusion on x ray. Pain on inspiration. Impaired percussion. Pleural rub

Table 2 Patient characteristics of 130 evaluable patients

Patient	Characteristics
Age	3 y 8 mth (2 mth to 16 y 8 mth)
Males	64 (49.2%)
Deaths after 24 hours	3 (2.3%)
PRISM, mean (SD)	13.41 (10)
GMSPS, mean (SD)	6.35 (0.89)
Duration of PICU stay (days), median (range)	4 (1–46)
Duration of total stay (days), median (range)	14.5 (3–100)

- Leucocytosis: white blood cell count $\geq 20 \times 10^9/L$.
- Increased ESR: ≥ 20 mm in the first hour.
- Increased CRP: ≥ 50 mg/l.
- Secondary fever: a temperature over $38.5^\circ C$ after at least one afebrile day, excluding day of admission.

The following demographic data were collected: age, sex, diagnosis, severity of disease score (PRISM, GMSPS), duration of IAC stay, duration of hospital stay, and serogroup typing.

Standard treatment for meningococcal disease in our PICU is ceftriaxone 100 mg/kg once daily as empiric antibiotic treatment; this is switched to penicillin G as soon as bacteriological confirmation and results of susceptibility testing of *Neisseria meningitidis* are available.

Statistical analysis

Statistical methods used were Fisher's exact test for nominal variables and *t* test for comparing means of independent samples. Data were analysed with SPSS for Windows, release 8.0.0 (SPSS Inc., Chicago, IL). A *p* value ≤ 0.05 was considered significant.

RESULTS

Clinical parameters

The study group consisted of 130 patients. Table 2 presents patient characteristics. One hundred patients had systemic disease (76.9%; meningococcal sepsis with or without meningitis) and 30 (23.1%) had only meningitis. All patients responded to antibiotic therapy and no patient had persisting infections.

In 52 patients (40%), serogroup was recorded. In five patients serogroup typing revealed group C infection. No conclusions could be made about risk of IAC in different serogroup infections.

Twenty patients (15.3%) developed IAC during the subacute phase. There was no correlation between the development of IAC and age, sex, PRISM, or GMSPS.

IAC presented as arthritis in 18 (13.8%), vasculitis in 11 (8.4%), and pleuritis in five (3.8%). No clinical clues to indicate pericarditis or episcleritis were present in this study group. Twelve (60%) patients had more than one manifestation of IAC. Pleuritis presented on median day 4 (range 3–15), arthritis on day 7 (2–15), and vasculitis on day 11 (3–16). Arthritis/arthralgia involved the knee joint in ten cases (55%), the ankle in five cases (27.7%), and the elbow in two (11%). Six patients (33%) had polyarthritis. Seventeen patients

received some sort of additional treatment specifically aimed at IAC: ten were treated with additional antibiotics, four with NSAIDs, four received physiotherapy, and one patient was treated with steroids (dosage 1 mg/kg/day prednisone). Patients with IAC were admitted for longer than patients with an uncomplicated course, although not significantly so: 19.5 versus 13.8 days (*p* = 0.08).

Sixty six of 130 patients (50.8%) had secondary fever during the subacute phase of meningococcal disease. A secondary rise in temperature occurred in 18 of 20 patients in the IAC group (90%) and in 48 (43.6%) in the non-IAC group (*p* < 0.001). The median duration of fever was 3 days (range 0–23).

Thirteen of 130 patients (10%) developed an erythematous rash coinciding with the occurrence of secondary fever. These patients were not included in the IAC group as the clinical picture could not be differentiated from penicillin allergy.

Laboratory parameters

Fourteen of 17 (82.3%) patients had leucocytosis at the time of IAC complaints in the subacute phase versus 43/90 (47.7%) patients without IAC at the same time (*p* < 0.05). Patients who later developed IAC had a significantly lower leucocyte count at admission: mean 8.6 (95% CI 1.2 to 9.0) versus $13.8 \times 10^9/L$.

CRP was measured in 15 patients with IAC at the time of complaints; 13 children had values ≥ 50 mg/l. Of patients who did not develop IAC, 25/53 (47.2%) had CRP ≥ 50 mg/l (*p* < 0.01).

In all 13 patients with IAC where ESR was measured, it was increased beyond day 5. In patients without IAC, 46/56 (82.1%) had increased ESR, which is not significantly different from patients with IAC.

DISCUSSION

Recently, little attention has been given to complications of meningococcal disease in the subacute phase. This so-called type 3 immune complex hypersensitivity reaction presents as arthritis, vasculitis, episcleritis, or pericarditis. In our study 15.3% of children admitted to PICU developed IAC; this is a high incidence compared to that reported in the literature (table 3). Risk factors for development of type 3 hypersensitivity reactions named in the literature are severe disease,^{1–24} serogroup C infections,²⁶ and age (more IAC in adolescents or adults).^{1–23, 24} The fact that our patients were more severely ill compared to previous study groups may explain the higher

Table 3 Incidence of IAC reported in the literature compared to this study

Manifestation	Literature (%)	This study (%)
Total	6–11 ^{1 18 23 24}	15.3
Arthritis	1.6–16.6 ^{1 12 18 20 21 23–25}	13.8
Vasculitis	1.7–4.7 ^{1 24}	8.4
Pericarditis	0.9–19 ^{19 20}	–
Pleuritis	–	3.8

incidence of IAC. Most of our patients (76.9%) suffered from systemic disease (sepsis), in contrast to previous studies where most patients only had meningitis. This may be another explanation for the higher incidence of IAC, since these patients have a higher antigen load in the acute phase of the disease with a higher risk of developing IAC. No investigations into immune complexes and complement in blood and synovial fluid have been done in our study.

Arthritis was the most common presentation of IAC (13.8%), similar to that reported in the literature (table 3). As in the literature, the most involved joint in our patients with reactive arthritis was the knee, followed by the elbow and ankle. The time at which symptoms occurred in our study group, though slightly later, is comparable to that reported in the literature.

Pleuritis or pleural effusion is described in four case reports.^{6 16 18 19} No other references could be found, but it seems likely that the same mechanism that causes pericarditis can also cause pleuritis.

Edwards and Baker²⁴ found shock, purpura, leucocytosis $\geq 20 \times 10^9/l$, or leucopenia $\leq 5 \times 10^9/l$ on admission and persisting fever to be prognostic for IAC. In our group no correlation was found between leucocytosis on admission and IAC, but we did find a correlation with leucopenia on admission. We also found an association between IAC and leucocytosis in the subacute phase.

We found the occurrence of IAC is associated with secondary fever and secondary increased ESR and CRP, so persisting fever as mentioned by Edwards and Baker²⁴ is probably not a prognostic sign for development of IAC but a symptom of IAC per se, sometimes occurring before symptoms of arthritis/vasculitis.

In our group a high frequency of erythematous, non-purpuric rash was found (10%). Sometimes this was diagnosed as suspected penicillin allergy, but often diagnosis was unclear and symptoms subsided spontaneously. The frequency is too high to attribute all these cases to penicillin allergy (incidence normally 1%). We would like to argue that this may well be a manifestation of IAC, as van Deuren and colleagues²⁷ suggested, yielding an even higher incidence of 25% of IAC in our cohort.

Implications for clinical practice

This study shows that the incidence of secondary fever and raised inflammatory parameters in IAC is high; unfortunately this fact can not be used as a diagnostic tool since other complications like secondary infection and tissue necrosis are also accompanied by raised inflammatory parameters.

In patients with secondary fever or raised inflammatory parameters after SMD, IAC should always be considered in differential diagnosis. Symptoms and signs of IAC should be looked for on physical examination, since they can easily be missed, especially in severely ill patients. Fever can also be a sign of other complications such as secondary infection, subdural effusion, and persisting infection. In these cases extensive physical examination will reveal clues for the diagnosis, without the necessity of extensive additional investigations.

Primary meningococcal arthritis and allergic reaction to medication have to be excluded, preferably with as little additional and invasive diagnostics as possible. Primary meningococcal arthritis is a purulent arthritis with positive cultures that may occur without meningococcaemia.

Patients with IAC were admitted for a longer period than patients with an uncomplicated course. The difference is not significant ($p = 0.08$), but studying the charts of patients with IAC, it was often noted that children were hospitalised longer for antibiotic treatment or physiotherapy and additional investigations (bone scans). These measures are ineffective or unnecessary in IAC.

According to the literature, specific treatment for arthritis is not indicated, except for pain relief. The prognosis is excellent.^{15 23 24}

Contrary to other immune complex associated complications, pericarditis has a substantial mortality related to cardiac tamponade. Occasionally the effusion clears spontaneously, but usually treatment is required. Therapy consists of salicylates, steroids, pericardiocentesis, or a combination of these.⁶

Conclusions

IAC is a common complication of meningococcal infections in children. Arthritis is the most common manifestation of IAC. Apart from clinical symptoms, IAC presents with fever, leucocytosis, and increased CRP. IAC often leads to prolonged hospital stay and unnecessary diagnostic procedures and treatment.

In comparison to reports in the literature, this study shows that the incidence of reactive complications after meningococcal disease has not declined despite better treatment modalities, and that it also occurs in patients with sepsis.

Because of the limitations of a retrospective study, we recommend that a prospective study is done, in order to investigate risk factors, serogroup typing, and complement profile in IAC.

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