Epidemiology of pulmonary eosinophilia in rural south India—a prospective study, 1981–86

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Abstract
Study objective—The study aimed to determine the prevalence and incidence of pulmonary eosinophilia, with special reference to tropical pulmonary eosinophilia, in a rural community.

Design—This was a five year prospective study from 1981–86.

Setting—The study was conducted in four villages of Tamil Nadu in south India.

Subjects—The study population consisted of 24,950 subjects.

Measurements and main results—After being questioned about pulmonary symptoms, the selected subjects had peripheral blood examined for total leukocyte and eosinophil counts; stools for ova, cysts, and parasites; sputum for acid-fast bacilli, and chest radiography. Subjects with blood eosinophilia of ≥2000/mm³ were classified as having pulmonary eosinophilia. One of the 200 asymptomatic control subjects had blood eosinophilia >2000/mm³. Twenty two (7.7%) of a further 286 subjects selected at random were found to have microfilaremia. Between 1981 and 1984 the annual incidences of pulmonary eosinophilia were estimated at 4.1, 3.1, and 2.7/1000 while the prevalence rates were 6.4, 9.3, and 11.9/1000 respectively. This rising prevalence over time occurring simultaneously with a falling incidence suggests that the final incidence rate (2.7/1000) was likely to be the most accurate of the three estimated. At resurvey in 1986, 314 cases were classified as pulmonary eosinophilia giving a prevalence rate of 12.6/1000. Altogether 214 of them also had intestinal worm infestations, including 58 in whom eosinopenic remission was recorded after deworming alone. Eosinopenic remission was documented in 135 of 182 cooperative patients who were considered to have tropical pulmonary eosinophilia and agreed to be treated with diethylcarbamazine.

Conclusions—This study found that tropical pulmonary eosinophilia, either alone or with worm infestation, was a major cause or morbidity in this rural population.

Methods
An epidemiological study of pulmonary eosinophilia was carried out in a rural population of about 23,000 people residing in four villages of the K V Kuppam community development block about 20 to 25 km from Vellore in North Arcot Ambedkar District of Tamil Nadu between 1981 and 1986 as part of a research project on chronic pulmonary diseases in a rural community. K V Kuppam block has a population of a little over 100,000. It is one of the most economically backward blocks of North Arcot Ambedkar District. People living in this region work predominantly in agriculture. The major crops are groundnut, rice, millets, sugar cane, banana, and local vegetables.

The work of the present research project was based at the Rural Unit for Health and Social Affairs (RUHSA) of CMC Vellore, which serves the entire population of K V Kuppam block. The service is provided at three levels. The primary level is a village family care volunteer who visits...
every home to identify health problems, provides health education, motivates and follows up patients using the essential health services. She serves a population of approximately 800-1000 people. She is supported by a female health aide who covers a population of 5000-6000. Each of the two health aids is supported by a male rural community officer. For the present project, additional temporary paramedical and junior medical personnel were recruited.

A preliminary census completed on 31 March 1981 showed a total population of 22 947 distributed between 4262 families residing in 16 hamlets of these villages. The residents of the villages were interviewed by health visitors who filled in a questionnaire about respiratory symptoms. The following questions were asked routinely (in Tamil). Do you have:

(a) Persistent and disturbing cough which is more than ordinary, with or without sputum, for more than two weeks duration?
(b) Breathing difficulty with or without wheeze?
(c) Associated fever or any other symptoms which could remotely be attributed to respiratory system?
(d) Recollection of similar respiratory symptoms of cough with or without sputum and dyspnoea/ wheeze in the past which lasted for weeks and was considered more than ordinary.
(e) Anyone in your family with similar symptoms?

Question (e) requested additional information for discretionary use. Subjects with any of the other four symptoms (a)–(d) were asked to report to the health centre for further interview, examination, and investigation by medical personnel, including routine blood tests; examination of stool for ova, cysts, and parasites; sputum examination for acid-fast bacillus; and radiography of the chest.

A diagnosis of TPE was made where there was a history of paroxysmal, mainly nocturnal, cough with or without sputum; wheeze; an absolute blood eosinophil count of \( \geq 2000/\text{mm}^3 \); and successful remission with diethylcarbamazine therapy.

All patients with pulmonary symptoms and an absolute eosinophil count (AEC) of \( \geq 2000/\text{mm}^3 \) were included in the study as cases of PE. Patients who also had stool infestation with helminths or any other parasite were dewormed, after which blood eosinophil counts were repeated. Patients with persistent pulmonary symptoms and blood eosinophilia of \( \geq 2000/\text{mm}^3 \) after deworming were considered to have TPE and were treated with diethylcarbamazine. One of the following three regimens of diethylcarbamazine was given at random: regimen 1: 6 mg/kg body weight daily for three weeks; regimen 2: 12 mg/kg body weight daily for two weeks; regimen 3: 18 mg/kg body weight for one week.

At the end of the initial survey it was estimated that about a fifth of the population, consisting of 289 adults (12.6%) and about 4000 young school children, had repeatedly been out during the house visits and had not been directly questioned about respiratory symptoms. Information about these subjects was obtained from members of the family who were present, and from parents in the case of children. Prevalence was calculated as at June 30, after the first round of house to house visits had been completed. It was felt that the number of children with PE detected was disproportionately low and the possibility that relatively minor symptoms (as can happen in some case of PE) had not been reported by the parents was considered. Hence, from July 1981 onwards it was decided to visit the children at school. The 21 schools in the study area (which had 4282 pupils) were visited, taking care that subjects seen during house visits were not counted twice. To avoid absenteeism it was also decided to make full use of the local village workers of RUHSA: by visiting at odd hours of the day. In addition, all peripheral clinics run by RUHSA were fully utilised and the respective localities were visited by mobile medical vans with medical and paramedical personnel so that people could gather at fixed locations near their home at convenient times. Apart from asking all those with symptoms to gather at fixed locations, known subjects with symptoms were requested to attend the follow up clinics. From the second year onwards blood samples were collected and examined from all subjects with symptoms.

Because of our long-standing rapport with local people, and also the prospect of entirely free treatment and investigations, the response was encouraging. Even most of those who were uncooperative at first could be persuaded to come forward after subsequent visits, and at any given time a response greater than 95% of subjects with detected symptoms could be obtained. The success rate of initial examination and blood tests was not, however, reflected throughout subsequent investigations and follow up. As quite a few subjects with PE failed to report for follow up, collection of blood samples, and at later stages of the study collection of stool samples, were undertaken at the peripheral clinics when necessary and possible.

As TPE is believed to be of filarial origin and as it was not always possible to test night blood samples from PE patients for microfilaria, we conducted a filarial survey by a simple random sampling method to determine its prevalence in the study population. This technique gave each of the population an equal chance of being selected. A blood sample taken at night from these people was examined for microfilaria. A sample number of 286 was chosen as we assumed the attack rate of microfilaria to be 14%, which was the rate found in a recent filarial survey conducted at East Godavari District in Andhra Pradesh.11 Seven of 286 numbers allotted (members from two families, mostly young girls) did not participate. Seven extra numbers were allotted and blood samples were collected at night by prick method in all.

Another 200 consecutive consenting asymptomatic subjects had their venous blood collected and examined for blood eosinophil levels. Their stools were examined for ova, cysts, and parasites. Altogether, 210 persons were approached but 10 asymptomatic subjects did not consent to the tests.

After the initial survey, periodic visits were made by health visitors and any new patients detected were advised to attend the peripheral clinics and health centre for further examination and investigation. Thus, the entire population was...
kept under surveillance until 1984, at which time the incidence was calculated. After 1984, because of a shortage of personnel, frequent visits were not possible and any person with respiratory symptoms was advised to report to the health centre. At the end of the five year period another house to house survey of the population was conducted. This began in January and was completed by 31 March 1986. The population in the area was 24 950. Altogether 847 subjects (3-99%) were repeatedly away from home and could not be contacted. The prevalence rate was calculated for each thousand population considering an annual increase of 420 per year. Proportion tests and t-tests of significance were used wherever necessary.

Results
By June 1981, 261 subjects detected as having respiratory symptoms had been requested to report to the health centre. Twenty five (9-57%) were considered to have non-specific upper respiratory tract infection only and were rejected, nine (3-44%) were uncooperative, but the others agreed to further tests. Fifty three subjects were found to have blood eosinophilia >2000/mm$^3$; eight of them had a blood test but did not give a stool sample subsequently. By June 1982, out of 470 subjects with symptoms detected, only five (1-06%) failed to attend for further examinations. The others had blood tests and 96 were shown to have PE. Fourteen of the 96, however, did not subsequently give stool samples. By June 1983, 298 symptomatic subjects had been found. Seven (2-34%) did not respond. Seventy three subjects were found to have PE; six of them did not give a stool sample for examination. At the end of June 1984, 229 symptomatic subjects had been detected and requested to come for tests. Four (1-74%) failed to attend. Sixty five patients were found to have a blood eosinophilia >2000/mm$^3$; and a stool sample was collected from all but one of these. Because of improved methods in later years stool samples were collected and examined from all but two patients.

Further description of the patients with PE and of the subjects who were studied as control population for blood eosinophil levels are shown in table I. Out of a total 200 healthy control subjects, 109 males and 87 females had no respiratory or any other symptoms; examination of their stool showed no ova, cysts, or parasites. Their mean AEC levels were between 500-600/mm$^3$. Of the other two asymptomatic subjects, one had a blood eosinophilia of 1780/mm$^3$ with hookworm ova in the stool. Another subject had an AEC >2000/mm$^3$ (3045/mm$^3$) and had hookworm ova and a giardia cyst in the stool. This gave a false negative error rate of 5/1000.

Another 286 subjects selected by simple random sampling method had their samples of blood collected at night for filarial survey: 22 (7-7%) were found to be positive for microfilaria.

The age and sex distribution of the population and the prevalence rate of PE are shown in table II. There were 12 277 males and 12 673 females in the study population. Nearly 60-5% of males and 59-9% of females were below 30 years of age. A total of 15-2% of the males and 15-4% of the females were 50 years of age or above.

Altogether, 314 cases were broadly classified as PE: 174 of them were males and 140 were females. They had a mean (SD) age of 28-3 (16-0) years (range 3-70 years). Their mean (SD) total white blood cell count (WCC) was 12 923-2 (2145-1)/mm$^3$ and they had a very high mean AEC of 4245-8 (2847-6)/mm$^3$. The distribution of total blood eosinophil counts in the patients with PE by age group is shown in the figure. Most of the patients had blood eosinophil counts between 2000 and 4000/mm$^3$.

Overall, the prevalence of PE, as estimated by March 1986, was 12-6/1000 population. The
Table III Prevalence and incidence rates (/1000) of patients with pulmonary eosinophilia from 1981–84

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence (/1000)</th>
<th>Incidence (/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>2.3</td>
<td>4.1</td>
</tr>
<tr>
<td>1982</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>1983</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>1984</td>
<td>1.9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Prevalence rate as recorded on 30 June each year and the incidence rate was from July-June each year.

The prevalence of PE in males was higher (14.1/1000) than that in females (11.8/1000). The maximum prevalence in males was observed in the age group of 20–29 years whereas that for females occurred in the age group of 50–59 years. With the advance of age, the rate of the decline in the prevalence rate from its peak was slower in males but more rapid in females.

Based on the follow up of community based observations, the prevalence and incidence during the study period between 1981 and 1984 are shown in Table III. The prevalence rate increased steadily from 2.3/1000 in June 1981 to 9.9/1000 in June 1984, while the annual incidence decreased steadily from 4.7/1000 in June 1982 to 2.7/1000 in June 1984.

The prevalences of PE in the four health service units in 1986 are shown in Table IV. Though these are contiguous areas, the rates varied. The rate was smallest in Pasumathur, at 8.4/1000, and largest in Kilalathur, at 17.1/1000.

Further details of the patients and the treatment given are shown in Table V. 214 of 314 patients with PE were found to have intestinal parasites; 31 patients failed to provide stool samples. Only 58 of the subjects responded to deworming alone; the others had an AEC >2000/mm³, even after successful deworming. Forty three patients did not cooperate further. Thus diethylcarbamazine treatment could be given to 182 subjects only, which included the 69 patients without intestinal parasites. Successful remission occurred in 41 of the 126 patients (32.5%) treated with diethylcarbamazine regimen 1 and in 19 of the 49 patients (28.5%) treated with regimen 2 (table VI), while others needed repeat courses of diethylcarbamazine. The difference in response between the above two drug regimens was not statistically significant. Altogether 15 patients were given regimen 3. Eight patients, however, were shifted to regimen 1 and regimen 2 (four each) as they complained of headaches, giddiness, and feeling generally unwell after one or two days of taking the drug. Seven patients who completed regimen 3 treatment, however, responded. One hundred and fifteen of the patients who had diethylcarbamazine therapy did not respond after the first course. A second course of regimen 1 was given to 58 patients and regimen 2 to 57 patients. Thirty seven patients defaulted and 38 responded to treatment, while 20 patients failed to respond even after a second course of diethylcarbamazine. Five patients were uncooperative and the remaining 15 were given a third course of the drug. Five of these did not have a remission even after a third treatment course. Thus, in only 135 of the 182 patients was eosinopenic remission achieved with diethylcarbamazine. This did not, of course, rule out a diagnosis of TPE in the non-cooperative patients who did not comply with complete follow up.

Discussion

In clinical practice in south Asia and in published medical reports, the existence of a syndrome of TPE, with characteristic symptoms, has been established for some time. Some authors of later studies of PE felt, however, that the desirability and utility of considering TPE as a distinct entity was limited and more detailed epidemiological studies were necessary. In a group of industrial workers, Chernin et al found normal eosinophil levels in blood to be 6.9%: the manual workers had higher levels (7–10%) than the supervisors (3%). They observed that younger people more frequently had a higher blood eosinophilia, and those with higher eosinophil counts had intestinal parasites. In south Indian towns normal eosinophil counts were found to be 4.4% by previous investigators. Napier and Dagshuta found levels of blood eosinophils in a rural population to be relatively higher (13.8%). In our study of normal subjects with no intestinal parasites, we found mean (SD) AEC of 583 (4682)/mm³ for males and 524 (3571)/mm³ for females with an average total white blood cell count of 9000–10 000/mm³.

Table IV Prevalence rates (/1000) of patients with pulmonary eosinophilia (PE) by four health service units in 1986

<table>
<thead>
<tr>
<th>Health service unit</th>
<th>Population</th>
<th>No.</th>
<th>Rate (/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasumathur</td>
<td>5744</td>
<td>48</td>
<td>8.4</td>
</tr>
<tr>
<td>Kilalathur</td>
<td>6774</td>
<td>115</td>
<td>17.1</td>
</tr>
<tr>
<td>Veppanpeti</td>
<td>7405</td>
<td>95</td>
<td>12.8</td>
</tr>
<tr>
<td>Kavanur</td>
<td>5027</td>
<td>56</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Table V Details of deworming and diethylcarbamazine (DEC) therapy in 314 patients with pulmonary eosinophilia (PE)

<table>
<thead>
<tr>
<th>Details of ova and parasites</th>
<th>No of patients with PE</th>
<th>No of patients with worm infestation</th>
<th>Details of ova and parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hookworm ova</td>
<td>31</td>
<td>31</td>
<td>Stool samples not given</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>31</td>
<td>31</td>
<td>No of patients dewormed*</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>1</td>
<td>1</td>
<td>No of patients who had eosinopenic remission with deworming</td>
</tr>
<tr>
<td>Anisakis sericinaria</td>
<td>1</td>
<td>1</td>
<td>No of patients with persistent eosinophilia after deworming</td>
</tr>
<tr>
<td>Stool negative cases</td>
<td>69</td>
<td>69</td>
<td>No of patients with persistent eosinophilia after deworming who refused DEC therapy</td>
</tr>
<tr>
<td>Total</td>
<td>314</td>
<td>314</td>
<td>Total number of patients treated with DEC</td>
</tr>
</tbody>
</table>

* Deworming agents used—Mebendazole for G lamblia and E histolytica and benomethoxyn/ methendazole for the others.

Table VI Details of remission of tropical pulmonary eosinophilia cases by three diethylcarbamazine (DEC) regimens

<table>
<thead>
<tr>
<th>DEC regimen</th>
<th>Treated (no)</th>
<th>Remission (no (%))</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>12b</td>
<td>41 (32.5%)</td>
<td>(R1 vs R2)</td>
</tr>
<tr>
<td>R2</td>
<td>49</td>
<td>14 (38.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>R3</td>
<td>7</td>
<td>7 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Altogether 15 patients were allotted R3 but eight dropped out complaining of giddiness, nausea, and weakness.
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...and was considered to be of minor importance, however, compared with other manifestation of filariasis. In comparison, we found an overall prevalence of PE of 12.6/1,000 population. The first incidence rate (4.1/1,000) estimated by us was the highest. This could be attributed to the missing cases at baseline and also to the false negatives. The rising prevalence over time that occurred simultaneously with a falling incidence (table III) suggests that the final estimate of the incidence rate in 1984 (2.7/1,000) may be taken as the best estimate of the three recorded. We based our diagnosis of TPE on clinical grounds—peripheral blood eosinophil levels and the response to diethylcarbamazine therapy. Of the cooperative patients available for follow up, 182 required and were given this treatment. Only in 135 patients, however, was complete follow up and documentation of successful eosinopenic remission possible.

In 214 of 314 patients with pulmonary eosinophilia, worm infestation was associated. A total of 181 patients had infestation with hookworm ova, either alone or in combination with giardia cysts. Our observation of an increased prevalence of hookworm infection compared with other parasitic infections was similar to the finding of an earlier study in rural areas. Schacher and Danaraj in an earlier study of 569 patients showed that there was no difference between the frequency of intestinal parasitic infestation in patients with tropical eosinophilia and that in a group of control subjects. Kamat et al found evidence of parasitic infestation in one third of their patients but they did not consider it necessary to exclude them from being diagnosed as having TPE. Our patients with intestinal parasitic infestations were dewormed first. Then the persistence of symptoms and high blood eosinophil counts of over 2,000/mm³ after deworming were taken as necessary criteria before considering a diagnosis of TPE. A successful response to diethylcarbamazine therapy was also considered an essential criterion.

Several studies have reported that the prevalence of TPE was higher in school children, agricultural workers, clerks, businessmen, and technicians. In the series of Kishore et al the male:female ratio was 5:1, and in another study by Viswanathan this was found to be 4:1. In the present series, 78 of 314 patients with pulmonary eosinophilia were school children, and five were below 5 years in age; 174 of 314 patients were males; and nearly 90% of the adult patients were engaged in agricultural work.

The dosage schedule of diethylcarbamazine recommended for TPE has varied widely. Proponents of a higher dosage have advocated 18 to 30 mg/kg body weight daily, but workers in India found that a small daily dose of 5 to 8 mg/kg body weight given for about a week to 10 days was effective. Shanker et al thought that some of the relapses might be due to inadequate treatment. Ganatra and Lewis, and later Shanker and Gaur, observed that the cure rate in TPE was to some extent dependent upon the total quantity of the drug administered and was irrespective of the duration of therapy. Kamat et al observed that 40 to 60% of their patients did not respond fully to this treatment. Our data also showed that only 67 of 182 patients treated with diethylcarbamazine responded fully to the first course of either of the three regimens, and many needed repeat courses. There was no significant difference between the results obtained from the three week course of 6 mg/kg body weight daily or the two week course of 12 mg/kg body weight. The 18 mg/kg body weight regimen, however, was unacceptable to most of the patients. Successful eosinopenic remission with this drug was documented in 135 patients.

Weingarten observed that TPE was confined to the coastal districts of India. Cases have been reported, however, from eastern Uttar Pradesh, Madhya Pradesh, Bihar, Delhi, and Agra, which belong to the northern heartland away from the sea. The first definitive cases of TPE were reported from Madanapalle of Andhra Pradesh, which is about 450 km from the coast. Cases in the present study were from K V Kuplum, which is 165 km from the coast.

In conclusion, we found TPE either alone or in association with worm infestation to be a major cause of morbidity in this rural population. The association of worm infestation with pulmonary eosinophilia in general was also found to be frequent. In patients with worm infestation, the persistence of symptoms and eosinophilia after successful deworming and the requirement for diethylcarbamazine remission were considered essential to a diagnosis of TPE, as was the case for the eosinophilic patients without worms. Thus, in the patients with PE we found that there was a distinct group who had all the characteristics of TPE.

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