Natural history of Ross River virus-induced epidemic polyarthritis

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ABSTRACT

Objective: To describe the natural history, treatment and cost of Ross River virus-induced epidemic polyarthritis (RRV disease).

Design: Questionnaire-based longitudinal prospective study.

Participants and setting: Patients in the greater Brisbane area, Queensland, diagnosed with RRV disease by their general practitioners based on clinical symptoms and paired serological tests between November 1997 and April 1999.

Main outcome measures: Scores on two validated quality-of-life questionnaires (Clinical Health Assessment Questionnaire and Medical Outcomes Study Short Form 36) were obtained soon after diagnosis and one, two, three, six and 12 months thereafter. Scores were compared between patients diagnosed with RRV disease alone and those with RRV disease plus other conditions.

Results: 67 patients were enrolled. Most patients with RRV disease alone had severe acute symptoms, but followed a consistent path to recovery within three to six months. Other conditions, often chronic rheumatic diseases or depression, were identified in half the cohort; their quality-of-life scores suggested stable chronic illness between six and 12 months after diagnosis. Non-steroidal anti-inflammatory drugs (NSAIDs) were taken by 58% of patients (average use, 7.6 weeks; range, 2–22 weeks). Time off work averaged 1.9 days, and direct cost to the community was estimated as $A1018 per patient.

Conclusions: Symptom duration and frequency of long-term symptoms may have been overestimated by previous studies of RRV disease. Disease persisting six to 12 months after RRV diagnosis was largely attributable to other conditions, highlighting the need to seek other diagnoses in RRV patients with persistent symptoms.

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ROSS RIVER VIRUS (RRV) is endemic in Australia and New Guinea and is the aetiological agent of epidemic polyarthritis, or RRV disease. In Australia, where this disease is notifiable, up to 8000 cases are reported annually. The principal symptoms are polyarthritis and arthralgia, with about half the patients also experiencing a rash, fever, myalgia or fatigue.[1,2]

Several surveys of RRV disease have produced conflicting data, particularly on duration of disease.[1,3-6] However, most of these surveys were retrospective, none used objective measures of ill-health, and few sought to differentiate between RRV disease and other potentially confounding diseases. The only determination of the financial burden of RRV disease estimated an epidemic of 1196 cases to cost about $A3 million.[6]

Our study involved a survey of patients with RRV disease using two validated quality-of-life questionnaires to describe duration and severity of RRV disease more objectively than heretofore. Additional illnesses were documented in consultation with patients and treating doctors. Drug treatments were also recorded, and the direct cost of RRV disease was estimated.

METHODS

The study was a prospective longitudinal survey carried out in Brisbane between November 1997 and April 2000.

Study population

Patients were eligible if they were diagnosed with RRV disease by a general practitioner in the greater Brisbane area based on clinical symptoms and results of paired RRV serological tests using standard enzyme-linked immunosorbent assay. They were recruited through requests to GPs printed on all pathology reports from the Queensland Medical Laboratory showing a positive result for

1: Demographic characteristics of a cohort with Ross River virus disease

Sex distribution (% female)	57%
Mean age in years (range)	41.6 (20–89)
Age and sex distribution (male, female)	
20–29 years	7%, 6%
30–39 years	12%, 22%
40–49 years	12%, 15%
50–59 years	9%, 12%
60–69 years	2%, 2%
70–89 years	2%, 0
Marital status	
Single	16%
Married	69%
Defacto	6%
Divorced	9%
Employment	
Full time	66%
Part time	18%
Unemployed/retired	16%

RRV IgM in a patient in the recruitment area. GPs were asked to invite the patients to contact the enrolling nurse. Some patients were recruited through letters sent to GPs listed on the database of the Royal Australian College of General Practitioners.

The study was approved by the ethics committees of the Royal Australian College of General Practitioners, the Queensland Institute of Medical Research, and the Princess Alexandra Hospital, Brisbane.

Patient assessment

Patients attended an initial interview with a research nurse soon after the first positive IgM result, and were given an information leaflet and asked to sign a consent form. They were followed up one, two, three, six and 12 months later.

At each visit, they were asked to describe their medications, which were confirmed with the treating doctors. They were also asked to complete the Medical Outcomes Study Short Form 36 (SF-36)[7] and the Clinical Health Assessment Questionnaire (CLINHAQ).[8] The SF-36 questionnaire is used to assess health-related quality of life in a variety of diseases and conditions,[9] while the CLINHAQ was developed primarily to assess patients with chronic rheumatic disorders.[10]

Premorbid diseases were documented at the first visit, and concurrent diseases at the first and subsequent visits, in consultation with patients and their doctors. Nearly all patients were also reviewed by a rheumatologist (P C V) to identify or confirm concurrent conditions at one to two months after diagnosis and, for those with suspected or confirmed comorbidities, again at three to six months after diagnosis.

Statistical and cost analyses

At each visit, patients were classified as having a diagnosis of RRV disease alone or RRV disease plus other conditions. Mean quality-of-life scores were compared between the two groups using *t* tests, the Wilcoxon rank-sum test and ANOVA.

We estimated the direct cost of RRV disease per patient by summing the cost of RRV serological tests (including costs of negative tests), a conservative estimate of other co-ordered tests, lost income from time off work, and costs of medications and GP visits, including patient travel costs.

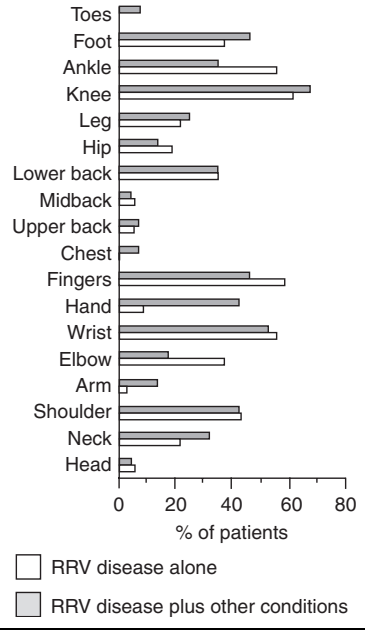
RESULTS

Study population

Sixty-seven patients with RRV disease were enrolled. A further three patients who otherwise met the criteria were excluded as paired serological tests failed to confirm RRV disease. Seven patients left the study, and at each visit up to seven failed to answer all questions.

From data on notified cases by suburb and month (Queensland Health, personal communication), we estimate that the 67 enrolled patients represented about 20% of patients reported with RRV disease within the recruitment area. We also estimate that about half the GPs in this area received requests to ask their patients to enrol, suggesting that the study captured up to 40% of available patients.

2: Percentage of patients with pain at first interview



The demographic profile of the cohort (Box 1) was similar to that reported previously for patients with RRV disease.[1,3-6] The breakdown of occupations did not appear different from that seen in urban populations in Australia.[11] Patient homes were distributed evenly around the greater Brisbane area.

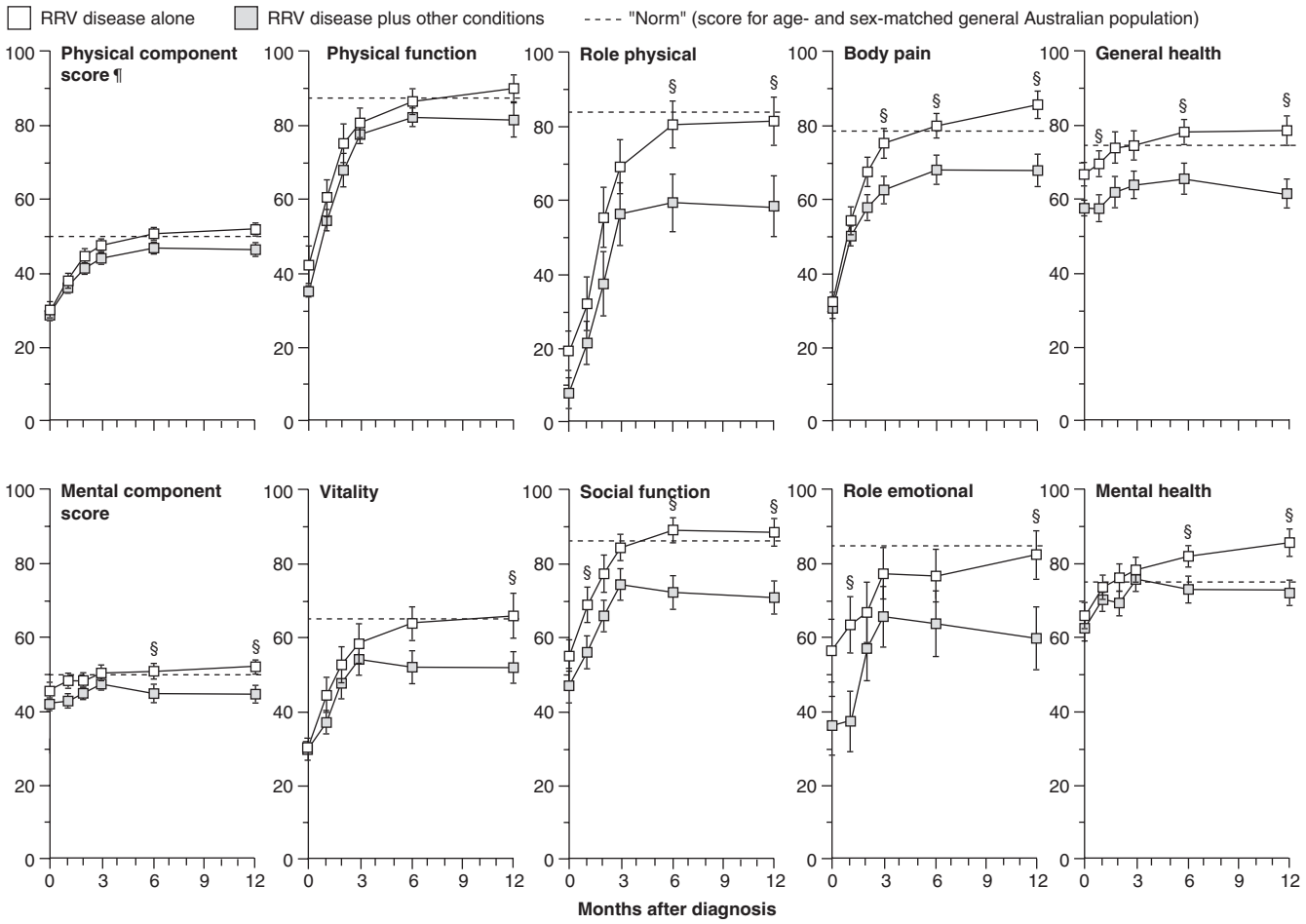
Comorbidity

Although some comorbid conditions were identified during the first three months after diagnosis, the full spectrum emerged only at six months after review by the rheumatologist.

At six months after diagnosis, 32 of 60 patients (53%) were classified with RRV disease alone. Twenty eight patients had additional diagnoses, including eight with other chronic rheumatic conditions (osteoarthritis, 3; rheumatoid arthritis, 2; psoriatic arthritis, 1; ankylosing spondylitis, 1; and osteoarthritis plus psoriatic arthritis, 1). Eight were taking medications for depression, and all but one of these had a history of depression or serious illness before RRV diagnosis. The prevalence of other rheumatic conditions and depression in the RRV disease cohort did not differ significantly from the expected prevalence.[12] Other diagnoses

3: Mean scores (±standard error) on two quality-of-life questionnaires for a cohort* with Ross River virus disease

***Medical Outcomes Study Short Form 36 (SF-36)*[7]†**



*Survey included 67 patients (0 months), 64 (1 month), 62 (2 months), 61 (3 months), and 60 (6 and 12 months). All questions were completed on both questionnaires by 32 (RRV disease alone) and 28 (RRV disease plus other conditions) (0 months), 31 and 27 (1 month), 29 and 25 (2 months), 31 and 27 (3 months), 29 and 28 (6 months), and 30 and 27 (12 months).
†SF-36 measures health on eight 100-point scales, where higher scores represent poorer health. Physical and Mental component scores are summary scores for the four physical and four emotional domains, respectively. "Role physical" and "Role emotional" represent role limitations due to physical and emotional problems, respectively.

at six months included carpal tunnel syndrome, back pain and obesity, herniated disc, melanoma, pneumonia, hypercholesterolaemia, polycystic ovaries, endometriosis, urinary tract infection, thrombocytopenia, allergy, and pregnancy (all with a prevalence of 1).

At 12 months after diagnosis, 29 of 60 patients (48%) had additional diagnoses.

Natural history of RRV disease

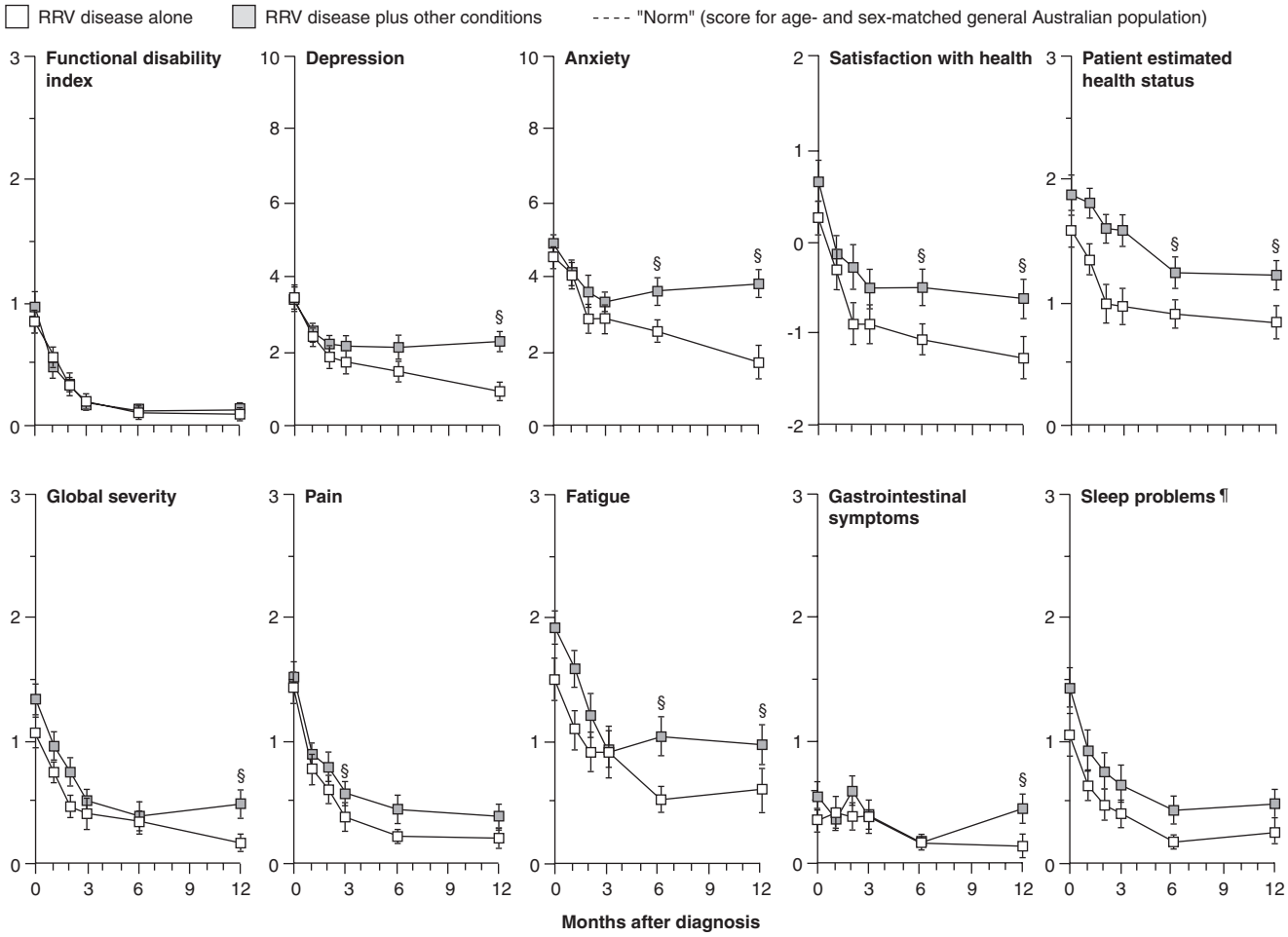
Frequency of pain in different joints at first interview is shown in Box 2. Knees, wrists and fingers were most often involved. The percentage of patients whose pain was symmetrical ranged from 36% (shoulder pain) to 100% (pain in the hands).

Mean SF-36 and CLINHAQ scores over the 12 months of follow-up are shown in Box 3. There was generally excellent concordance between the two measures, and both instruments illustrated that patients diagnosed with RRV disease alone tended to have a consistent path to recovery within three to six months. In contrast, the scores of patients diagnosed with RRV disease plus another condition usually failed to reach the population norm (defined as the score for the age- and sex-matched general Australian population). These patients usually had significantly worse illness at six and 12 months than those with RRV disease alone and also usually had stable chronic ill-health between the three- and 12-month reviews.

Twelve months after RRV diagnosis, 16 patients still had an SF-36 physical component (PC) score at least 5 points below the norm score of 50. They comprised:

- 11 patients with conditions in addition to RRV disease, primarily chronic rheumatic conditions or depression;
- three patients classified with RRV disease alone who had had significant illnesses before RRV diagnosis — a broken hip, stomach stapling procedure and burns plus pneumonia, respectively

***Clinical Health Assessment Questionnaire (CLINHAQ)*§‡**



‡Higher scores on the CLINHAQ represent poorer health.
§Scores differed significantly ($P<0.05$) between patients with RRV disease alone and those with additional conditions, as determined by *t* test (SF-36 scores) or Wilcoxon rank-sum test (CLINHAQ scores).
¶Physical component scores and sleep problem scores differed significantly ($P=0.01$) between patients with RRV disease alone and those with RRV disease plus other conditions when the overall mean differences for all time points were compared by ANOVA.

(all with PC scores 40–45, indicating marginal disease severity);

- one patient who was hospitalised for pneumonia six months after RRV diagnosis (PC score 28); and
- one patient with no other identified conditions (PC score 30), suggesting that RRV disease was the sole cause of symptoms.

Treatment

Non-steroidal anti-inflammatory drugs (NSAIDs) were taken by 58% of patients, aspirin or paracetamol by 15%, prescribed corticosteroids by 4%, and NSAIDs plus aspirin or paracetamol by 3%; 21% took no conventional medication. The percentage of patients taking NSAIDs decreased over the 12 months after diagnosis, from 55% (initial interview), to 31% (1 month), 21% (2 months), 15% (3 months), 5% (6 months), and 2% (12 months). NSAIDs were taken for an average of 7.6 weeks (SD, 5.9; range, 2–22 weeks). At each visit, from 70% to 100% of patients taking NSAIDs reported being satisfied with this treatment.

Direct cost of RRV disease

The direct cost to the community was estimated to be $A1018 per patient, with diagnostic costs and lost productivity representing the major components (Box 4). Average time off work was 1.9 days for the whole cohort (SD, 5.0), 3.1 days for the 43 patients in full-time employment (SD, 6.7; range, 0–37), and 2.4 days for the 35 in full-time employment who had RRV disease alone (SD, 4.3). Twenty-five of those in full-time employment (58%) took no time off work.

Costs were not included for mosquito control programs (an estimated $3 million for the Brisbane area), indirect costs of RRV disease morbidity, monitoring of RRV as a notifiable disease and RRV research expenditure (about $200 000–$400 000 per annum).

4: Estimated direct costs of Ross River virus disease per patient

Diagnostic tests*	$567 (56%)
Lost productivity†	$305 (30%)
GP visits‡	$88 (9%)
Medications§	$46 (4%)
Patient travel¶	$12 (1%)
Total	$1018

GP = general practitioner.
*At $23.80 per serological test for Ross River virus (RRV). Estimate includes costs of negative tests (23 patients were tested to detect one case of RRV disease) plus conservative estimate of other co-ordered tests, based on unpublished data gathered by Queensland Medical Laboratory on 54 790 patients between Oct 1997 and Apr 1999.
†Based on average gross weekly earnings of $795.20 and mean of 1.92 days off work for the whole cohort.
‡Mean of 3.25 visits (SD, 1.12), based on 20 randomly selected patients, at $27.00 per visit.
§Based on 12 representative patients using Pharmaceutical Benefits Scheme costs.
¶Estimated mean of 8 km per return trip to GP x cost of medium car ($0.45/km) x 3.25 visits.

DISCUSSION

This study illustrates that RRV disease is severe at onset but usually resolves within three to six months. Importantly, patients with continuing chronic disease beyond the three- to six-month follow-ups usually had additional conditions. These observations illustrate the importance of seeking differential diagnoses in patients presenting with long-term RRV disease.

These findings are consistent with those of a 1997 study of 103 Queensland residents with RRV disease, which also noted a high incidence of other rheumatic conditions.[14] The high incidence of long-term RRV disease and long duration reported by other studies[5] may be somewhat overestimated and unduly influenced by other chronic conditions. In our study, RRV disease lasting over a year was identified in only one patient with no confounding conditions (2% of the cohort).

At diagnosis, patients with RRV disease had SF-36 scores comparable to those of 55–64-year-olds with osteoarthritis awaiting hip or knee replacement surgery.[15] Scores for both groups were 50–70 points lower than the norm for the domains role physical, physical function and body pain; 25–35 points lower for vitality, social function and role emotional; and 10–20 points lower for general and mental health. At diagnosis, our cohort also had similar SF-36 physical and mental component scores as patients with persistent Lyme disease,[16] and similar average functional disability index and fatigue and pain scores as a US cohort of patients with chronic rheumatoid arthritis.[7,17] Depression and anxiety scores in our patients at diagnosis approached the cutoff scores for clinical depression and anxiety (about 4 and 6, respectively) and were similar to those found in patients with rheumatoid arthritis three months after onset.[17] Sleep problems have not been widely associated with RRV disease, but were also similar to those seen in chronic rheumatoid arthritis.[17]

A potential limitation of our study was the inability to enrol a greater percentage of eligible patients with RRV disease. The study was also of insufficient size to establish whether the single case of long-term RRV disease represents the true frequency.

To our knowledge, this study represents the first published use of validated questionnaires for investigating a viral arthritis and demonstrates their value for assessing these diseases. The results clearly highlight the need to consider alternative diagnoses in patients with persisting RRV disease symptoms. Patients with RRV disease can also be reassured that the disease, although severe at onset, is self-limiting, with a usual duration of three to six months, and does not have long-term sequelae.

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COMPETING INTERESTS

None declared.

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