



REPORT

CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

2002
RESULTS



Mission Statement

*To contribute to the improvement of the health
of children and youth in Canada
by national surveillance and research
into uncommon paediatric diseases and conditions.*

**For more information on the
Canadian Paediatric Surveillance Program
or a French version of this report,
please contact:**

Canadian Paediatric Society

Andrea Medaglia, CPSP Senior Coordinator
100-2204 Walkley Road
Ottawa ON K1G 4G8
Tel.: 613-526-9397, ext. 239; Fax: 613-526-3332
E-mail: cpsp@cps.ca; <http://www.cps.ca/english/cpsp>



Table of Contents

2	Acknowledgements
3	Foreword
3	Federal Minister of Health, Health Canada
3	Director General, Centre for Infectious Disease Prevention and Control
4	President of the Canadian Paediatric Society
4	CPSP Chairman
5	CPSP Steering Committee
5	CPSP Working Group
6	Publications in 2002
6	Published papers related to studies
6	Highlights published in <i>Paediatrics & Child Health</i>
6	Presentations in 2002
6	National
7	International
8	Funding
9	Surveillance at Work
9	Overview
12	Investigators' corner
13	Studies timeline
14	CPSP Principal Investigators
15	Surveillance Studies in 2002
15	Acute flaccid paralysis
18	Cerebral edema in diabetic ketoacidosis (final report)
20	CHARGE association/syndrome
24	Congenital rubella syndrome
27	Hemolytic uremic syndrome (final report)
29	Hepatitis C virus infection (final report)
31	Necrotizing fasciitis
33	Neonatal herpes simplex virus infection
35	Neonatal hyperbilirubinemia – severe
37	Neonatal liver failure/perinatal hemochromatosis (final report)
39	Smith-Lemli-Opitz syndrome (final report)
41	Vitamin D deficiency rickets
45	New Studies in 2003
45	Adverse drug reactions
45	Early-onset eating disorders
46	Lap-belt syndrome
47	Osteogenesis imperfecta
48	Prader-Willi syndrome
49	Survey Question
49	Injuries associated with baby walkers
50	International Developments
52	Highlights from other national paediatric surveillance units
56	Call for New Studies

Acknowledgements

The key strengths of the CPSP continue to be the participation of Canadian paediatricians, subspecialists and other health-care providers in the monthly collection of information on rare paediatric conditions, our principal investigators who review and analyze the data collected to provide us with knowledge and educational solutions to help children and youth around the world, and our Steering Committee members who continue to guide the program.

For their role in the verification of data collected, we thank:

- Canadian Association of Paediatric Health Centres
- Canadian Paediatric Decision Support Network
- IMPACT (Immunization Monitoring Program ACTIVE) centres
- Notifiable Diseases Reporting System, Centre for Infectious Disease Prevention and Control, Health Canada
- Canadian Institute for Health Information

We also gratefully acknowledge the financial support received to maintain and expand the program in order to improve the health of Canadian children and youth. A summary of supporters is found in this report (page 8).

The strong CPSP partnership between the Canadian Paediatric Society (CPS) and Health Canada's Centre for Infectious Disease Prevention and Control (CIDPC) allows the program to grow in Canada and to take a leadership role on the international scene.

A Special Tribute to Dr. Victor Marchessault

It was with much sadness and sorrow that we learned on March 27, 2003, of the sudden passing of Dr. Victor Marchessault. We lost a scholar, a champion for children's health and a true friend. In essence, Dr. Marchessault was the cornerstone and foundation of the Canadian Paediatric Surveillance Program (CPSP). He was a man of vision and an influential advocate for the advancement of paediatric research, both nationally and internationally. He recognized the importance and the value of active surveillance, and as a result of his tremendous dedication, commitment and influence in paediatric, public health and government circles, the CPSP was established in 1996.



Dr. Marchessault was well known not only as the Executive Vice-President of the Canadian Paediatric Society between 1964 and 1997, but also as Professor of paediatrics and infectious diseases at the University of Ottawa and the Children's Hospital of Eastern Ontario, Chair of the National Advisory Committee on Immunization, and President of the Ontario Chapter of the American Academy of Pediatrics. The International Network of Paediatric Surveillance Units (INoPSU) honoured Dr. Marchessault by unanimously electing him to be their convenor effective April 1, 2003. Sadly, this was not to be.

Dr. Gilles Delage, Chair of the CPSP Steering Committee, remembered him fondly saying, "We have suddenly lost the architect of our program. Sad as it may be, he gave us heritage, and our duty is to ensure that the program thrives."

Foreword

Federal Minister of Health, Health Canada

As Minister of Health, I wish to congratulate the Canadian Paediatric Society on the successful completion of the seventh year of the Canadian Paediatric Surveillance Program (CPSP). Such programs help to ensure that children are given the best possible start in life. They also provide the children's families and communities with appropriate resources to foster and nurture their mental and physical well-being.



The Honourable A. Anne McLellan

Canadian paediatricians play a crucial role by providing expert health care to our children. I wish to commend the paediatricians who take the time each month to complete the check-off form and return it to the CPSP. The few minutes the 2,304 paediatricians who participate in the program set aside each month have a collective impact on the lives of many young Canadians. The knowledge generated by the CPSP enables paediatricians, and the health-care community, to improve the quality of life for children with rare conditions, educate other paediatricians and health-care professionals, and increase public awareness.

I am pleased to support the partnership between Health Canada and the Canadian Paediatric Society in improving the health and well-being of Canadian children. In this time of health-care system renewal, it is important that we work together on all fronts to improve the health of the people of Canada. On February 5, 2003, Canada's First Ministers agreed to a new health plan to improve access to quality health care. Our goal is a sustainable and effective health-care system that reflects the needs of all Canadians.

Director General, Centre for Infectious Disease Prevention and Control

I am pleased to accept the seventh annual report of the Canadian Paediatric Surveillance Program (CPSP).

Acute flaccid paralysis (AFP) surveillance is Canada's commitment to the world polio eradication initiative. Although Canada and the rest of the American



Dr. Howard Njoo

region were certified free of indigenous wild poliovirus transmission in 1994, Canada remains at risk of importation of wild poliovirus from polio endemic countries. Through the CPSP's active surveillance of AFP, potential cases of paralytic poliomyelitis are monitored.

The surveillance of AFP and congenital rubella syndrome continues to be the cornerstone of the program, founded as a partnership between the Canadian Paediatric Society and the former Bureau of Infectious Diseases in the Laboratory Centre for Disease Control in 1996, serving as our national commitment to major public health initiatives.

The Centre for Infectious Disease Prevention and Control (CIDPC) continues to financially support the infrastructure of the program and to coordinate the funding for several Health Canada studies in 2002-2003 in addition to acute flaccid paralysis and congenital rubella syndrome: hepatitis C virus infection, hemolytic uremic syndrome, neonatal herpes simplex virus infection, and early-onset eating disorders.

CIDPC also acknowledges the importance of the surveillance of rare non-infectious conditions, recognizing that the research obtained through the CPSP will improve the quality of the day-to-day lives of every child with a rare genetic condition in Canada and throughout the world.

President of the Canadian Paediatric Society

The Canadian Paediatric Surveillance Program (CPSP) allows paediatricians an opportunity to participate in the collection of national scientific data on rare conditions and provides a mechanism for validating health guidelines.



Dr. Doug McMillan

In 1997, the Canadian Paediatric Society's Fetus and Newborn Committee revised its guidelines on vitamin K administration to newborn infants due to concerns that oral vitamin K might be associated with an increased incidence of late hemorrhagic disease of the newborn (HDNB). As principal researcher of the HDNB study to identify incidence and relationship of vitamin K prophylaxis at birth, I was pleased to see the value of the guidelines with very few cases of HDNB among 1.5 million births in Canada during the four-year study period. With this data, the CPSP participated in an international comparison of prophylactic regimens of vitamin K that illustrated the merit and importance of intramuscular vitamin K prophylaxis.

As participants in the CPSP, we have come to expect the monthly check-off form and realize the importance of a diligent response. For all of us, this simple task should become an integral part of the 'good practice' of medicine. CPSP conditions are so rare that only about 12% of us will report a case, yet a 'nil' report is essential to strengthen the denominator and establish more accurate incidence rates.

The Steering Committee and Working Group are to be congratulated on the progress of the program. Most importantly, program participants are thanked for their contributions of time and effort in returning the monthly questionnaires and providing further details when required.

CPSP Chairman

I have the privilege and honour to have been involved with the Canadian Paediatric Surveillance Program (CPSP) in various capacities since its inception, first as a representative of the Canadian Paediatric Society, then as the Immunization Monitoring Program



Dr. Gilles Delage

ACTIVE representative and now as the Chair. From such a vantage point, I have seen the program grow from the study of three conditions, funded by Health Canada, to a total of 19 conditions under study since its inception. Investigators have become increasingly eager to use the program as they come to understand the merits of the scientific data collected.

The CPSP is also growing within the international community, having been asked to take on the convenor and facilitator responsibilities of the International Network of Paediatric Surveillance Units (INoPSU) in April 2003.

From all outward appearances, the CPSP has been a success; however, hard questions need to be asked and answered objectively and truthfully by CPSP participants, investigators and the public health community. Is the CPSP achieving its objectives and goals? What are the economies of the program in comparison with other similar surveillance programs? Does the information collected by the CPSP have the potential to change public health policies?

A formal program evaluation is being undertaken to answer these questions and assess the strengths and weaknesses of the program. I look forward to the results of the program evaluation, as I am confident that they will confirm the scientific and public health value of the program, and further cement the CPSP's legacy in contributing to the health of children with rare conditions.

CPSP Steering Committee

Dr. Gilles Delage (Chair)	Canadian Paediatric Society
Dr. Garth Bruce	Canadian Paediatric Society
Dr. Rick Cooper	Paediatric Chairs of Canada
Ms. Marie Adèle Davis	Canadian Paediatric Society
Ms. Jo-Anne Doherty	Centre for Infectious Disease Prevention and Control, Health Canada
Dr. Danielle Grenier	Medical Affairs Officer, Canadian Paediatric Society
Dr. Richard Haber	Canadian Paediatric Society
Dr. Arlene King	Centre for Infectious Disease Prevention and Control, Health Canada
Dr. Susan King	Canadian Paediatric Society
Dr. Simon Levin	Liaison, Canadian Association of Child Neurology
Dr. Catherine McCourt	Centre for Healthy Human Development, Health Canada
Dr. Victor Marchessault	Honourary member, CPSP INoPSU representative
Ms. Andrea Medaglia	Senior Program Coordinator, Canadian Paediatric Society
Mr. Paul Muirhead	Consultant
Dr. Jeff Scott	Council of Chief Medical Officers of Health
Dr. Paul Sockett	Consultant, Centre for Infectious Disease Prevention and Control, Health Canada
Dr. Anne Summers	Liaison, Canadian College of Medical Geneticists
Dr. Wendy Vaudry	IMPACT (Immunization Monitoring Program ACTive)
Dr. Lynne Warda	Canadian Paediatric Society
Dr. Lonnie Zwaigenbaum	Canadian Paediatric Society

CPSP Working Group

Ms. Andrea Medaglia (Chair)	Senior Program Coordinator, Canadian Paediatric Society
Ms. Marie Adèle Davis	Executive Director, Canadian Paediatric Society
Ms. Jo-Anne Doherty	Chief, Division of Disease Surveillance, Centre for Infectious Disease Prevention and Control, Health Canada
Dr. Danielle Grenier	Medical Affairs Officer, Canadian Paediatric Society

Publications in 2002

Published papers related to studies

(See <http://www.cps.ca/english/cpsp>
for a complete list of abstracts with
hotlinks)

Smith-Lemli-Opitz syndrome: Carrier frequency and spectrum of DHCR7 mutations in Canada. Waye JS, Nakamura LM, Eng B, Hunnisett L, Chitayat D, Costa TM, Nowaczyk MJM. *J Med Genet* 2002;39(6):31e

Smith-Lemli-Opitz syndrome: New mutation with a mild phenotype. Prasad C, Marles S, Prasad AS, Nikkel S, Longstaffe S, Peabody D, Eng B, Wright S, Waye JS, Nowaczyk MJM. *Am J Med Genet* 2002;108(1):64-8

Real-time reporting of anaphylaxis in infants, children and adolescents by physicians involved in the Canadian Paediatric Surveillance Program. Simons FER, Chad ZH, Gold M. *Journal of Allergy and Clinical Immunology* 2002;109:S181

Highlights published in *Paediatrics & Child Health*

(See <http://www.cps.ca/english/cpsp>
for a complete list of highlights with
hotlinks)

A risk of northern climate! *Paediatr Child Health* 2002;7(10):680

Reaching the target for global polio eradication – Almost there! *Paediatr Child Health* 2002;7(9):616

Vitamin K injection – Best prevention for newborns. *Paediatr Child Health* 2002;7(8):588-9

Unravelling an acute flaccid paralysis event. *Paediatr Child Health* 2002;7(7):441

Baby walker survey: Results and next steps. *Paediatr Child Health* 2002;7(6):418

Surviving a hemolytic uremic syndrome (HUS). *Paediatr Child Health* 2002;7(5):322

Demonstrating the clinical impact of your CPSP monthly feedback. *Paediatr Child Health* 2002;7(4):237

Necrotizing fasciitis – A possible fatal varicella complication. *Paediatr Child Health* 2002;7(3):142

Announcing the new user-friendly CPSP Web site – A public health service resource. *Paediatr Child Health* 2002;7(2):104

Neonatal herpes simplex virus infection: A devastating newborn pathogen. *Paediatr Child Health* 2002;7(1):19

Presentations in 2002

(See <http://www.cps.ca/english/cpsp>
for a complete list of presentations with
hotlinks)

National

Congenital rubella syndrome – An international perspective: Are the results comparable? Grenier D, Doherty J, Medaglia A. *Paediatr Child Health* 2002;7 Suppl A:56A. Presented at the 79th Annual Meeting of the Canadian Paediatric Society, Toronto, June 14, 2002 and at the 5th Canadian National Immunization Conference, Victoria, December 1-3, 2002.

Hemorrhagic disease of the newborn – An international comparison of prophylactic regimens of vitamin K. Grenier D, Doherty J, Medaglia A.

Paediatr Child Health 2002;7 Suppl A:55A. Presented at the 79th Annual Meeting of the Canadian Paediatric Society, Toronto, June 14, 2002.

Features of hepatitis C virus (HCV) infection among children and adolescents in Canada. Lapointe N, the Canadian Paediatric Surveillance Program. *Paediatr Child Health* 2002;7 Suppl A:56A. Presented at the 79th Annual Meeting of the Canadian Paediatric Society, Toronto, June 14, 2002.

The Canadian and British perspectives of paediatric intellectual and neurological deterioration (PIND): Are the results comparable? Grenier D, Doherty J, Medaglia A. *Paediatr Child Health* 2002;7 Suppl A:56A. Presented at the 79th Annual Meeting of the Canadian Paediatric Society, Toronto, June 14, 2002.

Puberty and growth in CHARGE association/syndrome. Abi Daoud M, Gradstein J, Blake K. *Paediatr Child Health* 2002;7 Suppl A:54A. Presented at the 79th Annual Meeting of the Canadian Paediatric Society, Toronto, June 14, 2002.

Anaphylaxis: The Canadian Paediatric Surveillance Program. Simons E. Presented at the 79th Annual Meeting of the Canadian Paediatric Society, Toronto, June 13, 2002.

Cerebral edema associated with diabetic ketoacidosis: How common is it really? Muirhead S, Cummings E, Daneman D. Presented at the 79th Annual Meeting of the Canadian Paediatric Society, Toronto, June 13, 2002.

The incidence and prevalence of CHARGE association/syndrome (A/S) in Canada. Issekutz KA, Smith IM, Prasad C, Graham JM, Blake KD. Presented at Dalhousie University's Department of Pediatrics' Research Half-Day, Halifax, June 5, 2002.

The cranial nerve anomalies of CHARGE association/syndrome. Lawland CMD, Prasad C,

Graham JM, Blake K. Presented at Dalhousie University's Medicine Student Research Day, 2002.

Cerebral edema in DKA: Canadian Paediatric Surveillance Program. Muirhead S, Cummings E, Daneman D. Presented at the Annual Meeting of the Canadian Paediatric Endocrine Group, Niagara-on-the-Lake, February, 2002.

X-linked adrenoleukodystrophy presenting with severe cholestasis and liver disease in a neonate. McKenzie L, Butzner JD, Robertson MA, Trevenan C, Casey R. *Can J Gastroenterol* 2002;16(Suppl A):78A. Presented at the 41st Annual Meeting of the Canadian Association of Gastroenterology in conjunction with the Canadian Association for the Study of the Liver, Montreal, January 30 to February 5, 2002.

International

Carrier frequency of the Smith-Lemli-Opitz IVS8-1G>C mutation of the DHCR7 gene in African-Americans. Wright BS, Nwokoro NA, Waye JS, Wassif CW, Nowaczyk MJ, Porter FD. *Am J Hum Genet* 2002;71:S669. Presented at the 52nd Annual Meeting of the American Society of Human Genetics, Baltimore, October 15-19, 2002.

Molecular, biochemical and clinical aspects of Smith-Lemli-Opitz syndrome in Cuban patients. Nowaczyk MJM, Martin Garcia D, Aquino A, Rodriguez M, Eng B, McCoughey D, Waye JS. *Am J Hum Genet* 2002;71:S428. Presented at the 52nd Annual Meeting of the American Society of Human Genetics, Baltimore, October 15-19, 2002.

Canadian Paediatric Surveillance Program for progressive neurological diseases. Keene D, Harman P, Sutcliffe T, on behalf of members of the Canadian Paediatric Surveillance Program. *Annals of Neurology* 2002, Suppl 1:S150. Presented at the 31st Annual Meeting of the Child Neurology Society, Washington, October 9-12, 2002.

Cerebral edema associated with diabetic ketoacidosis. Muirhead S, Cummings E, Daneman D. Presented at the Royal College of Paediatrics and Child Health Spring Meeting, Second INoPSU Conference, York, England, April 15, 2002.

The Canadian and British perspectives of paediatric intellectual and neurological deterioration (PIND): Are the results comparable? Grenier D, Doherty J, Medaglia A. *Paediatr Child Health* 2002;7 Suppl A:56A. Presented at the Royal College of Paediatrics and Child Health Spring Meeting, Second INoPSU Conference, York, England, April 15, 2002.

Congenital rubella syndrome – An international perspective: Are the results comparable? Grenier D, Doherty J, Medaglia A. *Paediatr Child Health* 2002;7 Suppl A:56A. Presented at the Royal College of Paediatrics and Child Health Spring Meeting, Second INoPSU Conference, York, England, April 15, 2002.

Real-time reporting of anaphylaxis in infants, children and adolescents by physicians involved in the Canadian Paediatric Surveillance Program. Simons E. Presented at the 58th Annual Meeting of the American Academy of Allergy, Asthma, and Immunology, New York, March 4, 2002.

Funding

To date, funding for the surveillance program has been made available from the Centre for Infectious Disease Prevention and Control, Health Canada, as well as other government departments, organizations and companies interested in increased knowledge of uncommon childhood conditions and the practical improvement in prevention and treatment.

Funding is required for program management, including administrative and financial support. Educational grants are welcome from all interested in monitoring and contributing to the improvement of health of all Canadian children and youth.

We gratefully acknowledge funding from the following sources:

Government departments, Health Canada:

- Population and Public Health Branch
 - Centre for Healthy Human Development
 - Health Surveillance and Epidemiology Division
 - Centre for Infectious Disease Prevention and Control
 - Division of Disease Surveillance
 - Division of Enteric, Foodborne and Waterborne Diseases
 - Division of Immunization
 - Division of Sexual Health Promotion and STD Prevention and Control
 - Hepatitis C Division

Non-governmental sources:

- CHARGE Syndrome Foundation, Inc.
- Coady Family Fund for Liver Research
- Dairy Farmers of Canada
- GlaxoSmithKline
- Hamilton Health Science Foundation
- IWK Health Centre
- Mead Johnson & Company
- Merck Frosst Canada Ltd.
- Striving for Excellence Fund, Mount Sinai Hospital
- The Physicians' Services Incorporated Foundation

We also acknowledge Aventis Pasteur and Bristol-Myers Squibb Canada Inc. for assisting with a donation for the year-end draw to thank participants who responded each month in 2001 (see page 10 for names of prize winners).

Surveillance at Work

Overview

The CPSP is designed to study rare childhood disorders (less than 1,000 cases per year) or rare complications of more common diseases of such low frequency that data collection nationally is required to generate a sufficient number of cases to derive meaningful results. When the CPSP Steering Committee reviews new study proposals, preference is given to studies that have strong public health importance or could not be undertaken any other way. All studies must conform to high standards of scientific rigour and practicality.

Upon initiation of a new study, program participants receive a summary of the protocol, including the case definition and a brief description of the condition. In addition to providing a uniform basis for reporting, this approach serves to educate and increase awareness of unusual or rare conditions.

The CPSP uses a two-tiered reporting process to ascertain and investigate cases: an initial ‘check-off’ form and a detailed reporting form. The full process is summarized in Figure 1.

Initial reporting

The initial reporting form, listing the conditions currently under surveillance, is mailed monthly to practising Canadian paediatricians and relevant paediatric subspecialists and health-care providers. Respondents are asked to indicate, against each condition, the number of new cases seen in the last month, including ‘nil’ reports. A ‘nil’ report is very important in active surveillance because the CPSP cannot simply assume that no reply means no cases.

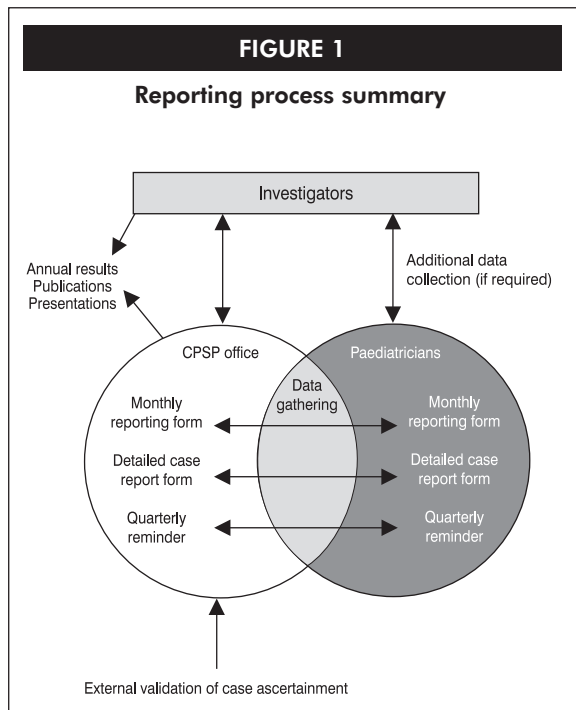
Participants report all cases meeting the case definitions, including suspect or probable cases where there is some doubt about reporting. This sometimes leads to duplicate reports but avoids missed cases. Duplicate cases are identified during case follow-up.

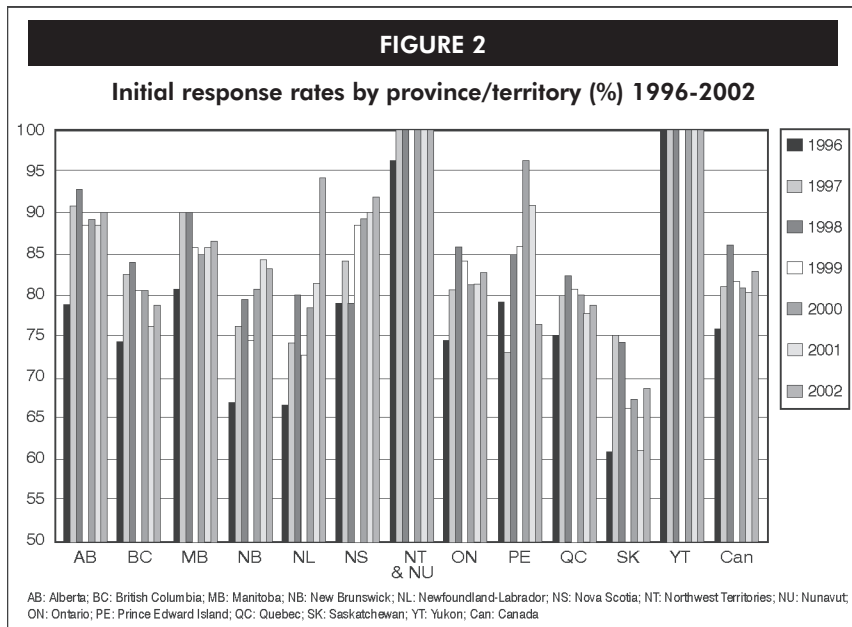
Case ascertainment is monitored and verified by investigating duplicate reports and comparing data with the following programs or centres:

- Canadian Association of Paediatric Health Centres
- Canadian Paediatric Decision Support Network
- IMPACT (Immunization Monitoring Program ACTive) centres
- Notifiable Diseases Reporting System, Centre for Infectious Disease Prevention and Control, Health Canada
- Canadian Institute for Health Information

Respondents who do not reply every month receive quarterly reminders. As well, information including the monthly compliance rates and the number of cases reported is mailed quarterly to all participants to keep them informed of progress.

Keeping the CPSP database current and increasing the initial response rate are continual challenges. To this end, all non-respondents (392) were sent a special





were entered in a draw for one of three palm pilots. The winners were: Dr. Heather Graham (Calgary, Alberta); Dr. Dany Harvey (Alma, Quebec); Dr. Elske Hildes-Ripstein (Winnipeg, Manitoba).

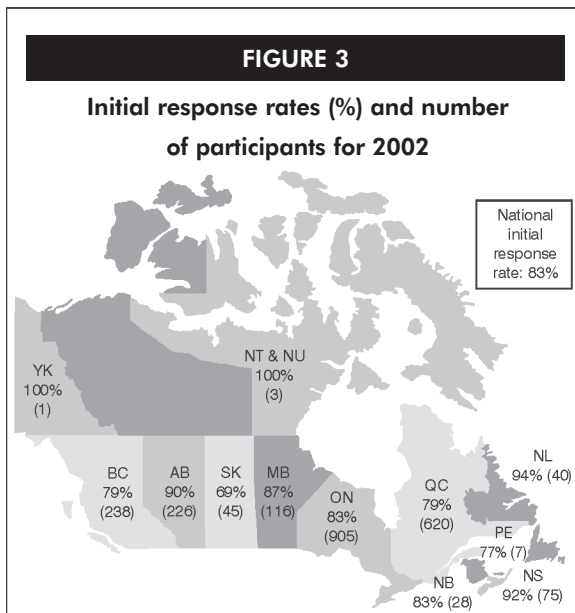
Follow-up and confirmation of case reports

The CPSP assures the confidentiality of all information provided to the program. Only non-nominal patient information, such as the date of birth, sex of the

questionnaire in 2002. This initiative reduced the number of non-respondents by 21.9% (86). Other methods will need to be devised to encourage the remaining non-respondents (306) to actively participate. See Figures 2 and 3 for reporting rates.

To thank participants for their continued support, participants who responded each month in 2001

child and comments on the condition, is requested for each reported case. This anonymous information is used to identify duplicates and is entered, as a reminder, on a detailed reporting form, which is sent to the original respondent to request case-specific information. Once the detailed report is returned to the CPSP, it is forwarded to the investigator for analysis. The investigator is responsible for contacting the respondent if further information is required. The CPSP is encouraged by the 95% response rate for completion of detailed questionnaires (see Table 1 for study breakdown).



Participant workload

Even with a total of 398 reported cases in 2002, the majority of participants (2,035 of 2,304, or 88.3%) had 'nil' cases to report. The importance of zero reporting must however be re-emphasized. As studies come and go, the workload shifts to different subspecialties. Such was the case with anaphylaxis and hemolytic uremic syndrome in 2000-2001 and now with the new study on hyperbilirubinemia that was added to the program in July 2002. Of the 398 total cases reported in 2002, 75 were hyperbilirubinemia cases reported by 51 participants in just six months. This demonstrates the commitment and buy-in of the participants to

TABLE 1			
2002 detailed questionnaire completion rates			
Studies/conditions	Reported cases	Pending	% Completion rate
Acute flaccid paralysis	91	6	93
CHARGE association/syndrome	47	1	98
Congenital rubella syndrome	4	0	100
Hemolytic uremic syndrome (3 months)	13	1	92
Hepatitis C virus infection	40	2	95
Necrotizing fasciitis	32	2	94
Neonatal herpes simplex virus infection	38	0	100
Neonatal hyperbilirubinemia — severe (6 months)	75	3	96
Neonatal liver failure/perinatal hemochromatosis	7	0	100
Smith-Lemli-Opitz syndrome	18	0	100
Vitamin D deficiency rickets (6 months)	33	3	91
Total number of cases (all studies)	398	18	95

this study; it is important for the prevention of kernicterus (bilirubin encephalopathy).

Figure 4 illustrates the number of cases reported by respondents in 2002. It shows that most participants (88.3%) had no cases to report and checked off the ‘nothing to report’ box each month. In fact, 8.5% of participants reported one case and 2.7% reported two or three cases. Only 11 participants (0.5%) completed four or more questionnaires. It is interesting to note that 110 of the 398 reported cases were duplicates, validating CPSP ascertainment. The CPSP is extremely grateful that the majority of participants faithfully complete the detailed questionnaires subsequent to reporting cases. This demonstrates that they appreciate the enormous value of the scientific data collected. To decrease the workload for participants, the Steering Committee will insist on short, precise and pertinent detailed questionnaires.

Program evaluation

The Canadian Paediatric Society and Health Canada are evaluating the CPSP to determine how well it is achieving its objectives and goals. To ensure that everyone has an opportunity to provide feedback to the program, surveys are being mailed to participants, principal investigators, public health officers and CPSP Steering Committee members.

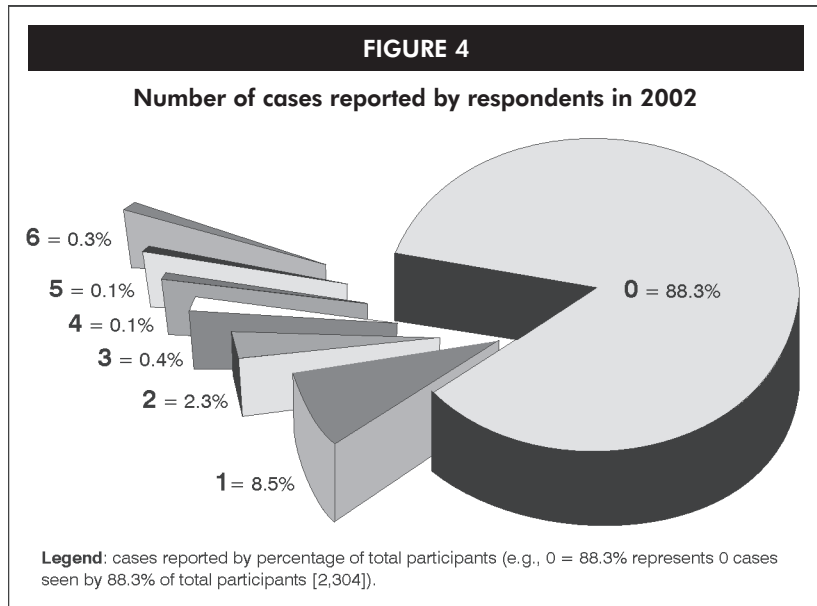


TABLE 2	
Criteria considered for inclusion of studies	
Rarity	Disorders of such low incidence or prevalence that national ascertainment of cases is needed (less than 1,000 cases a year).
Public health importance	Clearly addressing a public or paediatric health issue.
Scientific importance	Demonstrated scientific interest and importance.
Uniqueness	Proposal must demonstrate a clear need for data on a condition or disorder for which there is only limited information and for which surveillance is the most appropriate means of collecting the data.
Quality of proposal	Proposal must state clear and achievable objectives, practicability, patient confidentiality, adequate resources, clear questionnaire and method of evaluation.
Workload of paediatricians	Steering Committee must be convinced that reporting will not make excessive additional demands on the workload of paediatricians.
Priority will be given to diseases that are not currently notifiable or, if notifiable, have sufficient indication of under-notification. Investigators are expected to demonstrate that potential funding is available.	

Evaluation details, including the strengths and weaknesses of the program, will be published in the *CPSP 2003 Results*.

One-time survey questions

The CPSP is available as an inexpensive tool to survey participants on a one-time-basis in order to identify the prevalence of a problem or to answer a specific question. Once approved by the CPSP Steering Committee, the one-time survey question is sent to all participants with a monthly initial reporting form. Once collected, results are forwarded to the investigator for data analysis.

Results of the 2002 one-time survey question on baby walker injuries can be found on page 49.

Investigators' corner

The CPSP can offer investigators the use of a timely, active surveillance system to increase awareness of rare paediatric conditions among the health-care community. It provides an innovative means of identifying and obtaining data on rare diseases and

conditions from approximately 2,300 participants. The program is committed to a high-case ascertainment rate of over 90% and boasts a high response rate of 95% on detailed reports (Table 1), due to follow-up reminders to participants who have not responded. The CPSP offers an opportunity for

TABLE 3
Format for submission
<p>Proposals for new studies should include:</p> <ul style="list-style-type: none"> • name of principal author • brief abstract of proposal • proposed starting date • proposed duration • question(s) to be addressed by study • statement of justification, including how the information could be used • case definition • expected number of cases • availability of ethical approval (state source of approval) • funding arrangements • identification of projected date for completion of analysis and submission for publication

international collaboration with other paediatric surveillance units worldwide and a chance to make a difference in the health and well-being of Canadian children and youth.

Individual researchers are encouraged to submit proposals for new studies once they have reviewed the *Criteria considered for inclusion of studies* (Table 2) and the *Format for submission* (Table 3). The Steering Committee reviews submissions at its spring and fall meetings, giving preference to studies that have either strong public health importance or could not

be undertaken any other way. Studies must receive ethical approval and have funding in place before final acceptance to the program.

The CPSP is pleased to see established faculty members mentoring young researchers with their study proposals.

As previously mentioned in the *Overview* section, the CPSP is available to investigators as a cost-effective tool to survey participants on a one-time basis in order to identify the prevalence of a problem or to answer a specific question.

Studies timeline

TABLE 4			
CPSP studies timeline (by end date)			
Studies	Start date	End date	Total confirmed cases to December 31, 2002
Group B strep	January 1996	December 1996	178
Neural tube defects	January 1997	December 1998	107
Creutzfeldt-Jakob disease	January 1997	June 1999	1
Hemorrhagic disease of the newborn	January 1997	December 2000	6
Subacute sclerosing panencephalitis	January 1997	December 2000	3
Cerebral edema in diabetic ketoacidosis	July 1999	June 2001	23
Progressive intellectual and neurological deterioration	July 1999	June 2001	59
Anaphylaxis	January 2000	June 2001	732
Hemolytic uremic syndrome	April 2000	March 2002	140
Smith-Lemli-Opitz syndrome	January 2000	December 2002	35
Hepatitis C virus infection	February 2001	January 2003	58
Neonatal liver failure/perinatal hemochromatosis	February 2001	January 2003	10
Necrotizing fasciitis	September 2001	August 2003	23
Neonatal herpes simplex virus infection	October 2000	September 2003	43
Neonatal hyperbilirubinemia - severe	July 2002	June 2004	45
Vitamin D deficiency rickets	July 2002	June 2004	20
CHARGE association/syndrome	September 2001	August 2004	78
Acute flaccid paralysis	January 1996	December 2004	324
Congenital rubella syndrome	January 1996	December 2004	9
Prader-Willi syndrome	January 2003	December 2004	N/A
Early-onset eating disorders	March 2003	February 2005	N/A

CPSP Principal Investigators

Surveillance Studies in 2002

Dr. Paul Varughese
Acute flaccid paralysis
 and
Congenital rubella syndrome



Dr. Sarah Lawrence-Muirhead
Cerebral edema in diabetic ketoacidosis



Dr. Kim Blake
CHARGE association/syndrome

Dr. Paul Sockett
Hemolytic uremic syndrome (HUS D+)



Dr. François Proulx
Hemolytic uremic syndrome (SPAH)



Dr. Normand Lapointe
Hepatitis C virus infection



Dr. H. Dele Davies
Necrotizing fasciitis

Dr. Tom Wong
Neonatal herpes simplex virus infection



Dr. Michael Sgro
Neonatal hyperbilirubinemia – severe



Dr. Eve Roberts
Neonatal liver failure/perinatal hemochromatosis



Dr. Małgorzata Nowaczyk
Smith-Lemli-Opitz syndrome



Dr. Leanne Ward
Vitamin D deficiency rickets

New Studies in 2003



Dr. Bruce Carleton
Adverse drug reactions



Dr. Anne Morris
Early-onset eating disorders



Dr. Claude Cyr
Lap-belt syndrome



Dr. Leanne Ward
Osteogenesis imperfecta



Dr. Glenn Berall
Prader-Willi syndrome

Surveillance Studies in 2002

Acute flaccid paralysis

(January 1996 to December 2004)

Highlights

- No wild polio viruses have been isolated in Canada since 1988.
- The number of AFP cases was much lower than in previous years, but the number of duplicate reports was higher.
- Guillain-Barré syndrome accounted for at least 77% of confirmed AFP cases.
- No *Campylobacter* organisms were detected in stool specimens examined.
- Polio viral stool cultures are still essential.

Background

The elimination of indigenous wild poliovirus transmission in Canada, and the rest of the American region, was certified in September 1994. However, until global polio eradication is attained, there remains an ongoing risk of wild poliovirus importation from polio-endemic regions to Canada. Consequently, active surveillance of acute flaccid paralysis (AFP) in children less than 15 years old is used to monitor potential cases of paralytic poliomyelitis. Based on World Health Organization (WHO) criteria for AFP surveillance (Table 5), the estimated minimum number of cases in Canada is 58 cases per year. AFP surveillance in Canada was initiated in 1991 through the IMPACT (Immunization Monitoring Program ACTive) network of paediatric tertiary-care centres and, since 1996, has been implemented through the CPSP. This report presents the results of AFP surveillance in 2002 and compares them with previous years.

Objective

The objective of AFP surveillance is to identify AFP cases (including Guillain-Barré syndrome [GBS]) in

TABLE 5

World Health Organization quality assurance criteria for acute flaccid paralysis surveillance

- 1) one case per 100,000 in a population less than 15 years of age
- 2) adequate polio virus stool culture in 80% of cases

children less than 15 years of age to rule out paralytic poliomyelitis and thereby monitor the polio-free status of Canada.

Case definition

Acute onset of focal weakness or paralysis characterized as flaccid (reduced tone) without other obvious cause (e.g., trauma) in children less than 15 years of age. Transient weakness (e.g., post-ictal weakness) should not be reported.

Results and discussion

In 2002, out of 91 initial AFP reports, 39 were confirmed, 33 were duplicate reports and 19 either did not meet the AFP surveillance case definition or have adequate information. While 39 confirmed cases represents a rate of 0.7 per 100,000 which is below the minimum estimated background rate of one case per 100,000 in children less than 15 years of age, or 58 cases, the final number is likely to be slightly higher with the addition of anticipated 'late reports' for the current year.

While cases ranged in age from five months to 13.6 years (median 4.5 years, mean 5.1 years) in 2002, overall, Table 6 shows that the age distribution of AFP cases remained similar throughout the reporting period. Both sexes were almost equally distributed (males accounted for 46%).

Although most Canadian children are vaccinated against polio, in 2002 only 20 of the 39 cases (51%) had documentation of a routine childhood immunization, and 19 of these (95%) had received age-appropriate polio immunization. For the

remaining 19 cases, no polio vaccine-specific information was available on the detailed case report form.

Virological investigation for polio or other enteroviruses

A total of 20 (51%) cases had stool examination; virology was not done or the status was unknown for 19 (49%) cases. However, adequate stool investigation for the isolation of poliovirus or non-polio enteroviruses (i.e., stool specimen collected within two weeks of the onset of paralysis) was reported for only 13 (33% of 39) cases. For five additional cases, stool specimens were collected after two weeks of onset of paralysis, and for two cases dates were not indicated on the report. None were positive for polioviruses; one was characterized as ‘adenovirus’. None of the 14 throat and/or 22 cerebrospinal fluid specimens collected for viral isolation was positive for poliovirus. For 15 of the 39 cases (38%), stool specimens were also tested for *Campylobacter* organisms, but all were negative.

Neurological investigations consisted of at least one or more of the following:

CSF abnormalities (protein, glucose, WBC, neutrophils, lymphocytes, and RBC), nerve conduction studies, electromyography, MRI or CT scan; abnormal findings compatible with the neurological diagnosis were reported for one or more of the tests done. Twenty-five (71%) of the

35 CSF specimens indicated some abnormal findings; MRI or CT scanning was done for 27 cases (69%); nine of the 27 or 33% showed some abnormality. Electromyography and/or nerve conduction studies were done for 27 cases, 26 (96%) of which had abnormal findings.

Guillain-Barré syndrome was the final neurological diagnosis in 27 cases (69.2%), Miller-Fisher variant in three (7.7%) and transverse myelitis in six (15.4%) (Table 7). The remaining three diagnoses were myelopathy, acute demyelinating neuropathy, and cranial nerve palsy.

All 39 required hospitalization for periods ranging from one to more than 45 days (mean of 11.3 days); two cases were hospitalized for 30 days or longer. Of the 39 cases, seven (17.9%) recovered fully, 29 (74.3%) recovered partially with residual weakness, and three (7.7%) had an unknown recovery status at 60 days after the onset of paralysis.

None of the clinical specimens tested, i.e., stool, nasopharyngeal or cerebrospinal fluids, were positive for polio virus infection.

Conclusions

The 39 AFP cases identified to date for 2002 are below the expected rate in Canada, according to the World Health Organization criteria. For the corresponding period in 2001, a total of 52 cases were initially

TABLE 6							
Age distribution of AFP cases reported to the CPSP, 1996-2002							
Age group (years)	Number of cases (%)						
	1996	1997	1998	1999	2000	2001*	2002
0 – 1	2 (6.7)	—	2 (4.6)	3 (4.9)	2 (3.3)	8 (14.8)	9 (23.1)
2 – 5	11 (36.7)	13 (37.1)	15 (34.1)	18 (29.5)	24 (39.3)	18 (33.3)	16 (41.0)
6 – 10	9 (30.0)	12 (34.3)	18 (40.9)	23 (37.7)	22 (36.1)	14 (25.9)	10 (25.6)
11 – <15	8 (26.6)	10 (28.6)	9 (20.4)	17 (27.9)	13 (21.3)	14 (25.9)	4 (10.3)
Total	30 (100)	35 (100)	44 (100)	61 (100)	61 (100)	54 (100)	39 (100)

* Includes two delayed reports not included in the CPSP 2001 Results

TABLE 7							
Neurological diagnosis of AFP cases reported to the CPSP, 1996-2002							
Final Diagnosis	Number of cases (%)						
	1996	1997	1998	1999	2000	2001*	2002
Polio	0	0	0	0	0	0	0
Guillain-Barré syndrome	21 (70.0)	29 (82.8)	34 (77.3)	50 (82.0)	49 (80.3)	42 (77.7)	30 (76.9)
Transverse myelitis	6 (20.0)	2 (5.7)	6 (13.6)	7 (11.5)	4 (6.6)	8 (14.8)	6 (15.4)
Encephalitis/encephalomyelitis/encephalopathy	1 (3.3)	1 (2.9)	1 (2.3)	—	—	—	—
Myelopathy	—	1 (2.9)	—	—	—	—	—
Radiculopathy/radiculoneuritis	1 (3.3)	1 (2.9)	—	—	—	1 (1.9)	1 (2.6)
Plexitis/lumbosacral plexitis	—	—	—	2 (3.2)	—	—	—
Brachial neuritis	—	—	—	1 (1.6)	—	—	—
Rhombomyelitis	—	—	—	1 (1.6)	—	—	—
Other	—	—	—	—	8 (13.1)	3 (5.6)	2 (5.1)
Not specified/undetermined diagnosis or etiology	1 (3.3)	1 (2.9)	3 (6.8)	—	—	—	—
Total	30 (100)	35 (100)	44 (100)	61 (100)	61 (100)	54 (100)	39 (100)

* Includes two delayed reports not included in the CPSP 2001 Results

reported, although the final number has since increased to 54 with the inclusion of two additional ‘late’ reports.

The decline in the number of AFP cases documented by the CPSP over the past two years might be due to under-reporting or epidemiological peculiarities; both need to be further investigated. However, the high number of duplicate case reports, combined with the number of cases reported in older children and the continued involvement of IMPACT, may in fact indicate that this is a true reflection of the changing trend.

It is still encouraging to note that the AFP reporting rate has improved since the introduction of paediatrician-based reporting through the CPSP from 0.5 per 100,000 children less than 15 years in 1996 (30 cases) to 1.04 per 100,000 in 2000 (61 cases). For unknown reasons, the rate has decreased since then. Undoubtedly, the expansion of AFP surveillance to the CPSP has improved the completeness of surveillance by ensuring that AFP cases seen at non-tertiary hospitals are reported in addition to those cases admitted to paediatric tertiary-care hospitals and reported through IMPACT.

A major area in which the AFP surveillance could be improved is the performance of polio-specific investigations and timely reporting of results. The proportion of cases where polio-specific laboratory investigations were reported remained low in 2002, with only 33.3% of cases having had an adequate stool investigation during this period. This compares with the 33% to 51% reported for the period 1996-2001. These rates of adequate stool investigation remain significantly lower than the WHO target of 80%. While neurological investigations provide supporting evidence for the final diagnosis in the majority of reported AFP cases, polio-specific laboratory investigations remain vital for the evaluation of all cases, including those in which poliomyelitis is not being considered as a possible diagnosis. Negative results of appropriate polio-specific investigations are as important as a positive result would be in AFP case evaluations. The single most important laboratory investigation, recommended by the National Working Group on Polio Eradication, to confirm or rule out a diagnosis of paralytic poliomyelitis, is a stool specimen collected within two weeks of onset of paralysis for isolation of

wild or vaccine strain poliovirus. Specimens may be collected up to six weeks after the onset of paralysis, although after two weeks, the sensitivity of virus isolation decreases. The examination of paired serum samples for evidence of a four-fold or greater rise in poliovirus antibody titre in paired sera and/or the presence of poliovirus-specific IgM antibody in a single serological specimen further enhance the evaluation of cases.

Principal investigator

Paul Varughese, DVM, MSc, Immunization and Respiratory Infections Division, Centre for Infectious Disease Prevention and Control, Population and Public Health Branch, Health Canada, Tunney's Pasture PL 0603E1, Ottawa ON K1A 0L2; tel.: 613-957-1344; fax: 613-998-6413; e-mail: paul_varughese@hc-sc.gc.ca

Cerebral edema in diabetic ketoacidosis

(July 1999 to June 2001) – Final report, including case control study undertaken in 2002

Highlights

- The CE-DKA incidence was lower than expected at 0.5%.
- The mortality rate for CE-DKA was five out of 23 children (22%) which is comparable to other reported studies.
- Survival outcome was better than previously reported with only two in 23 showing evidence of mild neurological sequelae.
- Risk factors for CE-DKA included new onset diabetes and low initial serum bicarbonate and high urea indicating more severe acidosis and dehydration at presentation.

Background

Diabetic ketoacidosis (DKA) is a common complication of diabetes, occurring in up to 25 to 40% at diagnosis of diabetes and in approximately

5% of patients per year with established diabetes.

Previous reports have found that one to three percent of cases of DKA are complicated by cerebral edema (CE) which is associated with significant morbidity (21 to 35%) and mortality (21 to 24%). A recent population study through the British Paediatric Surveillance Unit showed the calculated risk of developing cerebral edema was 6.8 per 1,000 episodes of DKA. The risk factors for the development of CE-DKA remain controversial. Those implicated have included features at presentation (age under five years, new onset diabetes, long duration of symptoms, high initial urea, low initial pCO₂) and treatment factors (too rapid or inadequate fluid administration, use of hypotonic fluids, failure of serum sodium to rise during treatment).

Objectives

- 1) To determine the incidence of cerebral edema in association with DKA in Canadian children.
- 2) To determine outcome of cerebral edema in association with DKA.
- 3) To identify risk factors for cerebral edema in association with DKA.

Case definitions

- Children up to their 16th birthday.
- Sudden or unexpected deterioration in level of consciousness in a child or adolescent with DKA (pH < 7.35 and/or bicarbonate < 18 mmol/L in association with diabetes and ketonuria).
- Any death in a child or adolescent with type 1 or 2 diabetes, either during or unrelated to an episode of DKA.

After CT scan confirmed reports of CE occurring prior to initiation of DKA treatment, patients with CE suspected at DKA presentation were also included. A retrospective search of medical records, in all reporting centres, from 1995 to 1999, identified additional cases. Two unmatched controls/cases were reviewed.

Results and discussion

Through the CPSP, active surveillance of CE-DKA in patients less than 16 years of age (population

TABLE 8

Demographic characteristics and initial laboratory values of cases and controls

	Cerebral edema (N=23)	Controls (N=46)	P value
Age (years)*	9.6 ± 4.6	9.1 ± 4.6	0.48
Male sex (%)*	9 (39.1)	21 (45.7)	0.34
Newly diagnosed (%)*	17 (39.1)	24 (52.2)	0.017
Glucose [†]	48.8 ± 29.0	34.6 ± 16.7	0.04
Urea[†]	11.8 ± 5.4	6.6 ± 13.5	0.01
pCO ₂ [†]	19.9 ± 9.7	25.2 ± 11.3	0.26
HCO₃[†]	5.7 ± 2.7	10.2 ± 5.5	<0.001
Corrected Na [†]	149.1 ± 13.3	147.3 ± 7.8	0.56

* Analysis of demographic variables by logistic regression analysis

† Analysis of initial laboratory data by chi ratio with Bonferroni adjustment

6.4 million) was carried out from July 1999 to June 2001. All cases of DKA in children less than 16 years of age were identified from the Canadian Institute for Health Information discharge database. All CE-DKA cases and two randomly selected DKA without CE controls per case from the same institution underwent review by a single individual to confirm the diagnosis and abstract clinical data. To increase the number of cases for risk factor analysis, other cases of CE-DKA occurring at reporting institutions from 1995-1999 were identified through medical record searches. With 23 cases in two years, the incidence of CE in DKA was lower than expected at 0.5%: 57% (13/23) of the cases were identified prospectively. Mortality rate was 22% (5/23); mild neurologic sequelae was present in 9% (2/23) of cases, and 70% (16/23) were reported as normal. Low initial bicarbonate ($p < 0.001$) and high initial BUN ($p = 0.010$) concentrations were associated with increased risk of CE-DKA. In logistic regression analysis of demographic and treatment factors, only new onset diabetes was associated with CE-DKA (OR 6.9, 95% CI 1.4-33.0). No association was found with previously reported risk factors (Table 8) including young age, duration of symptoms, low initial pCO₂ or treatment factors. Compared to previous reports, mortality from CE-DKA was much the same, but outcome in survivors was considerably better.

Conclusions

Mortality rates for cases of cerebral edema secondary to DKA were similar to previous reports, but the outcome in survivors was significantly better. Analysis of risk factors revealed associations only with new onset of diabetes and some factors denoting severity of dehydration and acidosis at presentation (low bicarbonate and high BUN).

Recommendations

These data indicate that primary prevention of DKA is the critical step in avoiding cerebral edema associated with DKA and its sequelae. Those presenting with new onset diabetes and/or more severe acidosis and dehydration should be most closely monitored for development of cerebral edema.

Principal investigator

Sarah Lawrence-Muirhead, MD, University of Ottawa, Division of Endocrinology and Metabolism, Children's Hospital of Eastern Ontario, 401 Smyth Rd, Ottawa ON K1H 8L1; tel.: 613-737-7600, ext. 2434; fax: 613-738-4236; e-mail: slawrence@cheo.on.ca

Co-investigators

Elizabeth Cummings, MD, Dalhousie University
Denis Daneman, MD, University of Toronto

CHARGE association/ syndrome

(September 2001 to August 2004)

Highlights

- The population of CHARGE A/S with all four major criteria has a 67% female and 33% male distribution.
- The facial nerve (VII) is identified more frequently with other cranial nerves and in individuals who are more severely affected with CHARGE A/S. There is emerging evidence to support involvement of the trigeminal cranial nerve (V) in CHARGE A/S.
- Health care for a child with CHARGE A/S can cost over \$100,000 for the first 3.5 years of life.

Background

CHARGE association/syndrome (CHARGE A/S) is a constellation of a number of congenital anomalies that was first given the acronym CHARGE (Coloboma, Heart Defect, Choanal Atresia, Retarded Growth and Development, Genital Hypoplasia, Ear Anomalies/Deafness) in 1981. Over the past 15 years, the specificity of this pattern of malformations has reached the level that many clinicians now consider it to be a discrete recognizable syndrome (Graham JM. *Am J Med Gen* 2001; 99:120-3). With increasing expertise, it became clear that the criteria originally proposed needed further refinement. The revised consensus diagnostic criteria by Blake et al. incorporated both major and minor features for CHARGE A/S and have been documented to enhance clinical diagnosis and facilitate research efforts. These criteria consist of four major

characteristics: coloboma, choanal atresia, characteristic ear anomalies, cranial nerve dysfunction (facial palsy, vestibular dysfunction, and swallowing difficulties) and seven minor criteria: heart defect, orofacial cleft, genital hypoplasia, growth deficiency, developmental delay, tracheoesophageal fistula and a distinctive facial appearance. The diagnosis is firmly established when all four major or three major and three minor criteria are present. Some of the criteria are difficult to detect in infants, and as the major characteristics are rare in other conditions, the CHARGE A/S diagnosis needs to be considered in any individual who has one or two major criteria and several minor characteristics. To define CHARGE A/S in these individuals, a cranial CT scan may show hypoplasia of the semicircular canals and/or cochlea and/or choanal atresia or stenosis. High resolution chromosome studies, fluorescence *in situ* hybridization (FISH) for 22q11 deletion and the subtelomeric deletion FISH testing help to rule out any chromosomal abnormalities accounting for the multiple congenital anomalies. An increase in paternal age of CHARGE A/S children has been recognized as a risk factor and needs to be confirmed.

The purpose of this study is to determine the incidence and prevalence of CHARGE A/S in Canada, as the true incidence is unknown. As CHARGE A/S presents with a wide spectrum of clinical severity, mildly affected patients may also be diagnosed and can be followed prospectively. The review article, entitled "CHARGE Association: An Update and Review for the Primary Paediatrician" (*Clin Pediatr* 1998; 37:159-74), summarizes current understanding of the management of this complex and chronic multiple congenital anomaly, giving physicians a guide to the management of CHARGE A/S.

Objectives

- 1) To determine the incidence and prevalence of CHARGE A/S in Canada by ascertaining all identified cases of CHARGE A/S (old and new).
- 2) To obtain demographic and medical information on patients with CHARGE A/S, and assemble a database to answer research questions.
- 3) To follow developmentally and behaviourally an identified group of CHARGE A/S infants who have been diagnosed at an early age and have obtained early intervention services. Will early recognition and treatment of these infants improve their clinical and behavioural well-being?

Case definitions

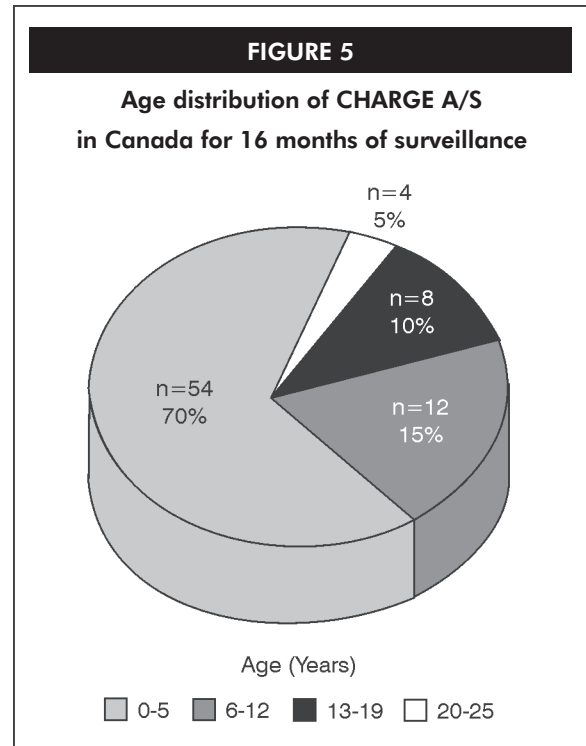
Infant/child/adult with four major criteria or three major and three minor criteria.

- Major inclusion criteria: coloboma, choanal atresia, characteristic ear abnormalities, cranial nerve dysfunction.
- Minor inclusion criteria: genital hypoplasia, developmental delay, cardiovascular malformations, growth deficiencies, orofacial cleft, tracheoesophageal (TE) fistula, characteristic face.

Exclusion criteria

Exclude other conditions such as velocardiofacial syndrome (VCS) and DiGeorge Sequence (DGS)

TABLE 9				
Parental age at child's birth				
	N	Average	Range	Standard deviation
Maternal age	62	29.6	17-44	5.9 yrs
Paternal age	43	32.5	22-49	5.3 yrs



using FISH test (fluorescent *in situ* hybridization) to exclude 22q11 deletion.

Results

In 16 months, 78 confirmed individuals, 39 males and 39 females, were reported with CHARGE A/S. Forty percent of these families agreed to be contacted for further follow-up studies. Seventy percent of the confirmed reports fall within the age of infancy to five years old, while only 15% are 13 years of age or older (Figure 5). The mean paternal age (n=42), at the CHARGE individual's time of birth, is 32.5 years; the mean maternal age (n=61) is 29.6 years (Table 9). This is higher than the Canadian average of 27.1 years for maternal age and 30.9 years for the paternal age (Nova Scotia only).

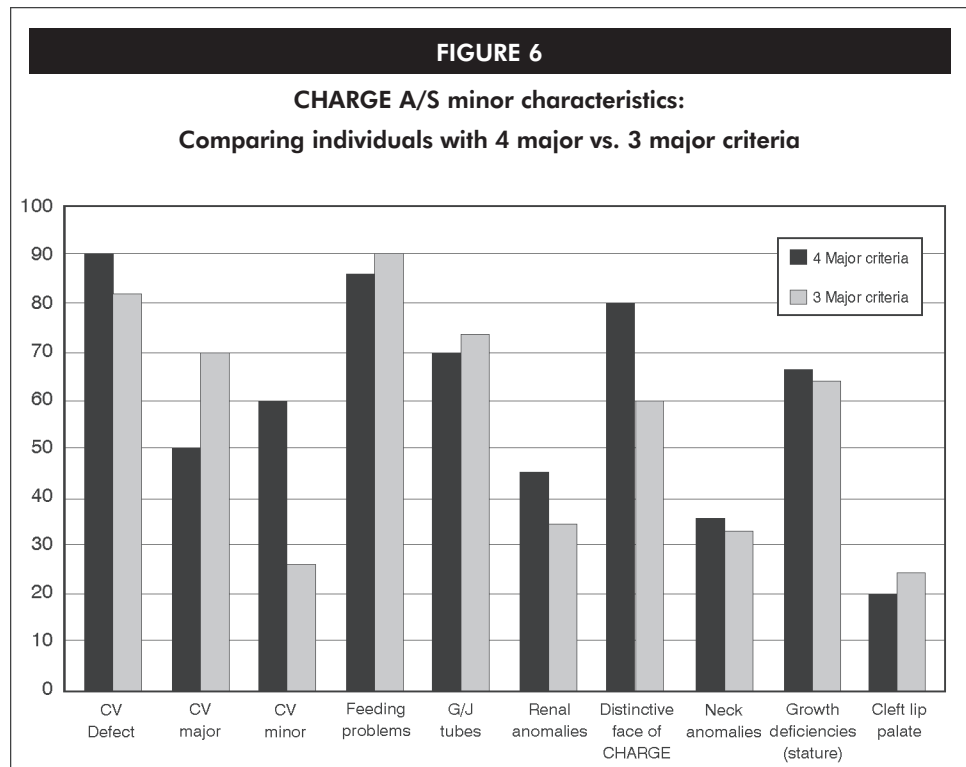
All four major criteria were present in 35% (27/78) of individuals reported with CHARGE A/S. There

were more females, 67% (18/27), than males, 33% (9/27), with the four major criteria. Alternatively, individuals with three major and three minor criteria made up 58% (45/78) of the confirmed reports with slightly more males, 58% (26/45), than females, 42% (19/45), (Figure 6).

Based on the number of reported individuals with CHARGE A/S born between

December 31, 1998 and December 31, 2002, an estimate of regional incidence was calculated (Table 10). Results indicate that the incidence of CHARGE A/S (using births from 01/01/99 to 31/12/02) varies between provinces, ranging from zero cases in Alberta to 8-12 per 100,000 live births in the Maritimes. This probably represents an under-reporting of CHARGE A/S nationally.

The mean age of diagnosis decreased dramatically from 22.5 months (1994-1996) to 4.8 months (2000-2002). It is surprising to note that between 1997 and 1999 the average age of diagnosis was as low as 1.7 months. The current increase in age at diagnosis is a result of three cases diagnosed in 2002 with an average age of 17.4 months at diagnosis. These three individuals all have the same three major criteria while lacking the fourth major criteria of choanal atresia/stenosis.



Further data analysis may reveal particular characteristics that result in late diagnosis. Early intervention is critical in children with sensory deficits, as early diagnosis can affect developmental outcomes.

The health-care costs for the first 3.5 years (inpatient, outpatient and lab costs) of one individual with four major criteria of CHARGE were calculated at over \$110,000 (Canadian). Inpatient costs totaled over \$90,000 for the first 3.5 years, 94% of which were incurred during the first year of life. These costs did not include anesthesia, ophthalmology, genetic testing, radiologic investigations and costs of cochlear implant. Having data to substantiate the health-care costs for a child with a complex condition such as CHARGE A/S is important to assess the allocation of health-care funds.

The central nervous system manifestations of CHARGE A/S were explored by analyzing

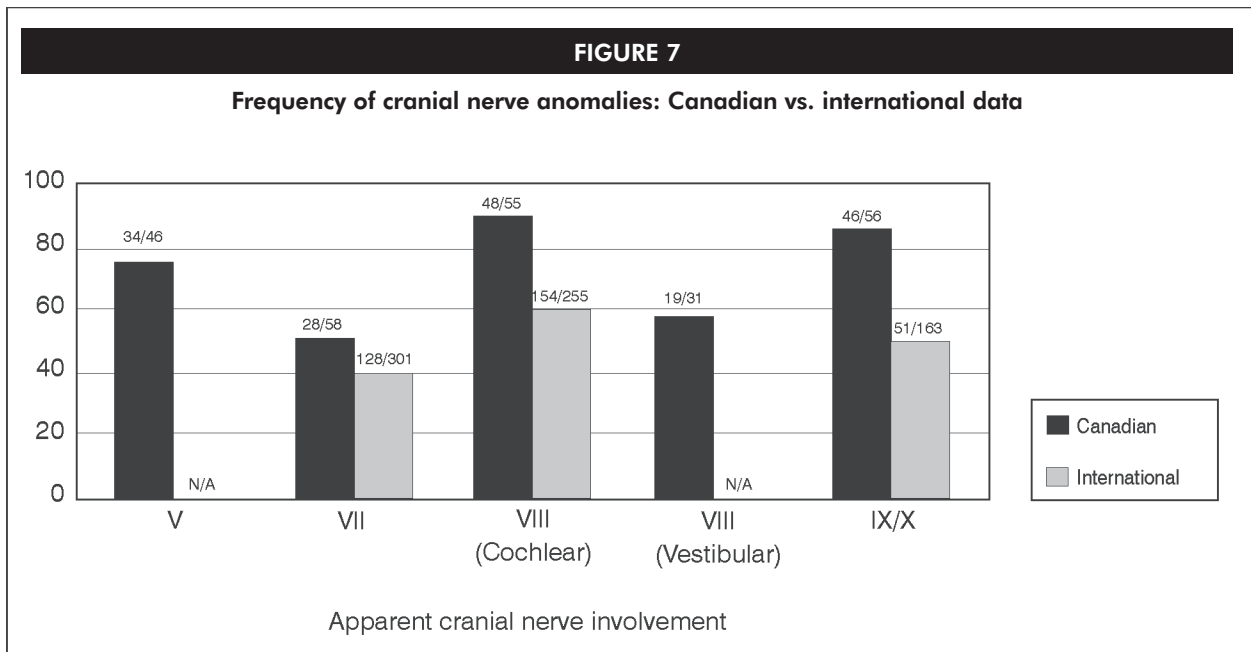
TABLE 10				
Incidence of CHARGE association/syndrome in Canada				
	Number of cases	Number of cases per year	Number of live births*	Incidence per 100,000†
British Columbia	6	1.50	39,987	3.75
Alberta	0	0.00	37,517	0
Saskatchewan	3	0.75	11,896	6.30
Manitoba	4	1.00	13,940	7.17
Ontario	13	3.25	127,479	2.55
Quebec	8	2.00	72,397	2.76
Maritimes	9	2.25	17,525	12.84
Newfoundland	2	0.50	4,689	10.66
Canada	45	11.25	327,187	3.43

* Based on Statistics Canada rates for July 2001 to July 2002

† All provincial incidences of CHARGE A/S have increased from the 2001 data (except Alberta)

the frequency and type of cranial nerve (CN) anomalies. Of the 78 confirmed reports of CHARGE A/S, 94.6% exhibited symptoms of at least one CN anomaly. Study results identified strong evidence of CN V (trigeminal nerve) involvement which has

not been previously documented in the literature (Figure 7). Cranial nerve VII (facial nerve) is seen more frequently in association with other CN anomalies as well as in those individuals who are more severely affected with the CHARGE A/S



characteristics. The extent of cranial nerve involvement may reflect the clinical spectrum of CHARGE A/S and needs further exploration.

Conclusions

- To validate or improve case ascertainment in certain provinces, the targeting of ENT and ophthalmology specialists in tertiary-care centres will help to identify the unreported cases. A focus on the Canadian Deaf Blind and Rubella Association may also help to identify more adolescents and adults with CHARGE A/S.
- The cranial nerve anomalies of CHARGE A/S need further exploration with objective testing of CHARGE individuals.
- Study data confirms older paternal and maternal mean ages at birth of an individual with CHARGE A/S.

Principal investigator

Kim Blake, MB, Division of Medical Education, IWK Health Centre, Halifax NS B3J 3G9; tel.: 902-470-6499; fax: 902-470-7216; e-mail: kblake@is.dal.ca

Co-investigators

John M. Graham, Jr, MD, Clinical Genetics and Dysmorphology, Cedars Sinai Medical Center

Chitra Prasad, MD, Section of Genetics and Metabolism, University of Manitoba

Isabel M. Smith, PhD, Departments of Paediatrics and Psychology, Dalhousie University and IWK Health Centre

CHARGE parents (for families of CHARGERS in Canada)

Lisa Weir, tel.: 506-633-8445; families, 1-866-874-2474; email: gweir@nbnet.nb.ca

Congenital rubella syndrome

(January 1996 to December 2004)

Highlights

- In 2002, the CPSP captured two confirmed cases of CRS (one born in Canada and one born abroad).
- From 1996 to 2002, zero to two newborns with CRS per year were identified through the surveillance systems in Canada (0 to 0.5 per 100,000 births).
- Canada's very low incidence of rubella and CRS is a reflection of the impact of rubella elimination strategies.
- Standing orders for vaccination of all rubella susceptible women in the immediate postpartum period are essential.

Background

In Canada, rubella immunization programs were introduced in the 1970s. However, the program strategies varied; some provinces initially opted for selective immunization of pre-adolescent females and others opted for immunization of all infants. By 1983, all provinces and territories across Canada had implemented routine measles-mumps-rubella combined vaccine (MMR) at 12 months. During 1996 and 1997, all provinces and territories introduced a routine second dose MMR or measles-rubella combined vaccine (MR) given at 18 months or four to six years. Some jurisdictions used the MR vaccine for their second dose catch-up campaigns.

Since 1970 the incidence of rubella in Canada has declined markedly; fewer than 30 cases were reported annually in the past two years. During a national consensus conference in 1994, a goal of eliminating indigenous rubella infection during pregnancy by the year 2000 was established. In November 2001, a National Expert Working Group on Rubella recommended that all rubella infections be included for enhanced surveillance.

In Canada, passive reporting of congenital rubella syndrome (CRS) to the Notifiable Diseases Reporting System (NDRS) began in 1979. Active surveillance of CRS began in 1992 through a network of tertiary-care paediatric hospitals (now representing more than 85% of paediatric tertiary-care beds in Canada) participating in IMPACT (Immunization Monitoring Program ACTive).

Objectives

- 1) To estimate the incidence of congenital rubella syndrome.
- 2) To obtain detailed epidemiological data, including maternal histories, on reported cases of congenital rubella syndrome and infection.

Case definitions

Confirmed case

Live birth

Two clinically compatible manifestations (any combination from Table 11, columns A and B) with laboratory confirmation of infection:

- isolation of rubella virus from an appropriate clinical specimen;
- or
- detection of rubella-specific IgM in the absence of recent immunization with rubella-containing vaccine;
- or
- rubella-specific IgG persisting at elevated levels for longer than would be expected from passive transfer of maternal antibody, or in the absence of recent immunization.

Stillbirth

Two clinically compatible manifestations with isolation of rubella virus from an appropriate clinical specimen.

Note: The following cannot be classified as a CRS case:

- rubella antibody titre absent in the infant;
- or
- rubella antibody titre absent in the mother;

TABLE 11	
Congenital rubella syndrome: clinically compatible manifestations	
Column A	Column B
<ol style="list-style-type: none"> 1. Cataracts or congenital glaucoma (either one or both count as one) 2. Congenital heart defect 3. Sensorineural hearing loss 4. Pigmentary retinopathy 	<ol style="list-style-type: none"> 1. Purpura 2. Hepatosplenomegaly 3. Microcephaly 4. Micro-ophthalmia 5. Mental retardation 6. Meningoencephalitis 7. Radiolucent bone disease 8. Developmental or late onset conditions, such as diabetes and progressive panencephalitis and any other conditions possibly caused by rubella virus

or

- rubella antibody titre declining in the infant consistent with the normal decline after birth of passively transferred maternal antibody.

Congenital rubella infection

Confirmed case

A case with laboratory confirmation of infection but with no clinically compatible manifestations:

- isolation of rubella virus from an appropriate clinical specimen;
- or
- detection of rubella-specific IgM in the absence of recent immunization with rubella-containing vaccine;
- or
- persistence of rubella-specific IgG at elevated levels for longer than would be expected from passive transfer of maternal antibody, or in the absence of recent immunization.

Rubella in clinical illness

Confirmed case

Laboratory confirmation of infection in the absence of recent immunization with rubella-containing vaccine:

- isolation of rubella virus from an appropriate clinical specimen;
- or
- significant rise in serum rubella IgG antibody levels by any standard serological assay;

or

- positive serologic test for rubella-specific IgM;

or

- clinical illness* in a person who is epidemiologically linked to a laboratory-confirmed case.

* Clinical illness is characterized by fever and rash, and at least one of the following: arthralgia/arthritis, lymphadenopathy, conjunctivitis. Up to 50% of rubella infections are reported to be subclinical.

Results and discussion

Two cases of CRS were reported in Canada in 2002. One case involved a non-Aboriginal Canadian-born mother who acquired rubella infection (asymptomatic according to her) while visiting India during the first trimester of her pregnancy. The other infant, African-born, was diagnosed with CRS at four months of age in Africa. This diagnosis was reconfirmed soon after the child immigrated to Canada in the fall of 2002.

From January 1996 to December 2002, with active surveillance in place, nine new reports of newborns with CRS were reported in Canada (Table 12). Of those whose status was recorded, three were born to immigrant women, one to an aboriginal woman, and three to non-aboriginal women. These seven cases illustrate the need for documentation of previously received rubella vaccination, of maternal immunity

status by a reliable method, and postpartum rubella vaccine when indicated.

Conclusions and recommendations

The very low incidence of CRS and rubella infection suggest that Canada is getting closer to achieving the goal of eliminating indigenous rubella infection during pregnancy.

Health-care providers are requested to ensure that: 1) all patients receive their rubella vaccinations at the recommended age and 2) all women without documented proof of rubella immunization receive the vaccine. Special attention should be given to assess the immunization status of women from regions with poor vaccination coverage, including women in immigrant populations. Routine rubella antibody screening antenatally by a reliable method is central to the congenital rubella prevention strategy, and all women found to be susceptible should be vaccinated in the immediate postpartum period. Standing orders for vaccination of susceptible women before discharge from hospital is the most effective way to ensure that the opportunity is not missed.

The degree of under-diagnosis and under-reporting for congenital rubella infection (CRI), CRS with less severe manifestations and CRS with delayed-onset manifestations is unknown. Physicians are reminded that it is important to investigate all infants born to mothers who have confirmed or suspected rubella infection during pregnancy, even if the infants have no obvious abnormalities on examination. Prenatal rubella screening and postpartum vaccination will continue to be essential in the quest to eliminate rubella infection during pregnancy.

Principal investigator

Paul Varughese, DVM, MSc, Immunization and Respiratory Infections Division, Centre for Infectious Disease Prevention and Control, Population and Public Health Branch, Health Canada, Tunney's Pasture, PL 0603E1, Ottawa ON K1A 0L2; tel.: 613-957-1344; fax: 613-998-6413; e-mail: paul_varughese@hc-sc.gc.ca

TABLE 12				
Cases of CRS by year of birth reported to CPSP/IMPACT and NDRS from January 1996 to December 2002				
Year of birth	Reported to NDRS* only	Reported to CPSP only	Reported to both NDRS* and CPSP	Total
1996	1	0	1	2
1997	0	0	1	1
1998	0	0	1	1
1999	0	0	1	1
2000	0	0	2	2
2001†	0	0	0	0
2002†	0	1	1	2
Total	1	1	7	9

* Notifiable Diseases Reporting System

† NDRS data for 2001 and 2002 are provisional

Hemolytic uremic syndrome

(April 2000 to March 2002) – final report

Highlights

- Thirty-four percent of children with diarrhea-associated hemolytic uremic syndrome (HUS D+) required dialysis during the acute phase of the illness.
- The mortality rate of HUS D+ was 4%.
- All cases of *Streptococcus pneumoniae*-associated HUS (SPAHS), one definite and three possible cases, required dialysis during the course of their illness.

Background

HUS is one of the leading causes of acute renal failure in many developed countries, commonly associated with prodromal symptoms, including diarrhea and bloody stools. Cases may occur singly, in family outbreaks, or linked to ingestion of contaminated food or water.

Objectives

To determine:

- 1) the incidence of HUS D+ in Canadian children, including illness caused by *Escherichia coli* O157:H7 and non-O157 strains,
- 2) the incidence of SPAHS in the same population,
- 3) Canadian surveillance data that will permit international comparisons with both developed and developing countries,
- 4) national baseline surveillance data for future HUS investigations.

Case definitions

Diarrhea associated hemolytic uremic syndrome (HUS D+)

A prodrome of enteric symptoms in a child under 16 years of age with all the following:

- 1) Acute renal impairment with serum creatinine:
 - >50 $\mu\text{mol/L}$ if <5 years
 - >60 $\mu\text{mol/L}$ if 5-9 years
 - >90 $\mu\text{mol/L}$ if 10-13 years
 - >110 $\mu\text{mol/L}$ if >13 years
- 2) Microangiopathic hemolytic anemia (Hb <100 g/L) with fragmented red cells.
- 3) Thrombocytopenia (<150,000 $\times 10^9/\text{L}$) in the absence of septicemia, malignant hypertension, chronic uremia, collagen or vascular disorders.

The above criteria may not all be present simultaneously. Neurological impairment may be present.

***Streptococcus pneumoniae*-associated hemolytic uremic syndrome (SPAHS).**

A child under 16 years of age with:

- 1) Evidence of invasive *S. pneumoniae* infection (blood or another normally sterile biological fluid: cerebrospinal, pericardial, articular, peritoneal, pleural) excluding middle ear, sinus, tracheal aspirates.
- 2) Both renal and hematological organ failures defined as above for HUS D+.

These should occur in the absence of chronic underlying conditions that may have accounted for renal and hematological dysfunctions. The above criteria may or may not be present simultaneously. Other organ failures may also occur.

Definite case of SPAHS: evidence of thrombotic microangiopathy on renal biopsy or autopsy.

Possible case of SPAHS: distinction between pneumococcal sepsis with secondary organ failures and SPAHS will be determined through a Delphi process.

Results

Table 13 shows the breakdown and status of HUS cases reported.

TABLE 13													
Hemolytic uremic syndrome results													
	Reported			Confirmed			Duplicates			Discards			
	HUS D+	SPAH	Total	HUS D+	SPAH	Total	HUS D+	SPAH	Total	HUS D+	SPAH	Total	
2000*	122	2	124	79	0	79	35	0	35	8	2	10	
2001	87	4	91	50	3	53	25	1	26	12	0	12	
2002†	12	1	13	7	1	8	3	0	3	2	0	2	
Total	221	7	228	136‡	4	140	63	1	64	22	2	24	

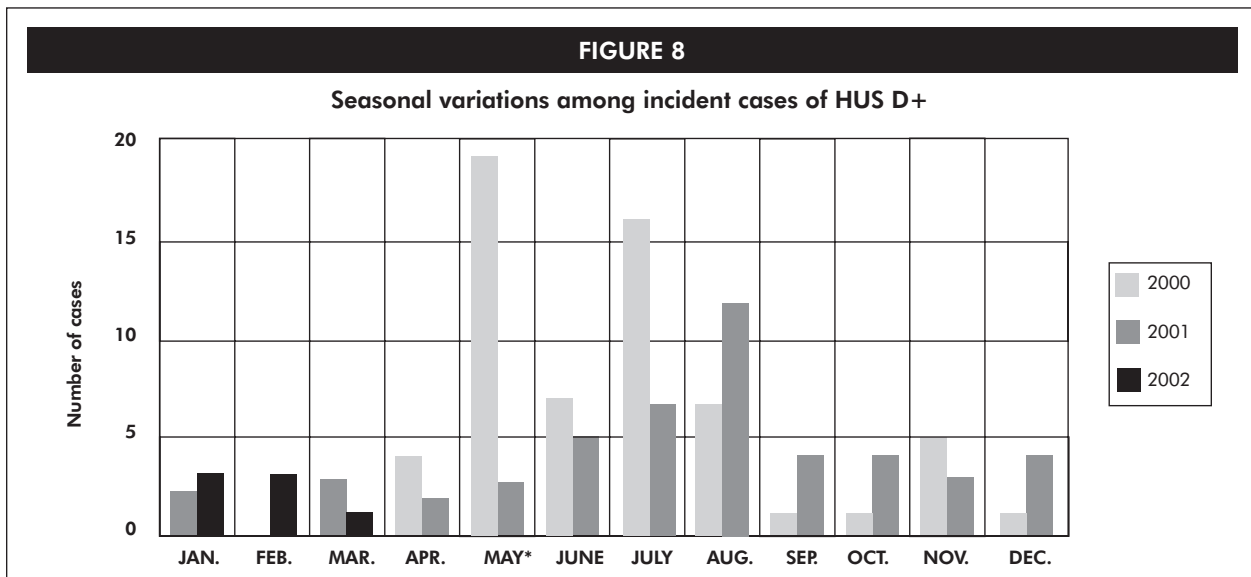
* April–December; † January–March; ‡ detailed reports were available for 121 cases

Based on the 121 detailed reports completed for confirmed cases of HUS D+, 61% were female (n=74) and 39% were male (n=47). Median age was 3.7 years (0.08-15.5). Most children with HUS D+ were within the 1-4 years old age group: <1 year (7%); 1-4 years (56%); 5-9 years (26%); 10-15 years (11%). Based upon population figures from Statistics Canada, (CANSIM II; <http://www.statcan.ca>), the incidence of HUS D+ was 1.92/100,000 of population, and 4.19/100,000 among those aged less than five years old.

Ninety-seven percent of patients (n=117) had diarrhea, 84% (n=102) bloody diarrhea, and 74% (n=90) presented with vomiting. Rectal prolapse

occurred in only one patient. Antibiotics were administered in 13% (n=16) and 3% (n=4) received antimotility agents prior to hospital admission.

Figure 8 shows the seasonal variation among incident cases of HUS D+. Sixty-three percent (n=76) of cases were reported between the months of May and August, reflecting the usual pattern of disease in the population. The high number of cases reported in May 2000 (n=19) reflects, in part, the community-based Walkerton waterborne outbreak. The summer months typically have the highest temperatures and families are on vacation and engage in a variety of potentially higher risk activities, including picnics and barbecues.



* Waterborne outbreak of gastroenteritis associated with a contaminated municipal water supply, Walkerton, Ontario, May–June 2000

The isolation of *E. coli* O157 or *E. coli* O157:H7 was noted in 67% (n=81) of the 121 confirmed cases with detailed reports. This includes one case with a mixed infection due to *E. coli* O157 and *Clostridium difficile*. HUS D+ also occurred with *Campylobacter* (n=1), *Shigella* (n=1) and *Salmonella* group B (n=1).

Thirty-one percent of cases (n=37) were treated in the intensive care unit and 34% (n=41) underwent dialysis. Moreover, 17% (n=21) of patients were evaluated for long-term renal impairment with measurement of the glomerular filtration rate. Six children (5%) were found to suffer from long-term renal impairment. Eight cases (7%) were treated for other sequelae. During the study period, the mortality rate was 4% (n=5).

In two years, three possible and one confirmed cases of SPAH were identified, all of which had evidence of oligoanuria, required dialysis and survived.

Conclusions and recommendations

- Study results have provided Canadian baseline incidence comparable to the Australian data.
- Study data shows that HUS D+ constitutes a significant public health concern in Canadian children less than five years of age.
- This information reinforces the importance of providing educational resources to families on possible exposure risks to *E. coli* O157:H7, in particular proper food preparation and food handling, especially in the barbeque season, and the need for meticulous hand-washing after preparing raw meat and other raw food produce.
- Preventive measures, such as official recalls of contaminated food products and notifications of unsafe water supplies, are imperative to prevent the disease, identify cases and minimize the magnitude of an outbreak.

Principal investigators

François Proulx, MD, University of Montreal, Paediatric Intensive Care Department, Hôpital Sainte-Justine, 3175 ch Côte-Sainte-Catherine,

Montreal QC H3T 1C5; tel.: 514-345-4675; fax: 514-345-4822; e-mail: fproulx_01@yahoo.ca

Paul Sockett, PhD, Division of Enteric, Foodborne and Waterborne Diseases, Centre for Infectious Disease Prevention and Control, Population and Public Health Branch, Health Canada, Tunney's Pasture PL 0603E1, Ottawa ON K1A 0L2; tel.: 613-941-1288 or 952-8227; fax: 613-998-6413; e-mail: paul_sockett@hc-sc.gc.ca

Hepatitis C virus infection

(February 2001 to January 2003) – final report

Highlights

- In two years of surveillance for HCV infection, 58 cases were confirmed.
- Nearly half of the children (45%) were infected by vertical transmission from mother to child. Blood transfusions were responsible for 35% of cases, and intravenous drug use for 12%.

Background

Hepatitis C virus (HCV) is now recognized as the most common cause of chronic viral hepatitis leading to cirrhosis, end-stage liver disease and hepatic carcinoma. Although HCV infection produces a more slowly progressive disease than does hepatitis B, it accounts for twice as many fatalities.

In Canada, it is reasonably estimated that the prevalence of HCV infection is about 0.8% for a total number of 240,000 infected persons. A mathematical model predicts approximately 2,200 new cases each year; 50 to 70% are unaware of their infection. Extrapolation from the general population data in Canada suggests that up to one out of 120 deliveries might occur to an HCV-infected woman. Since HCV is inefficiently spread by sexual contact,

and because screening of the blood supply is now in place, the relative epidemiological importance of vertical HCV transmission will gradually increase as it becomes the only risk factor for HCV acquisition in children.

Recent studies with long-term follow-up of HCV-infected children have suggested that infection in children is associated with milder disease than adults but this remains controversial. The clinical course in children is characterized by low or normal transaminase levels in 50-60% of children, less severe histological changes and a lower percentage with persistent presence of HCV RNA. The follow-up period in some of these children is close to 20 years. However, some children develop fibrosis on liver biopsy even within ten years of infection and the fibrosis progresses with increasing age and duration of illness. Thus, some individuals infected in early childhood will eventually progress to end-stage liver disease. A unique feature of HCV infection in children is the possibility for a limited number of patients to spontaneously eliminate the virus.

Data derived from studies and observations are dispersed and insufficient to warrant adequate care and treatment for HCV-infected pregnant women. Moreover, sufficient evidence is lacking on which to base recommendations for ante-, intra- and postpartum management of HCV-infected pregnant women to prevent transmission to their offspring. In addition, there is little information on the natural history of HCV infection in children.

Objectives

- 1) To estimate the relative burden of known HCV infection among children and adolescents followed by paediatricians.
- 2) To establish the regional distribution of known paediatric HCV infection among provinces and territories.
- 3) To estimate modes of transmission of HCV (infected blood products/organ transplantation, mother to child or intravenous drug use).
- 4) To describe the current management of HCV-infected patients.
- 5) To define the natural history of HCV infection in regards to date of infection with a special interest for HCV transmission from mother to child (prospective follow-up from birth).
- 6) To establish a pan-Canadian clinical cohort of HCV-infected children.
- 7) To standardize a questionnaire in order to compare data between different regions and countries (e.g., British Paediatric Surveillance Unit).

Case definition

Any child from birth to 18 years of age (inclusive) who is:

- a) positive for HCV by RNA PCR on two separate specimens taken two months apart after the age of one month and/or
- b) HCV antibody positive over the age of 18 months (immunosuppressed HCV-infected children may have negative antibody tests).

Results and discussion

During the two years of the study, 113 HCV infection cases were reported of which 58 were confirmed, 23 were discarded, 15 were duplicates, and 17 are still pending. Among the 58 HCV-infected children, the mean age was 10.30 years (0.15-18.52 years). Twenty-six cases were female and 32 were male. All children are alive, but two are lost to follow-up. Risk factors for HCV acquisition include vertical transmission from mother to child in 26 cases, infected blood products in 19 cases, intravenous drug use in seven, and six other less defined causes. Among 26 children vertically HCV-infected, six children were born to HIV/HCV co-infected mothers. The medical history of mothers indicates that 21 women were intravenous drug users, two had received infected blood products, one was at sexual risk and two women had unknown risk factors. Among 58 HCV-infected children recruited during these two years, 36 (62%) were Caucasian, seven (12%) were

TABLE 14									
Information from HCV-infected children									
Sex		Age group		Risk factors		Ethnic origin		Provincial distribution	
Female	36	<5 years	17	Vertical transmission	26	Caucasian	36	Alberta	12
Male	22	>5 years	41	Infected blood products	19	Aboriginal	7	British Columbia	5
				Intravenous drug use	7	Asian	3	Manitoba	3
				Other	6	Other	12	Ontario	11
								Quebec	23
								Saskatchewan	4
Total	58	Total	58	Total	58	Total	58	Total	58

Aboriginal, three (5%) were Asian and 12 were from other countries. Reports of HCV-confirmed cases come from six provinces: British Columbia (5 cases), Alberta (12 cases), Saskatchewan (4 cases), Manitoba (3 cases), Ontario (11 cases) and Quebec (23 cases) (Table 14).

Conclusions

A total of 58 new cases of HCV infection in children and adolescents were reported to the CPSP during the two-year study period. This number is lower than expected. Cases were reported from six provinces. There were no reported HCV cases from the Maritimes and the territories. It is important to note that mother to child transmission represents close to half of all confirmed cases in a context where detection of HCV among pregnant women is not generally recommended. In light of this data, the issue of HCV testing during pregnancy merits further consideration, particularly in areas of the country with higher prevalence of HCV infection. The development of a cohort of HCV-infected children of HCV-infected mothers would assist paediatric hepatologists in developing a better understanding of the natural history of HCV disease in children.

Principal investigator

Normand Lapointe, MD, Le CHU mère-enfant, Hôpital Sainte-Justine, Research Centre, 3175 ch Côte-Sainte-Catherine, Montreal QC H3T 1C5; tel.: 514-345-4836; fax: 514-345-4794; e-mail: cmis@justine.umontreal.ca

Co-investigators

Steven Martin, MD, Hôpital Sainte-Justine, Research Centre

Véronique Pelletier, MD, Hôpital Sainte-Justine

Eve Roberts, MD, The Hospital for Sick Children

Richard Schreiber, MD, Children's & Women's Health Centre of British Columbia

Lesley J. Smith, MD, University of Alberta Hospital

Necrotizing fasciitis

(September 2001 to August 2003)

Highlights

- Nearly 40% of the necrotizing fasciitis cases were preceded by varicella.
- In type II necrotizing fasciitis cases, 57% were related to group A streptococcal infection.
- Excellent outcomes may be related to high rates of surgical intervention, early use of antibiotics and use of IVIG.

Background

In 1999, the Canadian Paediatric Society issued a statement on the state of knowledge and management of children and close contacts of persons with all-invasive group A β -hemolytic

streptococcal (GABHS) infections. In that statement, it was noted that there was no national data for necrotizing fasciitis (NF) in Canada. The current study started in September 2001 using the Canadian Paediatric Surveillance Program (CPSP) to establish actual national rates and epidemiology of NF.

Objectives

To define the epidemiology, management and outcome of NF in Canadian children including:

- common presenting signs and symptoms;
- variable managements of this condition across the country, including antibiotics and intravenous immunoglobulin use, surgical procedures, and supportive care;
- relationship of varicella with type II NF;
- morbidity and mortality associated with NF;
- burden of illness for the different types of NF.

Case definitions

NF is a deep-seated infection of the subcutaneous tissue that results in progressive destruction of fascia and fat. In general NF is classified into two types.

- 1) Type I NF refers to mixed infections involving anaerobes (most commonly *Bacteroides* and *Peptostreptococcus* spp) and one or more facultative anaerobes, such as streptococci (non GABHS), and members of the *Enterobacteriaceae* (e.g., *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Proteus*).
- 2) Type II NF refers to that caused by invasive GABHS.

Results

During the 16-month duration of the study, 23 cases of NF were reported (see Table 15 for specific types), age 6.0 ± 5.1 years. Eleven were male and 12 were female. Sixteen of these cases were reported during 2002 (nine type II, six type I, and one type unknown), age 6.9 ± 5.5 years. Cases were reported

TABLE 15			
Necrotizing fasciitis cases reported by type			
	2001	2002	Total
Type I	1	6	7
Type II	5	9	14
Type unknown	1	1	2
Total cases	7	16	23

from all areas of Canada west of the Maritimes. During 2002, nine (56.3%) cases involved the lower extremities; two (12.5%) the upper extremities and five (31.2%) the head, neck, chest and abdominal areas. All 23 patients since the start of the study received a surgical procedure. See Table 16 for a list of the procedures performed. A wide variety of antibiotics were given, but most involved the use of clindamycin in combination with others. Overall, five of the 23 patients were noted to have received IVIG, while another seven patients received unspecified blood products. One patient died in 2001; no patient

TABLE 16			
Surgical procedures performed			
	2001	2002	Total
Fasciotomy	1	3	4
Fasciectomy	1	3	4
Debridement	13	17	30
Exploration	2	5	7
Wound closure	6	10	16
Skin graft	0	5	5
Radical excision	1	1	2
VP shunt replacement	1	1	2
Drainage/radical dissection/irrigation	0	1	1

died during 2002, but one remains in hospital at the time of this report. Nine (39.1%) of the 23 cases were preceded by varicella; one (14%) of the seven patients with type I and eight (57%) of the 14 with type II NF. Only one of the 23 patients had received the varicella vaccine.

The organisms involved in type I NF cases included methicillin-sensitive and -resistant *Staphylococcus aureus*, group B streptococcus, group G streptococcus and *E. coli*.

Discussion

Although the study has better defined the epidemiology of necrotizing fasciitis, some answers to the original questions remain due to the rarity of the condition. However, CPSP results suggest that NF appears nationally and affects Canadian children with a mean age of six years. The lower extremities are most commonly involved. Varicella remains an important risk factor preceding type II NF within a month, occurring in close to half of all patients. The outcomes were excellent and may be related to one or more of the high rates of surgical intervention, early use of antibiotics and use of IVIG.

Conclusions

As 39.1% of all cases (types I and II) are related to varicella, implementing universal varicella immunization would impact significantly on the incidence of NF, particularly those related to group A streptococcus. Surveillance through the CPSP is leading to a better understanding of the epidemiology of paediatric NF in Canada. Continuing this study will help to better define provincial and national rates of the disease and provide answers for some of the remaining research questions.

Principal investigator

H. Dele Davies, MD, Pediatrics and Human Development, Michigan State University, B240 Life Sciences Building, East Lansing MI 48824-1317, USA; tel.: (517) 353-5042; fax: (517) 353-8464; e-mail: daviesde@msu.edu

Neonatal herpes simplex virus infection

(October 2000 to September 2003)

Highlights

- The case fatality rate was 16%.
- Seventy-one percent of fatal cases were typed HSV-2.
- More than one third of women were unaware of a history of HSV infection prior to delivery.
- The majority of cases (62%) were HSV-1 infections, which has implications for herpes vaccine development.

Background

Herpes simplex virus (HSV) infections are still a public health concern as a high proportion of maternal infections are unrecognized. The most serious direct consequence of genital HSV infection is the perinatal transmission from mother to infant. With limited data available, it is not possible to determine accurately the prevalence, incidence and trends of neonatal herpes infection in Canada. Data collection is essential to better understand the epidemiology and to monitor the trends. Canadian data on maternal and infant risk determinants, morbidity and mortality will allow comparison of neonatal herpes infection rates with other countries. These pre-vaccine baseline data will be used to define the burden of illness in Canada, promote prevention, develop program strategies, and enhance future research.

Objectives

- 1) To estimate the incidence of neonatal herpes infections (HSV-1 and HSV-2). For the purpose of this study, the neonatal period is being extended to 60 days of life so that late diagnosis is not missed.
- 2) To quantify the proportion of localized or disseminated HSV diseases.

- 3) To identify maternal risk determinants and HSV status prior to delivery.
- 4) To analyze trends of cases by age, sex and province.
- 5) To establish a cohort to document the morbidity/mortality of HSV neonatal infections.

Case definition

All cases will be laboratory-confirmed by at least one of the following tests:

- 1) Culture
- 2) HSV IgM
- 3) Polymerase chain reaction (PCR), in an infant equal to or less than two months (60 days) who demonstrates one of the following:
 - localized infection involving the skin, eyes or mouth,
 - disseminated infection:
 - a) to central nervous system (CNS), e.g., encephalitis,
 - b) to organs other than CNS.

Results and discussion

Since October 2000, 43 confirmed cases have been reported (5.8 per 100,000 live births), with five additional cases under investigation (Table 17). For reporting purposes, the year of diagnosis of a positive laboratory test for HSV was used.

The overall demographic and health profile of the 43 confirmed neonatal HSV cases is summarized in Table 18 for mothers and Table 19 for infants.

TABLE 17				
Neonatal HSV cases reported to the CPSP October 2000 to December 2002				
Status	2000 (3 mths)	2001	2002	Total
Confirmed HSV*	4	24	15	43
Possible HSV	0	2	3	5
Did not meet entry criteria†	4	7	4	15
Duplicates	2	19	16	37
Total	10	52	38	100

* Including fatal cases: 1 (2000), 3 (2001), 3 (2002), 7 (Total)

† Excluded due to case definition (12), date of diagnosis prior to October 2000 (3)

TABLE 18	
Neonatal HSV cases diagnosed October 2000 to December 2002 Demographic and health profile of mothers	
Mean age (years)	26
Ethnicity:	
• Caucasian	76%
• Aboriginal	7%
• Black	5%
• Other	11%
Delivery type:	
• Caesarian	21%
• Vaginal	79%
Absence of an HSV history prior to delivery*	36%
Presence of intrapartum genital HSV lesions	2%
HIV infected	0%

* Information available to paediatricians in 14 mothers

The majority of confirmed HSV cases (28/43, 65%) were reported equally from Ontario and Quebec, with an additional 7% from the Maritimes, and the remaining 28% from Western Canada. Of the 41 neonates with known treatment information, 98% received acyclovir. Six neonates developed seizures and seven died. The overall case fatality rate (CFR) was 16% with a CFR of 31% in disseminated infections versus 5% in localized infections, $p=0.02$. Seven infants died within 24 days of birth, with dissemination to CNS in over 70%, to the liver in 57%, and to the lungs in 43% of cases. The majority (71%) of fatal cases were typed HSV-2. Ten surviving infants (28%) were discharged home on oral acyclovir and one infant was entered into an oral acyclovir versus placebo trial.

Conclusions

With 43 confirmed cases in just over two years, the preliminary Canadian neonatal HSV incidence rate is 5.8 per 100,000 live births. This represents a rate that is closer to the United Kingdom rate of two per 100,000 live births than to the United States rate of 20-50 per 100,000 live births. In Canada, over

TABLE 19

**Neonatal HSV cases diagnosed
October 2000 to December 2002
Demographic and health profile of infants**

Female	47%
Mean gestational age (weeks)	37.7
Preterm birth (<37 weeks)	23%
Mean birth weight (grams)	2901
Median APGAR score at 5 minutes	9
Median age at laboratory diagnosis (range)	12 (0–45) days
HSV type:	
• HSV-1	62%
• HSV-2	38%
Classification of HSV infection:	
• Localized	62%
• Disseminated	38%

one third of the infections were disseminated cases, with an overall case fatality rate of 16%. Over half of the cases were HSV-1, which has implications for herpes vaccine development. Prevention of neonatal HSV infection presents a great challenge since a significant number of women were unaware of a history of genital herpes infection prior to delivery.

Principal investigator

Tom Wong, MD, Division of Community Acquired Infections, Centre for Infectious Disease Prevention and Control, Health Canada, Jeanne Mance Bldg., Room 701A, Tunney's Pasture AL:1907A4, Ottawa ON K1A 0K9; tel: 613-957-1080; fax: 613-957-0381; e-mail: Tom_Wong@hc-sc.gc.ca

Co-investigators

Joanne Embree, MD, University of Manitoba

I.D. Rusen, MD, Health Surveillance and Epidemiology Division, Health Canada

Marc Steben, MD, Régie régionale de la santé et des services sociaux, Montréal

Sandra Burton, BSc, Division of Community Acquired Infections, Health Canada

Neonatal hyperbilirubinemia – severe

(July 2002 to June 2004)

Highlights

- Confirmation of 45 cases in six months demonstrates the timeliness of the study.
- Laboratory evaluation for the etiology of the hyperbilirubinemia remains inadequate or incomplete in many cases.
- A complete hematological workup to identify the etiology of hyperbilirubinemia is required prior to discharge.

Background

Even though the occurrence of severe neonatal hyperbilirubinemia and bilirubin encephalopathy is very rare, it can be associated with significant morbidity. Bilirubin encephalopathy is a condition that is unfamiliar to most paediatricians practicing today. In the 1940s and 1950s, bilirubin encephalopathy was a common complication of hyperbilirubinemia associated with Rhesus (Rh) disease and occasionally with ABO hemolytic disease. With the introduction of exchange transfusions and Rh immunoglobulin, a reduction in the occurrence of bilirubin encephalopathy was noted. Also, better antenatal monitoring and the availability of intrauterine blood transfusion in Rh-affected women has eliminated most of the cases of erythroblastosis fetalis secondary to Rh disease. Phototherapy has drastically reduced the need for exchange transfusions. Despite this, in the last several years, reports of bilirubin encephalopathy associated with extremely high serum bilirubin levels have increased (Penn et al., 1994, MacDonald et al., 1995, Maisels et al., 1995). In most of these cases, term infants appeared to be healthy and breast-fed with no evidence of obvious hemolytic disease (Rh disease or other antibody-related hemolysis).

Based on epidemiological studies, a number of risk factors have been found to be associated with severe hyperbilirubinemia in the newborn. These include: jaundice presenting in the first 24 hours, jaundice noted at discharge from the hospital, previous sibling with jaundice, gestational age between 35 and 38 weeks, breast feeding and infant bruising and cephalhematoma (Dennery et al., 2001, Newman et al., 2000). Additional risk factors identified by laboratory investigations include Rh and ABO incompatibility and glucose 6 phosphate dehydrogenase (G6PD) deficiency.

The frequency of severe neonatal hyperbilirubinemia during the current era has not been well documented. Attempts to better quantify its frequency, etiologies and associated risk factors in Canada would be of value prior to identifying strategies for risk reduction. Information obtained from a screening program for the detection of G6PD deficiency or routine determination of blood group and Coombs' analysis on cord blood may help to achieve risk reduction.

Objectives

- 1) To obtain epidemiological data about the incidence and the burden of severe neonatal hyperbilirubinemia and bilirubin encephalopathy.
- 2) To identify the timing of presentation of jaundice, etiology and associated triggering or risk factors.
- 3) To help develop prevention strategies (G6PD deficiency screening program, cord blood group and Coombs' test, and educational programs).

Case definition

Term infants 60 days of age or less with unconjugated hyperbilirubinemia, who have had either:

- 1) peak serum total bilirubin >425 µmol/L; or
- 2) neonatal exchange transfusion.

Exclusion criteria

Infants who have had exchange transfusion for well-documented Rh isoimmunization disease or are less than 36 weeks of gestational age will be excluded.

TABLE 20				
Severe neonatal hyperbilirubinemia July to December 2002				
Reported	Confirmed	Duplicates	Discarded	Under review
71	45	5	6	15

Results

During the first six months of surveillance for severe neonatal hyperbilirubinemia, 71 cases were reported, with 45 confirmed and 15 still under review (Table 20). Duplication of reporting occurred in five, and a further six cases were discarded due to conjugated hyperbilirubinemia (n=3), preterm infants (n=2) and onset prior to start of the study (n=1).

In 17 cases, the cause of the hyperbilirubinemia was identified. The etiologies included: G6PD deficiency (n=7), ABO incompatibility (n=6) and other antibodies (n=4; one each with anti-c and anti-C antibodies and two with anti-E antibodies). The average peak bilirubin reported was 466 µmol/L with range from 156 to 640 µmol/L. The infant with a bilirubin level of 156 µmol/L had evidence of hemolysis with hemoglobin of 76 g/dL at one hour of age. Thirteen of the 45 neonates required exchange transfusion while all infants were treated with phototherapy.

Conclusions

Severe neonatal hyperbilirubinemia continues to occur in term neonates. In a significant proportion of reported cases, the underlying etiology could not be identified, which could be partly attributed to incomplete evaluation at the time of presentation. This finding highlights the importance of a complete hematological workup, including a screen for blood group and Coomb's testing, total and direct bilirubin, complete blood count with a peripheral smear, screen for G6PD, serum electrolytes and blood culture. If an etiology is not identified, further testing should be guided by the

clinical history and requested at the discretion of the attending physician.

Principal investigator

Michael Sgro, MD, University of Toronto,
Department of Paediatrics, Saint Michael's
Hospital, 30 Bond St, Toronto ON M5B 1W8;
tel.: 416-864-6060, ext. 6560; fax: 416-864-5344;
e-mail: sgrom@smh.toronto.on.ca

Co-investigator

Vibhuti Shah, MD, University of Toronto,
Department of Paediatrics, Mount Sinai Hospital

Neonatal liver failure/perinatal hemochromatosis

(February 2001 to January 2003) – final report

Highlights

- Ten cases of neonatal liver failure were identified over the two-year study period.
- Only one definite case of perinatal hemochromatosis was confirmed.
- 'Chronic-pattern' liver failure accounted for 60% of cases with the remaining 40% being 'acute-pattern' caused by viral or bacterial infections.
- No tyrosinemia type 1 patient was identified, demonstrating the success of early identification and treatment.
- The prognosis was better than expected with a survival rate of 50% overall.

Background

The conventional definition of acute liver failure in older children and adults involves a timeframe that does not make sense in the neonate, namely "features of liver failure developing four to eight weeks after the onset of clinical liver disease." Thus, the case

definition below was developed specifically for this study. The prevalence of neonatal liver failure (NLF) is unknown, because this definition is novel and the diagnosis is not always pursued. An example of a 'chronic-pattern' NLF is perinatal hemochromatosis, which is rare, poorly understood, and presents with cirrhosis and iron deposition in the liver and extrahepatic organs, excluding the reticulo-endothelial system. Although some infants with NLF recover spontaneously, the majority do not, requiring specific medical intervention or liver transplantation for survival.

Objectives

- 1) To obtain an unbiased, cross-sectional incidence of neonatal liver failure in Canada.
- 2) To collect epidemiological data for neonatal liver failure.
- 3) To determine the proportion of cases due to perinatal hemochromatosis.
- 4) To increase awareness in the paediatric community of the various etiologies that cause NLF.

Case definitions

Neonatal liver failure is defined as severe hepatic dysfunction with coagulopathy, metabolic instability and signs of liver damage presenting in the first (approximately eight) weeks of life. There are two patterns: acute liver cell injury or chronic hepatic insufficiency.

- In the 'acute-pattern', a previously normal liver suffers a severe insult, usually from viral infection.
- In the 'chronic-pattern', the liver is extensively damaged and may be cirrhotic at birth: serum aminotransferase levels are typically near-normal, coagulopathy is severe, serum albumin is low, and ascites (including fetal ascites) may be present. Genetic-metabolic diseases predominate with the chronic pattern.

Results

NLF is a good candidate for a surveillance study because affected infants are extremely memorable

TABLE 21			
Neonatal liver failure/perinatal hemochromatosis cases February 2001 to December 2002			
	2001	2002	Total
Confirmed NLF	6	4	10
'Acute-pattern'	2	2	4
'Chronic-pattern'	4	2*	6
Duplicates	4	2	6
Discards	5	1	6
Total reports	15	7	22
Perinatal hemochromatosis	0	1	1
Viral/bacterial infections	3	2	5
Survived	4	1	5
Died	2	3	5

* Includes one case of perinatal hemochromatosis

patients. These infants pose rare puzzling diagnoses, and they have difficult management problems. Geographical distribution of confirmed cases was nearly equal across the country. Notably, the ratio of 'acute-pattern' to 'chronic-pattern' cases was 2:3. Causes of 'acute-pattern' NLF included such classic etiologies as *Herpes simplex* infection in two, *Coxsackie B* virus infection in one, and overwhelming *Serratia marcescens* infection in the fourth. Metabolic disorders found in infants with 'chronic-pattern' NLF were: galactosemia in one, and X-linked adrenoleukodystrophy in another, representing the first reported case causing neonatal liver failure. No child was reported with neonatal liver failure due to hereditary tyrosinemia type 1 despite its high prevalence historically in the Saguenay-Lac-St-Jean region of Quebec. Two cases were classified as severe idiopathic neonatal hepatitis syndrome and will require further diagnostic clarification. One case of

perinatal hemochromatosis was confirmed. Sadly, after completion of this study, a second case of perinatal hemochromatosis was identified in the same family and confirmed at pathological examination of the fetus when the pregnancy was terminated. Another finding of interest was that survival was 50% when comprehensive medical support was offered in the neonatal intensive care setting.

Conclusions

No similar study relating to neonatal liver failure exists. The few studies currently in the literature are extremely interesting but feature significant ascertainment bias, since they emanate from tertiary-care paediatric hepatology or liver transplant units. The relatively small numbers of patients reported are by no means surprising because conditions leading to NLF are extremely rare. The absence of tyrosinemia reports might be due to the somewhat brief study duration or reflect the success of concerted efforts in Quebec to deal with this severe metabolic liver disease. The definition of neonatal liver failure used in this study is effective for identifying affected infants. The study data reinforce the importance of confirming the diagnosis because with adequate medical support, more of these infants survive than perhaps was previously appreciated. Interestingly in this study, neonatologists and general paediatricians made the majority of NLF diagnoses, later to be confirmed by gastroenterologists or paediatric hepatologists. Thus, raising awareness in the paediatric community of the many different causes of NLF is very important.

Principal investigator

Eve Roberts, MD, University of Toronto, Division of Gastroenterology and Nutrition, The Hospital for Sick Children, 555 University Ave., Toronto ON M5G 1X8; tel.: 416-813-7733; fax: 416-813-4972; e-mail: eve.roberts@sickkids.ca

Co-investigator

Andrew James, MD, University of Toronto

Smith-Lemli-Opitz syndrome

(January 2000 to December 2002) – final report

Highlights

- All confirmed cases were Caucasians of European ancestry.
- The estimated incidence in this population is one in 29,700.
- Three new *DHCR7* mutations were identified.

Background and rationale

Smith-Lemli-Opitz syndrome (SLO) is an inherited defect of cholesterol synthesis caused by mutations in the 7-dehydrocholesterol reductase gene (*DHCR7*). The enzymatic defect leads to a generalized cholesterol deficiency, and to an accumulation of the immediate precursor, 7-dehydrocholesterol (7-DHC), in all body tissues, resulting in a characteristic syndrome of multiple malformations, dysmorphic features, mental retardation, and behavioural abnormalities. SLO is readily diagnosed by demonstration of elevated levels of the cholesterol precursor 7-DHC that accumulates in body fluids and tissues of these patients. The use of a biochemical diagnostic test for SLO has led to the diagnosis of SLO in fetuses and in infants with multiple or lethal anomalies that previously defied diagnosis, as well as in individuals who have significant mental retardation and behavioural abnormalities, but minimal physical features. Many of the latter group of patients escaped detection for long periods of time; some were diagnosed with idiopathic mental retardation, pervasive developmental disorder, or autism. The behavioural phenotype of SLO is characterized by autistic features, tactile defensiveness, and significant sleep disturbance among other features. Treatment of SLO with dietary cholesterol supplementation has shown promise with improvement in the general health, as shown by reduction of frequency of infections, improved growth, and significant improvement in

behaviour. Families of children with SLO treated with cholesterol supplementation report great improvement in the quality of life in addition to the physical improvements. It is possible that early institution of treatment may improve the final developmental outcome of patients with SLO; thus, if SLO has a sufficiently high incidence, newborn screening of SLO may be indicated.

Objectives

- 1) To determine the incidence and prevalence of inherited deficiency of 7-dehydrocholesterol reductase in Canada by ascertaining all newly diagnosed cases of SLO.
- 2) To determine whether prenatal and neonatal screening for SLO is indicated in Canada.
- 3) To obtain demographic and medical information on patients with SLO and to assemble a database for demographic studies and future research use (e.g., evaluation of dietary and medical therapies, genotype-phenotype correlation).

Case definitions

Confirmed case

Elevated concentration of 7-dehydrocholesterol (7-DHC) in plasma (postnatal), or in chorionic villus sample or amniotic fluid (prenatal), or in blood spots obtained as part of neonatal screening.

Probable case (requires biochemical or DNA confirmation):

- A. Infant/child/adult with developmental delay/mental retardation, with behavioural abnormalities/attention deficit hyperactivity disorder (ADHD)/autistic features, with normal chromosomes, and any two of the following features:
 - i. 2-3 toe syndactyly (webbing)
 - ii. index finger clinodactyly ('zig-zag' index finger)
 - iii. abnormal facial features (epicanthal folds, short nose, micrognathia)
 - iv. ptosis
 - v. genital anomalies in the male

- vi. failure to thrive
 - vii. feeding difficulties requiring gavage tube feeding
- B. Stillbirth or newborn with normal chromosomes and any two of the following features:
- i. ambiguous genitalia/genital anomalies in male infant/female external genitalia in an infant with normal male chromosomes
 - ii. abnormal facial features (epicanthal folds, short nose, micrognathia)
 - iii. cleft palate/submucous cleft
 - iv. polydactyly of hands or feet
 - v. lobster hand deformity or missing fingers of hand
 - vi. 2-3 toe syndactyly (webbing)
 - vii. internal anomalies (any of the following: cystic renal dysplasia, nervous system malformations, unilobar lungs, adrenal lipid accumulation, cardiovascular malformations, punctate stippling of epiphyses)
 - viii. low unconjugated estriol on maternal serum screening during the second trimester of pregnancy
- C. Previous clinical diagnosis of SLO without documented elevation of 7-DHC or known 7-DHC reductase mutations

towards reporting of newly diagnosed infants and older patients. The overall reporting of newly diagnosed cases remained relatively constant throughout the duration of surveillance: five newborns and two older patients in Year I, five newborns in Year II, and three newborns and two older patients in year III.

The report of nine confirmed new cases born or predicted to be born between November 14, 1999 and October 18, 2000 yielded an expected incidence of one in 37,100 births across Canada. This finding is in keeping with previously observed incidence in Ontario. The rate of diagnosis/reporting of patients with severe SLO falls within the expected/predicted range.

Before the start of the study, 15 patients with SLO were known to live in Canada. An additional 18 patients with SLO who were alive on July 1, 2002 were identified during the study. Given that the population of Canada was 31,414,000, this number yielded a minimum prevalence of SLO of one in 951,939 on July 1, 2002.

All cases of SLO were reported in Caucasian infants of European origin representing Northern and Western Europe, as well as Greek, Portuguese, Italian and Slavic ancestries. In addition, French-Canadians of Acadian ancestry were well represented. The ethnic background of the cases reflects the ethnic groups in which SLO had been previously reported. Accordingly, the incidence of SLO in the defined population of Caucasians of European origin is estimated to be one in 29,700 births. Information on ethnicity is important in identifying populations at risk, and in turn, identifying which populations would most benefit from prenatal screening.

Overall, four older patients were diagnosed with SLO during the surveillance period. In Year I, two cases were diagnosed at eight months and ten years of age. In Year III, two cases were diagnosed at five and eight years of age. Cases with a previous diagnosis (and on

Results

TABLE 22					
Smith-Lemli-Opitz syndrome results					
January 1, 2000 to December 31, 2002					
	Reported	Confirmed	Duplicates	Discarded	Pending
Year I	36	19	10	7	0
Year II	32	11	13	8	0
Year III	18	5	9	4	0
Total	86	35	32	19	0

Discussion

In the first two years of the study, both new and previously diagnosed cases were reported at the same rate. In the third year, however, there was a shift

whom data are available) were diagnosed at 18 months and 2.5, five, and ten years of age, resulting in a mean age at diagnosis for 'late diagnosed patients' of 5.28 years. This finding underscores the delays in diagnosing patients with mild SLO.

During the study, the distribution of cases across Canadian provinces mirrored the population density. The majority of cases were reported in the most populous provinces (Ontario and Quebec, 23 confirmed cases), with no cases identified in Saskatchewan, and the Yukon, Northwest and Nunavut territories. Cases from New Brunswick and Prince Edward Island were reported through Nova Scotia as the local genetic centre, leading to an elevation in the case density in the latter province. However, even for the population of the combined provinces, the number of cases was higher than expected in the Maritime provinces combined (one per 368,000 of population). In Manitoba and in Newfoundland, the number of confirmed cases was approximately one in 500,000. In the remaining provinces, the rate was approximately one confirmed case per one million of population. These variables likely represent the ethnic make-up of the various provinces, as well as the possibility of a founder effect in the Maritime and Newfoundland provinces.

The majority of patients reported to the CPSP and confirmed to have SLO underwent mutation analysis. Three new *DHCR7* mutations were identified: two in patients with mild SLO (Y280C and I291T) and one in a newborn with severe SLO (W248R). The mutations found in patients with mild SLO are likely unique mutations. The underlying genetic background of *DHCR7* mutations was determined in some of the ethnic groups.

Data results on incidence supported the extension of the National Institutes of Health-funded multi-centre international study on prenatal screening for SLO to include prenatal centres in Ontario and in British Columbia.

Conclusions

- The rate of diagnosis of SLO remained essentially the same throughout the study.
- All Canadian patients with SLO are of European ancestry.
- The minimum incidence of severe SLO in Canada is one in 29,700 Caucasian births.
- The minimum prevalence of SLO in Canada was one in 951,939 on July 1, 2002.

Principal investigator

Małgorzata J.M. Nowaczyk, MD, McMaster University, Department of Pathology and Molecular Medicine, Department of Paediatrics, Room 3N16, McMaster University Medical Centre, 1200 Main St W, Hamilton ON L8S 4J9; tel.: 905-521-5085; fax: 905-521-2651; e-mail: nowaczyk@hhsc.ca

Vitamin D deficiency rickets

(July 2002 to June 2004)

Highlights

- In six months, 20 nutritional rickets cases were confirmed with significant morbidity at diagnosis, including fractures, limb deformity, poor growth and delayed gross motor milestones.
- The disease has been mostly confined to darker-skinned infants who have been breast-fed without vitamin D supplementation.
- The mothers have often been veiled, had poor dietary intake of vitamin D, and did not receive vitamin D supplementation while breast-feeding.

Background

Vitamin D is necessary for calcium homeostasis and for mineralization of the growing skeleton. A deficiency in vitamin D during childhood is

associated with potentially significant clinical consequences, as it leads to a mineralization defect of the growth plates (rickets) and of bone tissue (osteomalacia). Poor linear growth and skeletal deformity are hallmarks of vitamin D deficiency during childhood, in addition to hypocalcemic seizures, abnormal dentition, and delayed developmental milestones. The disease is entirely preventable through such simple measures as ensuring adequate dietary intake of vitamin D or administration of a daily supplement.

Recent literature has proposed that the incidence of vitamin D deficiency rickets (VDDR) is rising in many countries worldwide, and clinical experiences suggest that Canada may be no exception. This is despite the regulated, Canadian public health policy that all fluid dairy products (excluding yogurt drinks) are fortified with vitamin D, as infants and children living in Canada cannot depend upon adequate skin exposure to sunlight for vitamin D synthesis. Furthermore, the Canadian Paediatric Society has recommended that all exclusively breast-fed infants receive a daily supplement of oral vitamin D, since breast milk is not a rich source of this nutrient. Despite these preventative measures, VDDR appears all too frequently in Canada, with certain geo-ethnic groups continuing to be at heightened risk for developing the disease. The main purpose of this study has been to determine the incidence of VDDR among children living in Canada by seeking reports of all newly diagnosed cases between July 2002 and June 2004.

Objectives

- 1) To ascertain the incidence of simple vitamin D deficiency (nutritional rickets) among children living in Canada by identifying all newly diagnosed cases over a two-year period.
- 2) To obtain demographic and medical information that will assist in the identification of children at risk for developing the disease.
- 3) To evaluate the efficacy of current strategies to prevent the development of the disease in Canada.
- 4) To supply data that will assist with the development of novel public health policies to prevent nutritional rickets among children living in Canada.

Case definition

Children up to and including 18 years of age with calcipenic rickets secondary to simple vitamin D deficiency (also known as nutritional rickets).

Inclusion criteria

- 1) Low serum 25-hydroxyvitamin D (25OHD)
- 2) Elevated serum alkaline phosphatase

Exclusion criteria

- 1) Vitamin D deficiency rickets associated with underlying disease, such as fat malabsorption, liver disease and renal insufficiency, and with illnesses necessitating total parenteral nutrition.
- 2) Vitamin D deficiency secondary to heritable disorders of vitamin D metabolism, including:
 - 1α -hydroxylase deficiency (pseudo-vitamin D deficiency rickets, PDDR)
 - Vitamin D receptor defects (hypocalcemic vitamin D resistant rickets, HVDRR)
- 3) Phosphopenic rickets of any etiology (where hypophosphatemia is the primary cause of the rickets, and not due to calcipenic rickets with secondary hyperparathyroidism)

Results

In the first six months of active surveillance, 33 possible cases of VDDR were reported through the CPSP, of which 20 were confirmed, five were duplicate reports, two were discarded as they did not meet the case definition, and six are still under review (Table 23). The following summary includes clinical data from 15 of the 20 confirmed cases, as data analysis is still ongoing for the remaining five.

TABLE 23				
Vitamin D deficiency rickets				
July 1 to December 31, 2002				
Reported	Confirmed*	Duplicates	Discards	Under Review
33	20	5	2	6

* Data from 15 confirmed cases included in this report

Demographic data

The majority of confirmed VDDR cases (9/15, 60%) were from Ontario, with an additional 20% from Quebec and the remaining 20% divided equally among British Columbia, Alberta and Manitoba. Eight of the cases were female and seven were male, with a mean age at diagnosis of 1.36 years (SD 0.60). Eighteen percent of the cases had immigrated to Canada in the months preceding diagnosis. Sixty-six percent were of Middle Eastern or Black descent. One case was of Inuit origin, living in the far North of Ontario, while ethnicity for the remaining cases was unknown or not provided.

Risk factors for vitamin D deficiency

None of the reported cases were fair-skinned. Sixty percent were classified as dark-skinned, and 40% had intermediate skin colour. Almost half (47%) of the mothers were veiled during and following pregnancy. Physicians reported that all of the cases had been breast-fed except for one where the breast-feeding status was unknown. As expected, none of the cases had received vitamin D supplementation prior to the development of the disease. Only 11% of mothers had received vitamin D supplementation during pregnancy. Following delivery, none of the mothers had received vitamin D supplementation, and 75% of mothers did not drink milk postnatally.

Clinical and biochemical features at diagnosis

Bowing deformity of the limbs was universal at diagnosis, and two patients presented with a

fracture. Growth failure, irritability, and delayed gross motor milestones were also reported. Analysis of the serum biochemical parameters of bone and mineral metabolism prior to initiation of vitamin D therapy revealed an elevated alkaline phosphatase level in all cases, and PTH (parathyroid hormone) was increased in eight of the nine cases for which the information was available. A 25-hydroxyvitamin D level prior to treatment was available in nine of 15 cases, and was low in all but two cases. For the patients who presented with a low-normal 25-hydroxyvitamin D level at diagnosis, the response to typical doses of vitamin D for the treatment of nutritional rickets was consistent with the diagnosis.

Conclusions

In the first six months of this two-year surveillance study, 20 cases of nutritional rickets were confirmed among infants and toddlers residing in Canada. Intermediate- and dark-skinned children who were breast-fed without vitamin D supplementation were at risk for the disease. Among identified cases, the mothers were frequently veiled, did not receive vitamin D supplementation following delivery, and infrequently ingested milk (thus eliminating a potential dietary source of vitamin D). Only one case from the far North has been confirmed to date, which likely reflects the previously anticipated under-reporting in this region, since many Northern communities are served by family physicians who do not participate in the CPSP. Significant morbidity was present at diagnosis in all patients, including limb deformity, fractures and delayed developmental milestones.

While breast milk should continue to be advocated as the ideal fluid source for infants and children, it must be recognized that breast milk is not a rich source of vitamin D. This becomes particularly relevant for infants living in northern countries. In view of our northern latitude, the Canadian

Paediatric Society currently recommends that all exclusively breast-fed infants receive supplementation with vitamin D. However, these initial results suggest that this guideline is not universally implemented. A subset of residents in Canada are particularly at risk for nutritional rickets, including darker-skinned, breast-fed infants whose mothers adhere to a diet that is low in vitamin D and have limited sun exposure. It is important that this study be carried out to completion, so that comprehensive data is available to assist with the development of novel public health policies to prevent nutritional rickets among children living in Canada.

Principal investigator

Leanne M. Ward, MD, University of Ottawa,
Division of Endocrinology and Metabolism,
Children's Hospital of Eastern Ontario, 401 Smyth
Rd, Ottawa, ON K1H 8L1; tel.: 613-737-2253;
fax: 613-738-4236; email: ward_l@cheo.on.ca

Co-investigators

Stanley Zlotkin, MD, Departments of Paediatrics
and Nutritional Sciences, University of Toronto,
Research Institute, The Hospital for Sick Children

Moyez Ladhani, MD, McMaster University,
Department of Paediatrics, McMaster Children's
Hospital

New Studies in 2003

Adverse drug reactions

(September 2003 to August 2005)

“Adverse drug reactions are responsible for 10% of all hospital admissions, yet 95% are never reported to regulators.”

Adverse drug reactions (ADRs) are recognized in North America and Europe as an important cause of childhood morbidity and mortality. Despite this fact, health-care systems have relied steadfastly on the idea of voluntary surveillance systems for the identification and reporting of serious ADRs. The success of these voluntary systems is poor, with an estimated 95% of all adverse drug reactions never being reported. For children, the lack of reported information is particularly significant, as 75% of all marketed drugs have never been tested in a paediatric age group. Lack of information continues to put children at risk and it is thus critical that more information be gathered.

This study proposes to use the CPSP active surveillance program to gather information about serious or life-threatening ADRs from a large and geographically diverse paediatric population. These reports will help to address the serious information gap regarding adverse drug reactions resulting in emergency observation, hospitalization, persistent or significant disability or death of a child, and contribute to better understanding of the magnitude and nature of the problem in Canada.

Principal investigator

Bruce Carleton, PharmD, Faculty of Pharmaceutical Sciences, University of British Columbia, Pharmaceutical Outcomes Programme, Children’s & Women’s Health Centre of British Columbia, 4480 Oak St, Vancouver BC V6H 3V4; tel.: 604-875-2179; fax: 604-875-2494; e-mail: bcrln@interchange.ubc.ca

Co-investigators

Anne Smith, BSc (Pharm), MSc, Pharmaceutical Outcomes Programme, Children’s & Women’s Health Centre of British Columbia

Margaret Zimmermann, BSc, Paediatric Monitoring Project, Marketed Health Products Directorate, Health Canada

Early-onset eating disorders

(March 2003 to February 2005)

“Eating disorders in young children are still poorly understood but may have significant medical and psychological implications.”

The term ‘eating disorder’ generally includes anorexia nervosa, bulimia nervosa and the group of patients fulfilling some, but not all, of the diagnostic criteria for either anorexia nervosa or bulimia nervosa. Epidemiological studies suggest that the prevalence of anorexia nervosa in adolescents has been increasing over the last 50 years and that the age of onset of anorexia nervosa is becoming younger. However, very little incidence data is available for young children less than 13 years of age with eating disorders. Furthermore, the appropriateness of applying existing diagnostic criteria to children has been widely debated.

This study will provide both a minimum estimate of the incidence of eating disorders in children and young adolescents and a range of descriptive data on the features present at the time of diagnosis, including medical complications and concurrent psychiatric illness. This data will contribute to the international debate on definition and classification and will be instrumental in the development of improved age- and developmentally appropriate diagnostic criteria. As well, a better understanding of the spectrum and

presentation of this disorder will help promote the creation of developmentally appropriate interventions that will provide improved outcomes for children and adolescents with this disorder.

This CPSP study, using a definition and questionnaire modified from a similar study on early-onset eating disorders currently conducted through the Australian Paediatric Surveillance Unit, represents an exciting opportunity for the simultaneous collection of comparable international data on a condition for which paediatricians play an essential part in diagnosis and management.

For this study, early-onset eating disorder is defined as determined food avoidance AND weight loss or failure to gain weight during a period of expected growth in a child from five to 12 years of age inclusively. Children with identifiable organic causes of weight loss, such as celiac disease, and obese children in a supervised weight management program are not to be reported.

Principal investigators

Debra K. Katzman, MD, Division of Adolescent Medicine, Department of Paediatrics*

Anne Morris, MB, Division of Adolescent Medicine, Department of Paediatrics*

Leora Pinhas, MD, Psychiatric Director, Eating Disorders Program*

* The Hospital for Sick Children, 555 University Ave., Toronto
ON M5G 1X8; tel.: 416-813-7195; fax: 416-813-7867;
e-mail: leora.pinhas@sickkids.ca

Lap-belt syndrome

(September 2003 to August 2005)

“Seat belts are proven to save lives. Yet when they are worn incorrectly or do not fit smaller individuals properly, they can cause important lumbar spine and abdominal injuries.”

Seat-belt use has clearly reduced fatalities in motor vehicle crashes. In fact, studies report a decrease of

40 to 50% in mortality. The severity of injuries has also decreased. With the increasing use of seat belts over the last decades, a new association of injuries has emerged among adults and children involved in motor vehicle crashes. The ‘lap-belt syndrome’ was first described by Garrett and Braunstein in 1962 and refers to injuries to the intestinal viscera and to the lumbar spine associated with lap-belt restraints. Typically, it involves a tear or perforation of the intestine and its mesentery, which is accompanied by fracture or dislocation of the mid-lumbar spine. Children are especially vulnerable to these injuries. Their intra-abdominal organs are less protected by the thorax and pelvis, they have a lower centre of gravity and their iliac crests are less developed than those of adults, allowing the belt to ride up over the abdomen.

Very few paediatric studies on the incidence of the lap-belt syndrome have been undertaken. In fact, most current knowledge comes from case reports or studies done in limited regional areas. In these studies, the number of cases was relatively low, ranging from ten to 50 cases over years. This syndrome is quite rare but can be of great clinical importance. Permanent neurologic deficits have been associated with lumbar spine injuries in the lap-belt syndrome.

The objectives of this study are to obtain epidemiologic data on the incidence and pattern of lap-belt syndrome injuries most frequently encountered in the Canadian paediatric population. Identifying age groups that are most at risk will help to develop new strategies that will adequately protect children in motor vehicles. This study should provide health-care professionals with an education and awareness of this rare condition.

To verify that the CPSP is the best way to achieve these objectives, a survey was conducted to ensure that paediatricians see children with lap-belt syndrome at some point during their hospitalizations.

Results of this survey will be published in the 2003 *CPSP Results*. Given the low prevalence of this syndrome, only a national study can provide insight into the true incidence of this disease, estimated to be about 160 cases per year among Canadian children.

While the exact incidence of this syndrome is currently unknown, study results may well determine that this association of injuries is frequent enough to necessitate a review of child restraints in motor vehicles. The study will also provide data to re-evaluate prevention strategies, if needed.

Principal investigator

Claude Cyr, MD, Centre hospitalier universitaire de Sherbrooke, 3001 12^e Avenue N, Sherbrooke QC J1H 5N4; tel.: 819-346-1110, ext. 14634; fax: 819-564-5398; e-mail: claudio.cyr@courrier.usherb.ca

Co-investigators

Claude Lemoine, MD, Département de pédiatrie, Centre hospitalier universitaire de Sherbrooke

Miriam Santschi, MD, Département de pédiatrie, Centre hospitalier universitaire de Sherbrooke

Osteogenesis imperfecta

(September 2003 to August 2005)

“The early identification of children with osteogenesis imperfecta may prevent false allegations of child abuse and allow prompt initiation of medical therapy.”

Osteogenesis imperfecta (OI) is a heritable disease of bone characterized by low bone mass and bone fragility. Traditionally, the disease has been divided into four different types (OI types I-IV) based on clinical features and disease severity. In the majority of cases, OI is inherited as an autosomal dominant trait due to mutations in the genes encoding type I collagen, COL1A1 and COL1A2. Recently, three

new groups of OI patients (OI types V-VII) with distinct clinical and histological features were characterized expanding the Silience classification. The most reliable estimates of the frequency of OI to date are based on reports of fractures occurring in the newborn period. However, neonatal fractures are unlikely in OI type I, and may or may not occur in OI types III to VII. While the incidence of the disease is estimated to be one per 20,000 to one per 60,000 live births, the true incidence of OI is likely to be much higher. In Canada, the incidence of all OI types is presently unknown.

In recent years, the quality of life for children with moderate and severe OI has improved remarkably through the administration of cyclical intravenous pamidronate, in conjunction with multi-disciplinary (surgical and rehabilitative) care. Pamidronate is a bisphosphonate, which is thought to exert its beneficial effect through inhibition of bone resorption. The best response to pamidronate therapy appears to occur in children who are first treated in infancy. These findings highlight the importance of prompt diagnosis and initiation of medical and supportive therapy during early life.

Through the CPSP, the study will raise physician awareness in Canada regarding OI in general and the novel forms in particular, so that diagnoses can be made in a timely fashion and appropriate treatment initiated during the critical years of bone growth and development. Results may ultimately lead to the discovery of new mutations and identify geographic prevalence or ethnic specificity, such as OI type VII which is presently only reported in a Northern Quebec First Nations kindred. With national epidemiological data, the study will determine the incidence of OI in Canada by ascertaining all newly diagnosed cases during a two-year period. Recognition and confirmation of OI may also help prevent or minimize false allegations of child abuse.

Principal investigator

Leanne M. Ward, MD, Division of Endocrinology and Metabolism, Children's Hospital of Eastern Ontario, 401 Smyth Rd, Ottawa ON K1H 8L1; tel.: 613-737-2253; fax: 613-738-4236; e-mail: ward_l@cheo.on.ca

Co-investigators

Francis H. Glorieux, MD, PhD, Genetics Unit, Shriners Hospital for Children, Montreal

Frank Rauch, MD, Genetics Unit, Shriners Hospital for Children, Montreal

Prader-Willi syndrome

(January 2003 to December 2004)

"The earlier the diagnosis and appropriate management of Prader-Willi syndrome, the better the patient's outcome."

Prader-Willi syndrome (PWS) is a rare disorder that leads to hyperphagia and obesity. Early diagnosis and appropriate management can have a positive impact on a patient's health and quality of life, particularly regarding prevention and treatment of morbid obesity and its treatable and potentially fatal consequences.

Prader-Willi syndrome is a rare (one per 15,000) and multisystem genetic disorder. The major findings include: hypotonia, obesity, hypogonadism, developmental delay, hyperphagia, and characteristic facial appearance (narrow bifrontal diameter, almond-shaped eyes, and thin philtrum). As many manifestations of PWS can be managed or prevented, the earlier the diagnosis and medical intervention the better the outcome. Yet, despite the availability of both clinical diagnostic criteria and genetic testing, many diagnoses of PWS are delayed, often well into adulthood.

The CPSP provides a great opportunity to determine the incidence of diagnosed PWS in Canada, the

ensuing consequences of obesity, as well as the incidence of other manifestations included in the major and minor diagnostic criteria. Furthermore, surveillance through the CPSP raises awareness in the scientific community, both of the disease and the availability of clinical and cytogenetic/molecular diagnostic criteria.

Knowing the Canadian PWS incidence and clinical status on diagnosis will allow for a better understanding of the challenge to be faced in Canada, and it will help with health-care planning, particularly on a population basis.

Principal investigator

Glenn B. Berall, MD, Chief of Paediatrics, North York General Hospital, 4001 Leslie St., Toronto, ON M2K 1E1; tel.: 416-756-6222; fax: 416-756-6853; e-mail: gberall@nygh.on.ca

Co-investigators

Judith Allanson, MD, Department of Genetics, Children's Hospital of Eastern Ontario

Maria Virginia Desantadina, MD, Department of Nutritional Sciences, University of Toronto, The Hospital for Sick Children

Survey Question

Injuries associated with baby walkers

(January 2002)

The Injury and Child Maltreatment Section, Health Surveillance and Epidemiology Division of the Centre for Healthy Human Development at Health Canada, with the cooperation and support of the Product Safety Bureau, Healthy Environments and Consumer Safety Branch, decided to undertake this survey to obtain a better understanding of the frequency and extent of injuries associated with baby walkers in Canada by surveying the experience of Canadian paediatricians treating such injuries, both in hospitals and private practices.

The survey question was designed to focus on children less than 18 months of age, as this is considered to be the target age for use of these products. This age limit excluded injuries to older (walking) children incidentally interacting with (and being injured by) a walker more commonly used by a younger child or sibling. The limit was also intended to exclude reports related to walkers used as assistive devices by older children with mobility challenges.

A total of 1,214 paediatricians returned the survey, representing an overall return rate of 53.4%. However, 12 forms were blank with no response to the survey question, and one could not be categorized. This reduced the number of answered forms to 1,201 for a response rate of 52.8%. Of the returned forms, 84 were received from paediatricians who recalled treating one or more patients less than 18 months of age for injuries associated with baby walkers. Fourteen physicians indicated that due to the nature or subspecialty of their practice, they would not have treated injuries of this type during the past year.

In all, 7.1% (95% CI 5.6-8.6) of respondents reported treating one or more injuries related to baby walkers

during the past year. The breakdown summary of 'injuries seen in the past year' indicates that respondents treated a minimum of 132 children under the age of 18 months for injuries associated with baby walkers. Many paediatricians included comments with their response. Nineteen physicians indicated that they specifically counselled parents against the use of baby walkers. Only one respondent advocated their use by remarking that he/she did not have a problem with a properly supervised walker being used in a safe environment.

Conclusions

Overall, the findings of this survey offer a profile of the experience of Canadian paediatricians in treating injuries associated with baby walkers. In spite of more than a decade of effort to discourage their sale and use, baby walkers continue to be used in Canada, and ensuing injuries occur. Among paediatricians responding to this survey, 7.1% had treated one or more children less than 18 months of age for injuries associated with baby walkers in the past year.

Clearly, these injuries are both needless and preventable. To curb future incidents, in the months ahead, Health Canada will review options and work collaboratively with the Canadian Paediatric Society's Injury Prevention Committee, which is currently preparing a statement on baby walker safety, to consider the public health implications of the survey findings. In addition, information on baby walkers will be made available on the CPS Web site for parents.

Principal investigator

Margaret Herbert, MSc, Injury and Child Maltreatment Section, Health Surveillance and Epidemiology Section, Centre for Healthy Human Development, Population and Public Health Branch, Health Canada, Tunney's Pasture AL 0701D, Ottawa ON K1A 0L2; tel.: 613-952-2217; fax: 613-941-9927; e-mail: margaret_herbert@hc-sc.gc.ca

International Developments



The International Network of Paediatric Surveillance Units

(INoPSU), established in 1998, continues to enhance collaboration between national paediatric surveillance units. INoPSU provides a unique opportunity for simultaneous cross-sectional studies of rare diseases in populations with diverse geographic and ethnic characteristics.

Currently worldwide, there are 13 national paediatric surveillance units that are full members of INoPSU: Australia, Britain, Canada, Germany, Ireland, Latvia, Malaysia, Netherlands, New Zealand, Papua New Guinea, Portugal, Switzerland, and Wales. The Greece/Cyprus

surveillance unit is an affiliate member until such time as it fulfills the requirements of full membership. As well, the British Ophthalmological Surveillance Unit is an associate member.

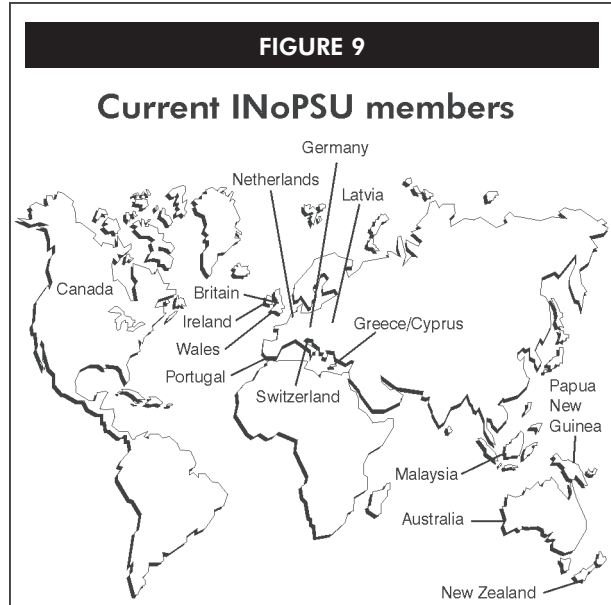


TABLE 24

Studies under surveillance by national paediatric surveillance units in 2002

Abdominal injury due to child abuse	BPSU
Acute cerebellar ataxia	NSCK
Acute flaccid paralysis	APSU, CPSP, NSCK, NZPSU, PNGPSU, SPSU
Acute lymphoblastic leukemia	LPSU
Acute myeloblastic leukemia	LPSU
Acute rheumatic fever	SPSU
Adverse effects from complementary or alternative medicine	APSU
Anaphylaxis following food ingestion	APSU
Apparent life threatening event	NSCK
Atypical mycobacterial infections	ESPED, NSCK
Autism in children under 5 years	IPSU
Brain tumors	LPSU
Bronchiectasis	NZPSU
Cerebrovascular disease	BPSU
CHARGE association/syndrome	APSU, CPSP
Childhood conversion disorder	APSU
Coeliac disease	IPSU
Congenital adrenal hyperplasia	NSCK
Congenital cytomegalovirus infection	APSU, BPSU
Congenital diaphragmatic hernia	IPSU
Congenital hypothyroidism	PNGPSU
Congenital rubella syndrome	APSU, BPSU, CPSP, NZPSU, SPSU
Congenital toxoplasmosis	BPSU
Diabetes mellitus, type I	ESPED, LPSU, PNGPSU, PPSU
Diabetes mellitus, type II	LPSU
Drowning	MPSU
Drugs (medication) related adverse events	BPSU, NSCK
Early-onset eating disorder	APSU
Group B streptococcus < 3 months invasive disease	PPSU ESPED

C P S P 2 0 0 2 R E S U L T S

Fetal alcohol syndrome	APSU
Glycogen storage disease	MPSU
Gut insufficiency and gut transplantation	NSCK
Hemolytic uremic syndrome	CPSP, LPSU, NZPSU, PPSU, SPSU
Hepatitis C virus infection	CPSP
Histiocytosis	LPSU
HIV/AIDS	APSU, BPSU, NSCK, NZPSU
Hodgkin's disease	LPSU
Idiopathic nephrotic syndrome	NZPSU
Idiopathic thrombocytopenic purpura	NSCK
Imported tropical diseases: malaria, schistosomiasis, leishmaniasis	ESPED
Inflammatory bowel disease	NZPSU
Ingestion of lamp oil (intoxications)	ESPED
Inherited hypocalcemic salt-losing tubulopathies/Barter-like syndromes	ESPED
Intersexuality and severe genital malformations	ESPED
Invasive <i>Haemophilus influenzae</i> infections (all types)	ESPED
Kawasaki disease	NZPSU, PPSU
Lymphoma, B-cell & T-cell	LPSU
Medium chain Acyl-CoA dehydrogenase deficiency	NSCK
Mucopolysaccharidosis	MPSU
Munchausen by proxy syndrome	APSU
Narcolepsy	ESPED
Necrotizing fasciitis	CPSP
Neonatal herpes simplex virus infection	APSU, CPSP, SPSU
Neonatal hyperbilirubinemia – severe	CPSP
Neonatal liver failure/perinatal hemochromatosis	CPSP
Neonatal sinus venous thrombosis	ESPED
Nephroblastoma	LPSU
Nephrocalcinosis	IPSU
Neural tube defects	IPSU, NSCK, SPSU
Neuroblastoma	LPSU
Neurologic endemism cretinism	PNGPSU
Non-Hodgkin's lymphoma	LPSU
Osteosarcoma	LPSU
Paediatric malignancies	PNGPSU
Palliative care	WPSU
Pertussis	NSCK
Pigbel	PNGPSU
Pneumococcal sepsis/meningitis	ESPED
Polycythemia	LPSU
Progressive intellectual and neurological deterioration	BPSU
Prolonged artificial lung ventilation in newborns	LPSU
Renal tubular acidosis	PNGPSU
Respiratory syncytial virus (RSV) disease	ESPED, SPSU
Retinoblastoma	LPSU
Reft syndrome	APSU
Rhabdomyoma	LPSU
Septo-optic dysplasia	WPSU
Shaken baby syndrome	SPSU
Smith-Lemli-Opitz syndrome	CPSP
Splenectomy and hyposplenism	WPSU
Steroid-resistant nephrotic syndrome	ESPED
Subacute sclerosing panencephalitis	PNGPSU
Subdural hemorrhage (<2 years)	NZPSU, WPSU
Teratoma	LPSU
Thrombosis	BPSU
Tick-borne encephalitis	SPSU
Tuberculosis	WPSU
Varicella/zoster infection	BPSU, SPSU
Vitamin D deficiency rickets	CPSP
Vitamin K deficiency bleeding/hemorrhagic disease of the newborn	APSU, BPSU, NZPSU

Legend: APSU (Australian Paediatric Surveillance Unit); BPSU (British Paediatric Surveillance Unit); CPSP (Canadian Paediatric Surveillance Program); ESPED (German Paediatric Surveillance Unit); IPSU (Irish Paediatric Surveillance Unit); LPSU (Latvian Paediatric Surveillance Unit); MPSU (Malaysian Paediatric Surveillance Unit); NSCK (Netherlands Paediatric Surveillance Unit); NZPSU (New Zealand Paediatric Surveillance Unit); PNGPSU (Papua New Guinea Paediatric Surveillance Unit); PPSU (Portuguese Paediatric Surveillance Unit); SPSU (Swiss Paediatric Surveillance Unit); WPSU (Welsh Paediatric Surveillance Unit)

The first formal INoPSU meeting was held in Ottawa in June 2000. A second successful INoPSU meeting was hosted by the British Paediatric Surveillance Unit in York, England, in April 2002, in conjunction with the Royal College of Paediatrics and Child Health spring meeting. The first day brought together 20 representatives from 11 of the 14 national surveillance units for a business meeting to discuss communication between existing units, encourage the sharing of information between researchers and assist in the development of new units. A series of lectures on the second day demonstrated the work of INoPSU. Drs. Sarah Lawrence-Muirhead and Danielle Grenier presented papers on behalf of the CPSP. As a result of the success of these meetings, a third INoPSU meeting is planned for Portugal in the spring of 2004.

Highlights from other national paediatric surveillance units

Australia

The study of the burden of disease from hospitalized-pertussis (whooping cough) identified 140 confirmed cases in Australian children under the age of 12 months in 2001, or 56 per 100,000 live births (95% CI 47-66). The majority (60%) of infants were under two months of age at admission and thus too young to receive diphtheria-tetanus-pertussis (DTP) vaccine, according to the Australian immunization schedule. Important information about contact with a person with a coughing illness compatible with pertussis was recorded for 118 out of 140 infants. The presumptive 'coughing contact' in most of these cases was familial, either the infant's parents (51%) or siblings (32%). This study has led to the development of several recommendations to inform strategies for limiting pertussis infection in infants.

Britain

The British Paediatric Surveillance Unit (BPSU) collected data on Reye syndrome (RS) from June 1986, when the first warning about the association between aspirin and RS was made public, to April 2001, when the survey ended. Of the 17 confirmed RS cases associated with aspirin, ten were related to children 12 years of age and older. Subsequent to reviewing the data, the Medical Control Agency and the Committee on Safety of Medicines issued the following new warning in the United Kingdom: "Do not give aspirin to children under 16 years of age unless on the advice of a doctor." A publicity campaign will be initiated in the near future. Dr. Hall said, "This is another example of the contribution that the BPSU has made to public health and we are most grateful to paediatricians who participated in the survey."

Germany

An active surveillance of symptomatic children with inherited organic acid disorders (OADs) and fatty oxidation disorders (FAODs) was conducted over a two-year period (1999-2000) in Germany. The German Paediatric Surveillance Unit (ESPED) sent monthly inquiries to all departments of paediatrics and quarterly to all specialized metabolic laboratories. Newly diagnosed patients were added to the database, and clinical and biochemical information was recorded via a standardized questionnaire.

Results were published in *Pediatrics* 2002;110(6): 1204-1211. Prospective surveillance enrolling 844,575 children identified a total of 57 symptomatic children with newly diagnosed OADs or FOADs in states with conventional neonatal screening, resulting in an estimated cumulative incidence of one per 14,800. The most frequent diagnosis among these children was medium-chain acyl-CoA dehydrogenase deficiency (n=20). The majority of symptomatic children revealed clinical symptoms during the first year of life (n=36), frequently presenting with acute

crises (n=31). Eight children died during these crises. Notably, 47 of the symptomatic children suffered from diseases potentially detectable by expanded neonatal screening programs. This subgroup included 29 children presenting with metabolic crises, and seven of the eight deaths.

Despite increased clinical awareness of OADs and FOADs, the mortality and morbidity of these children remain high, if they are diagnosed after manifestation of clinical disease. An introduction of nationwide neonatal screening programs would change the focus for organic acid analysis from patients presenting with acute metabolic crises to more chronic clinical presentations, especially the cerebral organic acid disorders.

Ireland

The Irish Paediatric Surveillance Unit studied the incidence of neural tube defects over a two-year period (2001-2002). Prior to this, there was no nationwide reporting in Ireland. Regional reporting of neural tube defects through the EUROCAT study, a concerted action of the European Union for the surveillance of congenital anomalies, has been in effect since 1980. Only the Eastern Health Board and the Galway regions report neural tube defects for the EUROCAT registry. In common with other European countries, the birth prevalence of spina bifida has been declining. The Eastern Health Board region data has suggested that the birth prevalence of neural tube defects is leveling off at a higher rate than in many European regions. While there may be several reasons for this, it is hoped that increasing peri-conceptual folic acid will enable a substantial fall in the number of neural tube defects in Ireland. Further ongoing analysis of the data obtained over the two-year period will help to elucidate the folic acid intake of mothers of babies with neural tube defect, as well as determine other factors that may be associated.

Latvia

The active mailing of a surveillance card has recently been adopted by the Latvian Paediatric Surveillance Unit. With a child population of 429,000, Latvia has only two major children's hospitals. Cards have been sent to comparatively few clinicians. Response rates are currently around 70%.

Malaysia

The Malaysian Paediatric Surveillance Unit (MPSU) is pleased to have a new basic infrastructure. A financial grant was secured from the Malaysian Paediatric Association to fund a permanent research officer and establish an executive, as well as scientific and advisory committees.

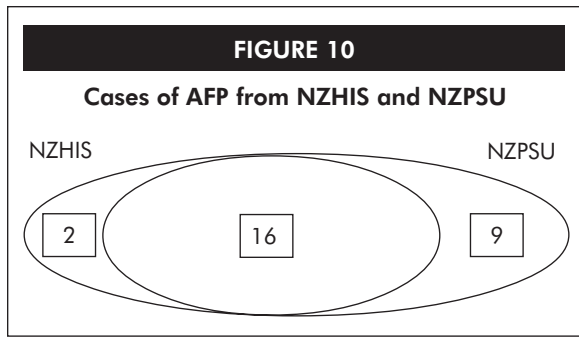
There has been a tremendous increase in the number of new paediatricians in Malaysia due to the success of the paediatric specialty training program in Malaysia. This will necessitate an update of the MPSU database. Also, since the MPSU has been suspended since 1999, many respondents, especially the new paediatricians, will need time to familiarize themselves with the new cards. For these reasons, an accurate measure of response rates is not possible at this time. The MPSU is confident of the success of the program with this new infrastructure and leadership.

Netherlands

The study of atypical mycobacterial infections and therapy (surgery and/or medical) was a highlight of the year. Follow-up immunological investigations are planned for these patients. A second highlight was medium-chain acyl-CoA dehydrogenase deficiency. In the northern region, tandem mass spectrometry was added to the neonatal screening program to evaluate the specificity and sensitivity of this screening tool.

New Zealand

In 2002, the New Zealand Paediatric Surveillance Unit (NZPSU) undertook an audit of all acute flaccid



paralysis (AFP) cases in 2000 and 2001 in an attempt to assess the unit’s sensitivity. The audit was performed utilizing a search of the New Zealand Health Information Service (NZHIS) hospital discharge database for all children less than 15 years of age with a discharge diagnosis code (ICD-10) consistent with AFP; specifically 357.0 (Guillain-Barré syndrome), 045 (poliomyelitis), 138 (late effects of poliomyelitis), and 341.8 (‘other’ demyelinating diseases of central nervous system, which includes transverse myelitis).

Out of a total of 25 cases that met the criteria, 16 had already been reported to the unit. For the remaining nine cases, a contact person at each of the hospitals was sent a letter explaining the purpose of the inquiry and a short questionnaire to assess whether the child actually fit the criteria for AFP. Of these nine cases, only two were true AFP cases – both Guillain-Barré syndrome. Of the remaining seven, six were hospital coding mistakes, and one was a sequelae of polio that had been diagnosed in another country before coming to New Zealand.

The Venn diagram (Figure 9) shows that of the total 27 cases detected by either the NZPSU or NZHIS, 25 (93%) were detected by the NZPSU system, 18 (67%) by the NZHIS, and 16 (59%) by both. The reasons why the cases were missed by the NZPSU or NZHIS systems were not explored directly. However, one child not notified to the NZPSU had been referred from a secondary- to a tertiary-care hospital.

The sensitivity of the NZPSU system was found to be around 93%, much better than that for most notifiable

diseases. Thus, the established process is picking up most cases of AFP. The NZPSU will however continue to remind paediatricians of the importance of timely reporting of cases.

Papua New Guinea

Insulin-dependent diabetes mellitus data (IDDM) collected by the Papua New Guinea (PNG) Paediatric Surveillance Unit was published in the PNG Medical Journal. There was an extremely low incidence (0.08 per 100,000) of IDDM Type I in children under 15 years of age.

Portugal

In the first 18 months, activity for the Portuguese Paediatric Surveillance Unit (PPSU) was clearly very positive. During this period, the PPSU confirmed four cases of hemolytic-uremic syndrome, 18 cases of Kawasaki disease, 30 cases of diabetes in children under five years of age, and 83 cases of group B streptococcal infection in infants less than three months of age.

While the reporting rate is lower than in other national surveillance units, much of this can be attributed to the uniqueness of this initiative. Improvement is expected once the potential of the system is realized and the scientific value is reinforced through the publication of current study results. The temporal relation between the improvement of the participation rate and the first public presentation of preliminary data at the 27th National Paediatric Conference (May 2002), reveals sensitivity and interest from paediatricians in the PPSU.

Switzerland

A study on intussusception started in April 2003. Study results will capture the medical burden (based on kind of complications occurring) and the financial implications (based on frequency and duration of hospitalization) caused by intussusception. No such data are currently available for Switzerland. Furthermore, the findings of this surveillance project will establish a background rate of intussusception in

this country. With a new rotavirus vaccine on the horizon, pre-vaccine intussusception data will allow for the possibility of a comparison study after vaccine release.

Wales

It would be difficult to say with any exactness the date on which paediatric palliative care began to develop in the United Kingdom (UK). There are many candidates: the appearance of articles on the subject in the British Medical Journal in the late 1970s, the first children's hospice in the early 1980s, or perhaps the appointment of the first palliative care paediatrician in 1986.

Certainly one turning point was the publication of *Guidelines for the Development of Paediatric Palliative Care Services* in 1997. The Guidelines, one of the first publications of the newly-formed Royal College of Paediatrics and Child Health, were drawn up in partnership with ACT (Association for Children with Life-threatening or Terminal Conditions and their Families), the umbrella group in the UK (and increasingly in Europe) for agencies working in paediatric palliative care. For the first time, the profession of paediatrics was taking palliative care seriously. Every paediatrician in the four countries that make up the United Kingdom received a copy.

The purpose of the Welsh Paediatric Surveillance Unit (WPSU) study was to ask the question: in the years that have elapsed since it appeared, how much of that ground-breaking publication has become part of paediatric culture in Wales? Four years later, what is palliative care in children understood to be? During 2001 and 2002, every paediatrician in Wales received a monthly card asking "Have you seen any child who, in your opinion, had palliative care needs?" Those who reported that they had seen such a child received a more detailed questionnaire enquiring about the nature of the perceived need, which could range from physical symptom control through respite to discussing prognosis and bereavement counselling.

The results were interesting. Only a small proportion – perhaps as little as 20% – of children who, according to data in the Guidelines, were likely to need palliative care were reported by paediatricians in Wales. However, those paediatricians who did recognize and report it also recognized the multidimensional ('holistic') nature of those needs. This contradicts the view that the doctors' role in palliative care in children is limited to the diagnosis and management of physical symptoms, or that paediatricians do not recognize the need for working closely with other disciplines and professions. On the other hand, it also suggests that, despite the RCPCH/ACT document, many paediatricians do not yet fully understand what is meant by 'palliative care' in children.

The survey will be published, and hopefully, this in itself will help to raise awareness. Perhaps even more importantly, the data will help in the development of the next edition of the Guidelines, to be published later this year (www.act.org.uk), which in turn will influence policy all over the UK and indeed the world. The WPSU study has provided a unique opportunity to assess the effectiveness of communicating to paediatricians the nature of, and need for, palliative care in children.

Call for New Studies

Research opportunities

Wanted:

- Investigators to initiate new CPSP studies on rare diseases or conditions for 2004 and beyond.
- The paediatric community to take up the challenge of proposing a wide-range of research studies.
- Interested individuals prepared to assume a leadership role in developing protocols and analyzing study data.

The tool: The CPSP is:

- A well-established, timely, cost-effective surveillance infrastructure.
- A multi-faceted surveillance tool capable of collecting reliable data in a variety of different fields.
- An effective means of monitoring rare diseases and conditions.

Track record

- An 83% overall initial response from more than 2,300 paediatricians.
- An impressive 95% data completion rate for the 398 cases reported in 2002.
- High duplicate reporting rate (27%) assuring case ascertainment and participant commitment.

International flavour

- Be part of INoPSU (International Network of Paediatric Surveillance Units) a growing network of national paediatric surveillance units that exists in 13 countries around the world.
- Take advantage of international collaboration, as INoPSU studies provide a remarkable opportunity to compare similar data and learn more about rare diseases worldwide.

Looking for ideas?

Here are a few examples of current INoPSU studies:

- Atypical mycobacteriosis
- Congenital adrenal hyperplasia
- Kawasaki disease
- Langerhan cell histiocytosis
- Pertussis
- Pneumococcal sepsis/meningitis
- Tick-borne encephalitis
- Varicella/zoster

The potential for new studies in different paediatric subspecialties is endless. If you have a research project in mind, please contact the CPSP Senior Coordinator at 613-526-9397, ext. 239, for more information.

RESERVA

