

Incidence and Clinical Associations of Childhood Acute Pancreatitis

Abdalmonem A. Majbar, MSc,^{a,b} Eleri Cusick, ChM,^b Paul Johnson, MD,^c Richard M. Lynn, MSc,^d Linda P. Hunt, PhD,^e Julian P.H. Shield, MD^{a,b}

abstract

OBJECTIVES: To establish the UK incidence and clinical associations of acute pancreatitis (AP) in children aged 0 to 14 years.

METHODS: Monthly surveillance of new cases of AP in children under 15 years of age through the British Pediatric Surveillance Unit conducted from April 2013 to April 2014 (inclusive) followed by 1-year administrative follow-up for all valid cases.

RESULTS: Ninety-four cases (48 boys) fulfilled the diagnostic criteria. The median age at diagnosis was 11.2 years (range 1.3–14.9). White children accounted for 61% of the cases compared with 28% from Asian and 5% from African ethnicities. Pakistani children accounted for 18 of 26 (69%) Asian patients and 19% of the total cohort. The incidence of AP in children in the United Kingdom was 0.78 per 100 000/year (95% confidence interval [CI] 0.62–0.96). The incidence in Pakistani children (4.55; 95% CI 2.60–7.39) was sevenfold greater than white children (0.63; 95% CI 0.47–0.83). Of the 94 cases, 35 (37%) were idiopathic; other associations were: drug therapy, 18 (19%); gallstones, 12 (13%); hereditary, 7 (7%); organic acidemias, 7 (7%); anatomic anomalies, 5 (5%); viral infections, 3 (3%); systemic diseases, 2 (2%); and trauma 1 (1%). The most common drug associations were asparaginase (28%), azathioprine (17%), and sodium valproate (17%).

CONCLUSIONS: Although still relatively uncommon in the United Kingdom, on average there is >1 case of childhood AP diagnosed every week. The associations of AP have changed significantly since the 1970–80s. Overrepresentation of Pakistani children is worthy of further investigation.

^aNational Institute for Health Research, Bristol Biomedical Research Unit in Nutrition and University of Bristol, United Kingdom; ^bMusculoskeletal Research Unit, University of Bristol, United Kingdom; ^cBristol Royal Hospital for Children, Bristol, United Kingdom; ^dNuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom; and ^eBritish Paediatric Surveillance Unit, Royal College of Paediatrics and Child Health, London, United Kingdom

Dr Majbar helped design the data collection instruments, collected the data, conducted all analyses, and drafted the initial manuscript; Ms Cusick and Dr Johnson contributed to study conceptualization and design, took part in data interpretation, and critically reviewed the manuscript; Mr Lynn contributed to study conceptualization and design and critically reviewed the manuscript; Dr Hunt supported and contributed to the statistical analysis and critically reviewed the manuscript; Dr Shield conceptualized and designed the study, supervised and assisted data collection and analyses, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Abdalmonem Majbar, MSc, Biomedical Research Unit in Nutrition, Research and Education Centre, Upper Maudlin St, Bristol, United Kingdom, BS2 8AE. E-mail: a.a.majbar@bristol.ac.uk

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WHAT'S KNOWN ON THIS SUBJECT: Acute pancreatitis in childhood is a relatively rare but potentially serious condition. In the past, trauma and mumps have been the most common associations. No study has estimated incidence within a childhood population on a prospective basis.

WHAT THIS STUDY ADDS: Acute pancreatitis has a childhood incidence in the United Kingdom of 0.78/100 000/year (95% confidence interval 0.62–0.96). Gallstones and drug therapy are the most commonly identified associations; mumps and trauma are identified rarely. Children of Pakistani heritage are disproportionately affected.

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Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas with variable involvement of peripancreatic tissues and/or distant organ systems.¹ AP is uncommon in children but leads to significant morbidity in the short-, medium-, and long-term. Recently, an increase in the number of pediatric AP cases in single institutions has been reported by centers in the United States,²⁻⁵ Australia,⁶ and Mexico.⁷ However, these studies are retrospective reviews, and the incidence of AP is usually reported as an absolute number of cases per center per year at individual referral institutions.

There are no recent UK data on AP in childhood and no robust estimate of incidence. Sibert conducted a retrospective review of all pancreatitis cases (acute and chronic) admitted to the hospital in the Newcastle area and Wales between 1968 and 1975 and estimated the annual rate of diagnosis of pancreatitis in children <16 years at ~1 in 400 000 in Newcastle and 1 in 250 000 in Wales.⁸ Until now, no national population-based study has been conducted, either prospectively or retrospectively, to investigate the frequency of this condition in children, in the United Kingdom or elsewhere.

In adults, the most common causes of AP are alcohol and gallstones,^{9,10} but in children, it is associated with a wide variety of potential etiologies, including abdominal trauma, drug therapy, infections, systemic diseases, and congenital anatomic anomalies.^{2,11} Trauma and mumps were the most common associations reported in the United Kingdom in the 1970–80s.^{8,12,13} However, there has been no effort to reexamine the associated agents of this disease in the United Kingdom in the past 3 decades. The last study conducted within the United Kingdom was performed in Scotland in the 1990s on retrospective data from 1978 to 1992, where mumps

(39%) and trauma (14%) were the most frequent associations.¹³

Several changes in population characteristics, including the introduction of the measles-mumps-rubella vaccine in 1988 and an increase in the prevalence of obesity-associated gallstones among children,¹⁴ may have changed the incidence and causative agents responsible for this relatively rare condition in childhood. Therefore, the aims of this study were to conduct the first prospective examination of the incidence of AP in UK children and to determine its current clinical associations.

METHODS

We conducted a prospective monthly surveillance of >3700 consultant pediatricians and pediatric surgeons in the United Kingdom and Ireland by using the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health (RCPCH) to detect all new cases of AP in 0- to 14-year-old children. The BPSU is an active reporting system in which an orange card containing a list of conditions is sent monthly, by post or electronically, to all consultant pediatricians and other specialists where appropriate. Respondents report cases they have seen in the previous month for conditions named on the card or tick a “Nothing to report” box. After the return of the card to the BPSU, the research team is informed of the reporting clinician's details who receive a short pro forma asking for patient's clinical details; this is returned to the researcher for analysis.^{15,16} AP in children under 15 years of age was included on the card for 13 months (April 2013–April 2014 inclusive). The orange card return compliance was 95.3% during the study period. To identify children directly referred to surgical departments, the British Association of Paediatric Surgeons

supported this study, and pediatric surgeons received the orange card. Almost all pediatricians belong to the RCPCH and thus receive orange cards. The vast majority of pediatric surgeons are members of British Association of Paediatric Surgeons or RCPCH. No general or emergency physicians in the United Kingdom manage children with AP without referral to either a pediatrician or pediatric surgeon.

Clinicians were asked to report any child under age 15 years seen in the previous month with a new diagnosis of AP. Diagnosis of AP required at least 2 of the 3 following features: (1) acute onset of upper abdominal pain, (2) serum amylase and/or lipase raised ≥ 3 times the upper limit of normal local range, and (3) imaging findings characteristic of AP. These criteria for diagnosis of AP were adapted according to revised Atlanta criteria,¹⁷ and a consensus of the International Study Group of Paediatric Pancreatitis: In Search for a Cure (INSPPIRE).¹⁸

Reporting clinicians were contacted with an initial study questionnaire to collect information about the patient, clinical presentation, diagnostic details, consultant at discharge, and again at 1 year after diagnosis. Upon receipt of a completed initial study questionnaire, the eligibility of the patient and case status was determined. This included the age of the child, time of diagnosis, and fulfillment of the study case definition. The clinicians' diagnoses were reviewed by the study investigators (A.A.M., J.H.S., P.J., and E.C.) in light of the questionnaire data supplied. Clinical associations were accepted after the investigators' review and special considerations. For example, viral infection and hereditary pancreatitis were only recorded as an association if a confirmatory serology test or genetic testing were conclusive. Associations were updated at the end of the follow-up period. Cases with no

identifiable association were then classified as idiopathic. If a child had >1 episode of AP during the study period, only the first episode was included as a new case.

Ethics Approval

The study was approved by the National Research Ethics Service Committee South West, Central Bristol (REC reference 11/SW/0132) and was granted Section 251 of the National Information Governance Board for Health and Social Care permission by its Ethics and Confidentiality Committee under reference ECC 6-02(FT12)/2012.

Statistics

The incidence rate was calculated by using the valid cases from the first 12 consecutive months and the population denominator obtained from "Population Estimates Summary for the UK, Mid-2013" table, published by the Office for National Statistics.¹⁹ Ethnicity specific incidence rates of AP were calculated for English and Welsh children only using the "Ethnic Group by Age in England and Wales 2011" data.²⁰ The ethnic groups by age were only available for these 2 countries. Ninety-five percent confidence intervals (CIs) for rates were calculated by using an "exact" method for Poisson. Poisson regression models were used to compare the rates for the main ethnic groups. The statistics software programs SPSS (version 21.0, IBM Corp, Armonk, NY) and Stata (version 12.1; StataCorp LP, College Station, TX) were used for analysis. A 5% level of significance was used.

RESULTS

Two hundred and twenty case notifications were received over the 13 months of the study. Of these, 202 (92%) responses to the initial study questionnaire were received, and the remaining 18 cases had no

TABLE 1 Ethnicity Specific Incidence Rates for AP in 0- to 14-Year-Olds in England and Wales

Group	Ethnicity	Population	No. of cases	Rate per 100 000 ^a	95% CI
1	All Ethnicities	9 891 138	83	0.84	0.67–1.04
	White: Total	7 781 925	49	0.63	0.47–0.83
2	Mixed: Total	523 782	2	0.38	0.05–1.38
	White and Asian	154 176	1	0.65	0.02–3.61
	Other Mixed	114 303	1	0.88	0.02–4.87
3	Asian: Total	979 148	24	2.45	1.57–3.65
	Indian	255 892	2	0.78	0.10–2.82
	Pakistani	351 384	16	4.55	2.60–7.39
	Bangladeshi	146 817	3	2.04	0.42–5.97
4	Other Asian	178 704	3	1.68	0.35–4.91
	Black: Total	478 863	4	0.84	0.23–2.14
	African	281 495	4	1.42	0.39–3.64
5	Other: Total	127 420	1	0.79	0.02–4.37
	Ethnicity not known		3		

^a Poisson regression was used to compare the rates for the 5 main groups (labeled 1–5 in the first column). There were significant differences between the 5 groups ($P < .001$ overall). Group 3 was significantly higher than group 1 ($P < .001$), whereas groups 2, 4, and 5 were not significantly different from 1 (min $P = .49$).

response. One hundred thirty-three episodes met the diagnostic criteria for AP during the study period; 95 were newly confirmed cases (94 from the United Kingdom and 1 from Ireland), 20 were duplicates, and 18 were recurrent episodes. Sixty-nine cases were excluded because they did not fulfill the case definition or were diagnosed outside the study period. Ninety-four newly confirmed UK cases were included in the final analysis, and 88 of these, who had been diagnosed in the first 12 consecutive months of the study period, were used in the calculation of the incidence.

Of the 94 UK cases, 46 were girls; the female-to-male ratio was approximately 1:1. The median age at diagnosis was 11.2 years (range 1.3–14.9 years). The cases were evenly distributed throughout the year, with no discernible seasonal trend. White children accounted for 61% of cases compared with 28% from Asian and 5% from African ethnic groups. Children of Pakistani origin accounted for the majority (18 of 26; 69%) of Asian heritage cases and 19% of the total cohort. Eighty-eight of 94 cases (94%) were screened by using amylase, 18 (19%) had amylase and lipase levels measured, and 6 cases were screened using lipase alone. Twelve children developed

AP while in the hospital during management for other conditions. In only 1 case was diagnosis made in the ICU.

Incidence Rates

The estimated UK population under 15 years of age in mid-2013 was 11 307 400, giving a national incidence of AP in children aged 0 to 14 years of 0.78 per 100 000/year (95% CI 0.62–0.96). The specific incidence rates of AP in different ethnic groups in England and Wales are shown in Table 1.

Clinical Associations

The main clinical associations of AP in the 94 children are listed in Table 2. Thirty-five cases (37%) had no reported associated agents and were classified as idiopathic. The most common associations identified were drug therapy (19%) and gallstones (13%). The majority of the 35 idiopathic cases were in older age groups: 17 (49%) cases in the 10- to 14-year age group and 14 (40%) in the 5- to 9-year age group, compared with only 4 (11%) in the 0- to 4-year group (2 were <3 years old). Of the 12 gallstone-associated cases, 5 were boys; body weight of 5 cases was >91st percentile (4 were >98th percentile), and 2 cases had chronic hemolytic disease (hereditary spherocytosis and sickle cell disease).

Overall, 6 of 7 organic acidaemia cases (86%) and 3 of 5 asparaginase (leukemia treatment)-associated cases (60%) were of Pakistani ethnicity. One child had recessive familial hypertriglyceridemia. The triglyceride level after fluid therapy was 4.8 mmol/L (normal range 0.4–2.1 mmol/L).

DISCUSSION

This study demonstrates that childhood AP remains an uncommon disease in the United Kingdom; the incidence of AP in children under 15 years old was 0.78 per 100 000/year (95% CI 0.62–0.96). To the best of our knowledge, this is the first prospective, nationally based estimation of childhood AP worldwide. Only 1 previous retrospective study has been conducted in the United Kingdom, but it was primarily designed to examine the etiology, complications, and outcomes of pancreatitis in children. It also estimated the incidence in only 2 regions.⁸ Although the previous study included all cases of pancreatitis and children up to age 16 years, our incidence rate is double that estimated in Wales (0.4/100 000/year) and threefold higher than Newcastle (0.25/100 000/year).⁸ This apparent increase in the UK incidence might be due to an increase in clinical awareness or to the change in its clinical associations, which was reflected by an increase in the proportion of some previously known associations, such as drugs, and the appearance of new associations not previously reported, such as organic acidemias.

We were unable to compare our incidence findings with Europe because no data exist. The rate of childhood AP reported here for the United Kingdom was lower than that reported for Australia (2.5/100 000 in 1993 and 3.6/100 000 in 2002)⁶ and the United States (2.4/100 000

TABLE 2 Clinical Associations of AP in 94 Children <15 Years Old in the United Kingdom

Clinical Association	<i>n</i>
Idiopathic	35 (37%)
Drugs	18 (19%)
Asparaginase	5
Azathioprine	3
Sodium valproate	3
Methylprednisolone	1
Mercaptopurine	1
Mesalazine	1
Carbamazepine	1
Clarithromycin	1
Opiates	1
Calcium carbonate/ alfacalcidol	1
Gallstones	12 (13%)
Hereditary	7 (7%)
<i>SPINK1</i> gene positive	5
<i>PRSS1</i> gene positive	2
Organic acidemias	7 (7%)
Propionic acidemia	4
Methylmalonic acidaemia	2
Isovaleric acidaemia	1
Anatomic anomalies	5 (5%)
Pancreas divisum	3
Choledochal cyst	2
Viral infections	3 (3%)
Mumps	1
EBV and CMV	1
Rotavirus	1
Systemic diseases	2 (2%)
Systemic lupus erythematosus	1
Henoch-Schonlein purpura	1
Trauma	1 (1%)
Handlebar injury	1
Others	4 (4%)
Cystic fibrosis	2
Hypertriglyceridaemia	1
α 1-antitrypsin deficiency	1

CMV, cytomegalovirus; EBV, Epstein-Barr virus; *PRSS1*, Protease, Serine, 1 (Trypsin 1); *SPINK1*, Serine Peptidase Inhibitor, Kazal Type 1.

in 1993 and 13.2/100 000 in 2004).³ However, both of these studies were retrospective reviews conducted at major pediatric referral centers, and the cases of AP were detected by reviewing either hospital laboratory databases⁶ or hospital discharge records.³ The retrospective nature, referral bias, and variation in the diagnostic criteria and age groups of these studies may explain these differences. In addition, the Australian study had a higher number associated with trauma (36%) and systemic disease (22%)⁶ compared with our study (1% for trauma and 2% for systemic

diseases), which might also have led to a higher incidence in Australia than the United Kingdom.

More than a quarter of our patients were of Asian or British Asian origin (28%). Interestingly, Pakistani children alone accounted for approximately one-fifth (19%) of the cohort, although they constitute only 3.6% of the population <15 years of age in England and Wales.²⁰ As a result, the incidence in Pakistani children (4.55; 95% CI 2.60–7.39) was sevenfold higher than in white children (0.63; 95% CI 0.47–0.83; data for England and Wales only). All 7 of the organic acidaemia cases, which represent disorders caused by inherited inborn errors of metabolism, were of Asian heritage, and the majority of these (6 of 7) were Pakistani. This may reflect the tradition for first-degree marriage among this ethnic group and may in part explain the overrepresentation of Pakistani children in our data. Because 3 of 5 asparaginase-associated cases were of Pakistani heritage, additional investigation to determine whether Pakistani children have a higher incidence of leukemia or are more sensitive to asparaginase than others is warranted.

This study shows that childhood AP has a wide variety of clinical associations in the United Kingdom, as in other countries; however, more than one-third of the cases (37%) were idiopathic. It should be noted that all idiopathic cases had imaging for gallstones, but only 20% were screened for genetic causes because the policy in the United Kingdom seems to be to screen mainly in cases with a history of recurrent pancreatitis. We found that associations of AP in this country have changed significantly compared with data from the previous 4 decades. Medication (19%) and gallstones (13%) were the most common associations, whereas trauma (1%) and mumps (1%)

were uncommon in our patients. Despite recent advances in diagnostic techniques, including pancreaticobiliary imaging and genetic testing, we found a high proportion of idiopathic AP in UK children, although this was within previously reported national ranges of 25% to 56%.^{8,12,13} Idiopathic AP seems to be more common in children. It has been reported globally in a wide range of proportions in children, from 15% to 36% of total cases.^{6,7,21–28} Lopez did not find idiopathic pancreatitis in children under age 3,⁵ but the current study supports Kandula's findings that idiopathic cases can be detected at this young age.²⁹

In 19% of our cases, AP was associated with drug therapy. The majority of these drugs (asparaginase, azathioprine, sodium valproate, methylprednisolone, mercaptopurine, and opiates) are a known association,³⁰ and others (mesalazine, carbamazepine, and clarithromycin) are recognized as possible inducers of AP.^{30,31} In 1 case, AP was associated with hypercalcaemia secondary to overreplacement of vitamin D/ oral calcium (alfacalcidol and calcium carbonate); a similar case was reported recently in an adult patient from the United Kingdom.³² Asparaginase, azathioprine, and sodium valproate, which are used for treatment of leukemia, inflammatory bowel diseases, and epileptic disorders, respectively, were the most commonly associated medications in our series. This is similar to previous pediatric findings.^{2,24,25} Asparaginase-associated pancreatitis has been reported in 6.7% to 18% of cases after leukemia treatment in children,³³ but the risk was only 1.5% in children and young adults with acute lymphoblastic leukemia in the United Kingdom.³⁴

Gallstones were the second most frequent association, accounting for 13% of the total patients, compared

with 4% in a previous study in Scotland,¹³ and no cases in other UK series.^{8,12} Gallstones were not exclusively associated with the overweight or hemolytic diseases; 5 of 12 cases had no recognized risk factors. The proportion of gallstone cases in our study (13%) was comparable to recent studies from France (13%)²³ and the United States (12%)²⁴ and higher than a study from Italy (6%),²⁵ but less than the 26% reported in another large US study.⁴

We found trauma and mumps, previously the most commonly reported associations in the United Kingdom, to have become uncommon. Mumps was previously responsible for 16% to 39% of AP cases in the United Kingdom,^{8,12,13} but we found only 1 case. This probably reflects the introduction of the measles-mumps-rubella vaccine in 1988. The most surprising finding in the current study was that only 1 case was associated with trauma during the study period. Trauma accounted for 13% to 16% of UK cases in the past^{8,12,13} and has been reported in 8% to 59% of children with AP internationally.^{2,4–6,21,23,24,29,35,36} One explanation might be that children these days are overly protected by their parents, less active, and spend more time sitting watching TV or playing electronic games than being outdoors. In addition, the younger age of our cohort may also be pertinent, as trauma is more common in older teenagers.

Recent case series of AP in children from Italy, France, and the United States indicated familial/hereditary AP in 6%, 8%, and 1% of patients, respectively.^{23–25} Seven of the children (7%) in our study who had recurrent episode(s) were diagnosed with hereditary pancreatitis. Although AP is a known complication of organic acidemias,^{37,38} this was not reported in previous studies from this country. We found 7 cases (7%), all of Asian origin, associated with

these rare inherited disorders. In total, 5% of our cases were attributed to anatomic congenital anomalies (pancreas divisum and choledochal cyst), which is similar to the 5% reported in the United States²⁴ but much lower than the 23% and 43% reported in Taiwan and Japan.^{21,27} Anatomic anomalies, particularly choledochal cyst, are known to be more common in Asian than in Western children.²⁷

Two cases in our study were associated with systemic diseases, namely, systemic lupus erythematosus and Henoch-Schönlein purpura. AP has been associated with systemic diseases in 2% to 53% of cases in pediatric series.^{2,4–6,21,23,24,26,29} This variation may be partly due to differences in the definition of AP and age of patients and to the variations in classification and assigning the associated agents. The changing incidence in Australia was attributed in part to an increase in cases associated with systemic illnesses.⁶

The main limitation of this study is the potential underestimation of incidence resulting from incomplete ascertainment inherent in the use of the BPSU methodology. Although the orange card return rate during the survey period and clinician responses for case information were high, at 95% and 92%, respectively, data collection solely through the BPSU may have resulted in incomplete ascertainment. In addition, it is possible that some mild cases or AP in those too young to exhibit classic abdominal pain were simply not diagnosed by clinicians caring for the children in primary or secondary care and thus were not reported. Despite this, the study provides the first epidemiologic data on AP in children and its current associations.

CONCLUSIONS

This study shows that AP is an uncommon disease in young children in the United Kingdom, but is

possibly becoming more frequent. Childhood AP has diverse clinical associations, although more than one-third of cases are idiopathic. The associations of childhood AP in the United Kingdom have changed significantly in the past 4 decades. Young patients of Pakistani ethnicity with organic acidemias or who are undergoing treatment with asparaginase are at greater risk for developing AP and the diagnosis should be considered early in the management of abdominal

symptoms. The overrepresentation of Pakistani children observed in this study merits further investigation.

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ABBREVIATIONS

AP: acute pancreatitis
BPSU: British Paediatric Surveillance Unit
CI: confidence interval
RCPCH: Royal College of Paediatrics and Child Health

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