Viral Exanthems - Why are They Good Choices for Research by Family Physicians?

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Abstract

Family physicians are well placed to study viral exanthems because they see patients at an early stage of the eruption, and can obtain early virological evidence. Several exanthems are under-reported and under-investigated in China and in Asia. Such provides good opportunities for clinical research. Epidemiological data are less biased in primary care than in secondary care settings. Family physicians are also interested in the entire illness instead of the disease only, and can thus evaluate impacts of management in a comprehensive and evidence-based manner.

Contrary to common belief, several exanthems of multiple or unknown viral aetiologies such as Gianotti-Crosti syndrome and pityriasis rosea are common conditions. These rashes might appear to be uncommon merely because of under-diagnosis and under-reporting.

Background

Viral exanthems are skin eruptions occurring as symptoms of acute viral diseases.1 Exanthem comes from the Greek word *exanthema*, meaning breaking out, and *anthos*, denoting blossoming flowers. We shall discuss in this article why viral exanthems matter much to family physicians, and why family physicians are well placed to investigate them. We shall also describe future challenges in researching viral exanthems.

Viral exanthems matter much to family physicians

The major viral exanthems are listed in Table 1. Viral exanthems are important for family physicians because most patients with such exanthems initially consult family physicians instead of specialists. Early accurate diagnosis removes the need for unnecessary investigations and treatments. Adequate symptomatic relief can be given by family physicians. Patients and parents can be advised on the likely course of the disease, and symptoms and signs of common and rare complications.

Early measures can also be taken by the family physician on isolation if necessary to prevent an epidemic. On the other hand, if isolation is unnecessary or not warranted, patients, parents, and school or kindergarten teachers may be reassured. Family physicians should also be aware that several exanthems are notifiable.

Family physicians are well placed to investigate viral exanthems

1. Early virological evidence

Family physicians see patients with exanthems at an early stage of the eruption. Early virological evidence is thus available. By the time these patients are referred to secondary care specialists such as dermatologists or paediatricians, viral DNA and mRNA transcripts will not be detectable in the tissue samples such as the plasma for many viruses, and virus loads will be low. Moreover, parallel serological investigation of acute and convalescent sera would not be possible. The analysis of results from the convalescent serum alone is of limited value in documenting acute infections.

Owing to such early presentation, we have been able to investigate for human herpesvirus (HHV)-6 and -7 DNA in the plasma and peripheral blood mononuclear cells, virus subtyping, HHV-6 virus load, HHV-6 U91 mRNA transcripts in peripheral blood mononuclear cells, and HHV-6 and -7 serology in acute and convalescent blood specimens of children with Gianotti-Crosti syndrome.2 We have been fortunate to be the first investigators confirming that primary infection of HHV-6B is a cause of Gianotti-Crosti syndrome (papular acrodermatitis of childhood).2

Owing to such early presentation, we have also been able to provide convincing evidence that patients with pityriasis rosea in Hong Kong do not exhibit evidence of primary infection or reactivation of HHV-7 and -6.3 We also reported that pityriasis rosea is not caused by infections by cytomegalovirus, Epstein-Barr virus, parvovirus,4 Chlamydia pneumoniae, C. trachomatis, Legionella longbeachae, L. micdadei, L. pneumophila and Mycoplasma pneumoniae.5 Our studies on the roles of other viruses are in progress.6

2. Rarity of reports in China and in Asia

Several exanthems are relatively under-reported and under-investigated for Chinese and Asian patients. This provides good opportunities for clinical research. Owing to such under-reporting, we have been fortunate to be able to report the first series of Chinese children with Gianotti-Crosti syndrome.7, 8 Another example is asymmetric periflexural exanthem. This exanthem is also known as unilateral laterothoracic exanthem, and has been reported in France,5, 10 Italy,11, 12 Germany,13 Spain,14 Hungary,15 United Kingdom,16 USA,17
and Canada.\textsuperscript{18} It is likely to be endemic in parts of Europe (Taieb - personal communication). To our best knowledge, the occurrence of this exanthem in Asia has not been reported in indexed journals. We reported the first patient with asymmetric periflexural exanthem in Asia.\textsuperscript{19, 20} We shall also report the first patients with a novel variant of asymmetric periflexural exanthem in the world, which we term unilateral mediothoracic exanthem.\textsuperscript{21}

3. Epidemiology data - least biased in primary care

Epidemiological data from primary care setting are the best proxy measure of community-based diagnoses such as viral exanthems. Such data from secondary care specialists might be biased due to selective referral and inevitable delay in the consultation.

With such unreferred data, we have been able to demonstrate significant temporal case clustering in pityriasis rosea.\textsuperscript{22} Temporal clustering is a well established method in investigating the infectious origin of a condition, and has been applied in Kawasaki disease\textsuperscript{23} and childhood leukaemia.\textsuperscript{24} There has been previous report on temporal clustering in pityriasis rosea.\textsuperscript{25} However, the statistical method previously used was based on a fixed scanning window. As epidemiology variables such as incubation period and infectious period of pityriasis rosea are unknown, adopting a fixed scanning window might not be the most appropriate. Collaborating with statisticians from France, we applied a novel regression analysis model with bootstrapped simulations.\textsuperscript{26} Our method is independent of cluster size, can detect multiple clusters, and has been validated by application on other data sets.

The demonstration of significant temporal clustering provided indirect evidence substantiating an infectious aetiology for pityriasis rosea. We subsequently validated our findings by collaborating with researchers from the US, France, Kuwait and Turkey, performing regression analysis on 1379 patients with pityriasis rosea in three geographic locations around the world.\textsuperscript{27} Further work by our group on spatial-temporal clustering in Gianotti-Crosti syndrome\textsuperscript{28} and other exanthems are in progress.

4. Family physicians care for the person, not only the disease

While some specialists might concentrate their efforts on the disease, family physicians have a heart for the patient and the illness as well. We are concerned about the impacts of exanthems on the quality life of patients, and whether schooling and work of patients are affected. We are therefore disheartened to find that major treatment trials on pityriasis rosea, for example, do not include quality of life as one of the outcome measures.\textsuperscript{29-32} Even pruritus, the major symptom in pityriasis rosea, was not investigated in some of the studies.\textsuperscript{29, 30} These investigators only measured how the rash severity and extendiveness were modified by medications. Many of the patients could have no or little pruritus, and the face and distal aspects of extremities are uncommonly affected in this exanthem. These patients might not warrant active intervention in the first place.

Recognising this gap in knowledge, we investigated and demonstrated that the effects on the quality of life are independent of rash severity in adult patients with pityriasis rosea.\textsuperscript{33} The implication of this finding is that active intervention might be unnecessary even for some patients with diffuse eruptions. We also documented that effects on the quality of life are minimal for children with pityriasis rosea,\textsuperscript{34} and that active treatment is unnecessary for most children with this exanthem.

5. Exanthems of multiple or unknown viral aetiologies are common conditions

Family physicians should concentrate their already limited research efforts and resources on common conditions. Contrary to common belief, there exists epidemiological evidence from primary care setting that several exanthems of multiple or unknown viral aetiologies including Gianotti-Crosti syndrome\textsuperscript{35} and pityriasis rosea\textsuperscript{36, 37} are in fact common conditions. The incidence of asymmetric periflexural exanthem is unknown. However, emerging data substantiate that it is endemic in European countries (Taieb - personal communication). These eruptions might appear to be uncommon merely because of under-diagnosis and under-reporting. It is known, for example, that primary care physicians significantly underdiagnose pityriasis rosea.\textsuperscript{38}

A pertinent analogy here is erythema infectiosum. In the 1960s and 1970s, this was assumed to be an uncommon disease entity,\textsuperscript{39} and many physicians had not even heard of the disease.\textsuperscript{39} It is now known that erythema infectiosum is likely to be the commonest viral rash in school children in developed countries,\textsuperscript{40} and that the previously assumed low incidence of erythema infectiosum is likely to be due to under-diagnosis only.\textsuperscript{41}

Discussion and future challenges for research

Viral exanthems serve as good models for which family physicians can collaborate with international and multidisciplinary investigators. We have good support and pleasurable collaboration with other family physicians, dermatologists, paediatricians, virologists, pathologists, epidemiologists, statisticians, quality of life investigators, linguists, systemic review experts and consumer reviewers (patients with the exanthem).

Our present network embraces investigators from Columbia, France, Hong Kong, India, Kuwait, Philippines, Romania, Switzerland, Turkey, United Kingdom and USA. We are amazed that several overseas investigators are in private practice, with honorary academic posts in prestigious universities and institutions. They are every bit as eager to contribute to research as their full-time academic colleagues, but for reasons other than promotions up the academic ladder. We hope to open up new horizons and opportunities for research with the aims of not only producing high quality publications but also exerting direct impact on the quality of management to patients.

There lies many future challenges in research. The aetiologies of many exanthems have not been elucidated
and further search for the roles of other viruses might shed light on the management strategies. 42 The roles of atopy and hyperimmunoglobulinaemia E states in viral exanthems, 33 and conversely, the role of early viral infections in atopic states 44 warrant further investigations. Further studies should be performed to establish the validity and reliability of diagnostic criteria for several exanthems. 45-47 The treatment of the exanthems are at present largely empirical. Clinical trials and systematic reviews 48 would rationalise patient management.

There lies rough water ahead, and we are acutely aware of our limitations such as constraints in time and resources. We also lack the clinical expertise possessed by our specialist colleagues. Dedication, commitment and perseverance might overcome some, but not all, of our hindrances. The rest will have to depend on support from specialist colleagues and the development of a sustainable infrastructure in family medicine research deliberated in the Editorial of this issue.

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References


Table 1 Viral exanthems

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