

trial of the Parkinson's Disease Research Group of the United Kingdom, as well as helping to write the paper. JO participated in the design of the cause of death inquiry study, procured all the material, and blinded all the notes for the drugs for Parkinson's disease. AJL was involved in the design and conduct of the trial of the Parkinson's Disease Research Group of the United Kingdom as well as helping to write the paper; he will also act as guarantor for the paper. AC designed the standardised form, reviewed all the case notes, and produced the vignettes for the cause of death inquiry study. BH, PO, YB-S, and AJL reviewed all the vignettes and assigned the causes of death for the cause of death inquiry study. All the contributors read and critically commented on the paper.

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Why do children have chronic abdominal pain, and what happens to them when they grow up? Population based cohort study

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Abstract

Objective: To test the hypotheses that children with abdominal pain have anxious parents and come from families with high rates of physical illness and that they grow up to suffer from high rates of medically unexplained symptoms and psychiatric disorders.

Design: Population based birth cohort study.

Setting: General population.

Subjects: Participants in the Medical Research Council (MRC) national survey of health and development, a population based birth cohort study established in 1946.

Main outcome measures: Abdominal pain present throughout childhood in the absence of defined organic disease, and measures of physical symptoms and psychiatric disorder at age 36 years.

Results: There were high rates of complaints about physical health among the parents of children with persistent abdominal pain, and the mothers had higher neuroticism scores. Children with persistent

abdominal pain were more likely to suffer from psychiatric disorders in adulthood (odds ratio 2.72 (95% confidence interval 1.65 to 4.49)) but were not especially prone to physical symptoms once psychiatric disorder was controlled for (odds ratio 1.39 (0.83 to 2.36)).

Conclusions: Persistent abdominal pain is associated with poor health and emotional disorder in the parents. Children with abdominal pain do not necessarily continue to experience physical symptoms into adulthood but are at increased risk of adult psychiatric disorders.

Introduction

Recurrent abdominal pain is a common reason for children to see a doctor.¹⁻³ In most cases no defined organic diagnosis can be found, and this has led researchers to seek psychosocial explanations for recurrent abdominal pain.⁴ Children presenting with abdominal pain may come from anxious families⁵⁻⁸

and from families in which one or more members suffer from physical health complaints.⁹⁻¹² Most studies have drawn from relatively small clinical samples, which may introduce selection bias with, for example, the most severely symptomatic children and the most anxious parents being overrepresented.

There is comparatively little literature on the long term outcome of children with recurrent abdominal pain. Studies from clinical samples suggest that between 25% and 50% continue to experience symptoms into adulthood.¹³⁻¹⁵ It seems plausible that children with recurrent abdominal pain might also grow up to suffer from irritable bowel syndrome and other functional (or medically unexplained) symptoms. As one of the commonest functional symptoms in childhood, it is tempting to view it as a precursor to non-specific physical symptoms in adulthood. In addition, the evidence that childhood recurrent abdominal pain is associated with a range of psychosocial risk factors suggests that common mental disorders (such as anxiety and depression) may be more common in later life.

This study describes the results of the Medical Research Council's national survey of health and development, a birth cohort which has followed the same group of 5362 subjects from birth in 1946 until the most recent wave of data gathering in 1989 (at age 43 years). We used this long follow up to test the hypotheses that children with persistent abdominal pain come from families with high rates of psychiatric disorder and neuroticism and physical illness and that children with persistent abdominal pain will have high rates of psychiatric disorders and medically unexplained symptoms in adulthood.

Subjects and methods

The MRC national survey of health and development—The national survey of health and development is a national birth cohort study set up in 1946.¹⁶ The survey was based on a sample stratified for social class of all single legitimate births that occurred in England, Wales, and Scotland in one week of March 1946. The sampling procedure and follow up has been described in detail elsewhere.¹⁶ The stratification was based on father's social class: all children born to non-manual workers and agricultural workers were surveyed, while those born to other manual labourers were sampled in a ratio of 1:4. Since 1946, 19 waves of data gathering have been performed. At each wave, information on admission to hospital has been sought. Whenever admission is reported the hospital is contacted for details of diagnosis and treatment.

Definition of cases of recurrent abdominal pain and controls—The usual definition of recurrent abdominal pain is of pain severe enough to affect activities and that occurs at least three times over a period of at least 3 months.¹ The data collected in the survey did not allow for this precise definition. Abdominal pain over the previous year was asked about on three occasions in childhood (at ages 7, 11, and 15 years). We therefore defined persistent abdominal pain as abdominal pain reported at each of these three points in time, which suggested that the pain was chronic. Hospital records for all such children were scrutinised by a paediatrician (SC), and those with a defined organic cause of pain

that was judged to have been present throughout childhood were excluded from the sample. Controls were defined as survey members who participated in the same waves of data collection during childhood but in whom either no abdominal pain was reported or it occurred only once or twice.

Parental illness in childhood—Parental illness was assessed when the survey members were aged 15. The mother was given a list of seven physical illnesses and asked to indicate whether she or her husband had any of them. The illnesses were asthma, cough, rheumatism in joints, anaemia, heart trouble, kidney trouble, and other health complaints. From this list it was possible to determine the number of health complaints each parent suffered from. The mother was also asked to indicate if either parent had "nervous" complaints. In addition, information was collected on the mother's perception of her and her husband's health. This was rated on a questionnaire as "excellent, good, average, not very good, bad." Finally, maternal neuroticism was assessed with the Maudsley personality inventory.¹⁷

Absence from school—Absence from school was assessed twice during childhood. Firstly, school records from the period 1952-6 (at ages 6-10 years) were used to determine the number and distribution of 1 week periods off school over that time. Secondly, the teachers were asked whether the child was below average, average, or above average in terms of absences at the age of 13 years and again at 15 years.

Childhood personality and behaviour—Two main sources of information were used. The children had the Pinter personality inventory administered at the

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Table 1 Relation between childhood abdominal pain and parental health complaints and maternal neuroticism

Risk factor (age (years) of child at assessment)	No exposed	No (%) cases	Odds ratio (95% CI)*	Ir χ^2 for trend; P value
Maternal neuroticism on Maudsley personality inventory (13)				
0	1144	16 (1.4)	1.00	13.62; 0.0002
1	765	11 (1.4)	0.76 (0.37 to 1.12)	
2-3	1037	23 (2.2)	1.05 (0.49 to 2.24)	
≥4	511	21 (4.1)	2.61 (1.23 to 5.52)	
Parental ailments (15)				
0	1604	15 (0.9)	1.00	13.62; 0.0002
1	1055	25 (2.4)	2.37 (1.12 to 5.01)	
2	500	16 (3.2)	3.01 (1.31 to 6.91)	
3	204	7 (3.4)	2.57 (0.85 to 7.74)	
	125	8 (6.4)	4.96 (1.73 to 14.17)	
Mother's perception of own health (15)				
Excellent/good	2353	24 (1.4)	1.00	13.64; 0.0002
Average	920	27 (2.9)	1.39 (0.75 to 2.58)	
Not very good/bad	171	1 (5.9)	4.54 (2.00 to 10.30)	
Mother's perception of father's health (15)				
Excellent/good	2453	37 (1.5)	1.00	6.13; 0.01
Average	723	22 (3.0)	1.69 (0.89 to 3.20)	
Not very good/bad	204	7 (3.4)	2.06 (0.80 to 5.29)	
Mother's self reporting of "nerves" (15)				
No	3059	54 (1.8)	1.00	6.13; 0.01
Yes	394	17 (4.3)	2.12 (1.05 to 4.31)	
Mother reports "nerves" in father (15)				
No	3193	64 (2.0)	1.00	0.46; 0.5
Yes	148	4 (2.7)	1.44 (0.43 to 4.79)	
Reported continual or repeated colds in other family members (6)				
No	2181	24 (1.1)	1.00	14.2; 0.0002
Yes	1427	48 (3.4)	2.48 (1.39 to 4.41)	

Ir = likelihood ratio test.

*Odds ratios corrected for sex and father's social class, weighted for sampling.

Table 2 Relation between abdominal pain and childhood personality and behaviour and school absences

Risk factor (assessor)	No exposed	No (%) affected	Odds ratio (95% CI)*	lr χ^2 for trend; P value
Neuroticism on Pintner personality inventory				
Non-neurotic	1183	21 (1.8)	1.00	0.99; 0.32
Mid-neurotic	1042	19 (1.8)	1.07 (0.50 to 2.25)	
Neurotic	1026	23 (2.2)	1.34 (0.67 to 2.68)	
Introversion on Pinter personality inventory				
Introvert	975	24 (2.5)	1.00	0.57; 0.45
Ambivert	1104	17 (1.5)	0.83 (0.40 to 1.68)	
Extravert	1172	22 (1.9)	0.79 (0.39 to 1.60)	
Energy level at age 13 (teacher)				
Never tired	233	1 (0.4)	1.00	1.82; 0.18
Normally energetic	3026	62 (2.1)	2.48 (0.34 to 18.12)	
Always tired	187	5 (2.7)	3.33 (0.37 to 30.08)	
Day dreaming in class at age 13 (teacher)				
Seldom or never	1664	25 (1.5)	1.00	4.77; 0.03
Sometimes	1602	36 (2.3)	1.55 (0.84 to 2.87)	
Frequently	212	8 (3.8)	2.37 (0.88 to 6.33)	
Disobedience in class at age 13 (teacher)				
Seldom or never	3145	64 (2.0)	1.00	0.74; 0.4
Sometimes	321	321 (0.9)	0.45 (0.19 to 1.02)	
Frequently	26	2 (7.7)	2.90 (0.77 to 10.93)	
Lying in class at age 13 (teacher)				
Seldom or never	2926	55 (1.9)	1.00	0.04; 0.83
Sometimes	483	13 (2.7)	1.36 (0.61 to 2.60)	
Frequently	49	1 (2.0)	0.36 (0.05 to 2.71)	
Periods of absence (weeks) at ages 6-10 (school doctor)				
0-2	855	14 (1.6)	1.00	5.3; 0.02
3-4	717	9 (1.3)	0.61 (0.22 to 1.69)	
5-8	851	22 (2.6)	1.66 (0.76 to 3.66)	
≥9	622	19 (3.1)	1.75 (0.77 to 4.01)	
School absence at age 13 (teacher)				
Seldom or never	824	12 (1.5)	1.00	2.24; 0.13
Sometimes	888	13 (1.5)	1.07 (0.41 to 2.79)	
Frequently	851	24 (2.8)	1.71 (0.70 to 4.14)	

lr = likelihood ratio test. *Odds ratios corrected for sex and father's social class, weighted for sampling.

age of 13, which defined personality according to two dimensions "neuroticism" and "extroversion."¹⁸ The second source of information on personality was from the child's form teacher, who was asked to rate the survey members on the following items: lying, disobedience, being a disciplinary problem, restlessness, quality of work, and energy levels. For each item they were asked to say whether the child was above average, average, or below average.

Other variables—Sex and social class were possible confounders. Social class was assessed according to the father's occupation in 1961 (when survey members were aged 15) and was classified as manual versus non-manual social group.

Adulthood variables—Outcomes during adulthood were measured at 36 years. Two main outcomes were used: psychiatric disorder and physical symptoms. The present state examination, a semistructured psychiatric interview which generates levels of severity of psychiatric disorder (the index of definition), was used for the first outcome.¹⁹ An index of definition of 5 is considered to be threshold for psychiatric disorder. The second outcome was self reported physical symptoms. These were headache, back pain, abdominal pain, dizziness, chest pain, and rheumatism. We identified survey members who suffered from inflammatory bowel disease during adulthood from self report and hospital notes. The survey collects death records for all survey members, and these were available to determine

whether persistent abdominal pain in childhood was associated with increased mortality.

Analytical strategy and statistical methods—Odds ratios and 95% confidence intervals were calculated to assess the strength of associations between childhood risk factors and persistent abdominal pain. These were subsequently controlled for father's social class and sex in a logistic regression analysis weighted for the sampling. Likelihood trend tests were used for ordered categorical variables. Ordinal regression was used for the adult outcomes, which were ordered categorical variables (index of definition and number of physical symptoms). This generated a single odds ratio for ordered categorical outcomes which represent the odds of having the outcome for those in the group with pain relative to those unaffected by pain.²⁰ Cox's proportional hazards were used to determine whether death rates for those with abdominal pain in childhood (corrected for sex, social class, and sampling weights) were raised during adulthood.

Results

At the age of 7 years, a fifth of survey members had suffered abdominal pain; at 11 years it was 19% and at 15 years it was 17%. Two fifths were reported to have suffered abdominal pain at least once in childhood and 10% at least twice. Seventy six (2.1%) of the 3637 children who participated at the three points in time had recurrent abdominal pain. Of these, three had hospital records that suggested that the pain was caused by a chronic disease, leaving 73 (2.0%) with persistent pain of unexplained origin. Of this group, 52 (71%) had consulted a doctor at least once during childhood. The follow up and representativeness of the survey have been described in more detail elsewhere.¹⁶ Of the risk set, 32 were followed up to the age of 36 years, and this proportion did not differ according to pain status in childhood ($\chi^2 = 0.001$; $P = 0.97$).

Children with persistent abdominal pain were evenly distributed between the sexes (odds ratio for girls 0.97; 95% confidence interval 0.56 to 1.68). Children whose fathers had manual occupations were more likely to suffer from pain (1.75; 1.02 to 3.03). Table 1 shows the relation between persistent abdominal pain and various measures of parental and family health during childhood. There was a strong association between pain and parental health complaints, parental ratings of health, maternal "nerves," maternal neuroticism, and reporting of the family being prone to "colds." Because the relation between pain and parental physical health complaints and health ratings could have been due to maternal neuroticism an additional logistic model, which included maternal neuroticism with these complaints, was included, but this caused only a modest reduction in these associations (results not shown).

Childhood personality and its association with persistent abdominal pain is shown in table 2. Neuroticism and introversion were not associated. The teacher's ratings suggested that persistent abdominal pain was no more common in children with antisocial traits such as lying, disobedience, or having disciplinary problems. There was a modest association between traits such as day dreaming in class and having low levels of energy and persistent abdominal pain. Children with abdomi-

Table 3 Relation between childhood abdominal pain and adult psychiatric disorder and physical symptoms at age 36 years

Outcome	No of children	No (%) with abdominal pain	Odds ratio* (95% CI)
Persistent abdominal pain			
No	2383	45 (1.9)	1.30 (0.50 to 3.38)
Yes	226	7 (3.1)	1.03 (0.39 to 2.73)†
Persistent headache			
No	2045	38 (1.9)	1.51 (0.73 to 3.13)
Yes	563	14 (2.5)	1.20 (0.57 to 2.56)†
Index of definition on present state examination			
1	1239	13 (1.1)	2.72 (1.65 to 4.49)‡
2	811	19 (2.3)	
3	225	9 (4.0)	
4	158	5 (3.2)	
5	129	1 (0.8)	
6	24	4 (16.7)	
7	6	1 (16.7)	
No of common somatic symptoms			
0	1312	20 (1.5)	1.74 (1.04 to 2.92)‡
1	786	16 (2.0)	1.39 (0.83 to 2.36)‡
2	345	9 (2.6)	
3	130	5 (3.9)	
4	30	1 (3.3)	
5	7	1 (14.3)	

*Derived by logistic regression unless marked otherwise.

†Corrected for psychiatric disorder at age 36 (see text).

‡Ordinal regression, corrected for sex, father's social class, marital status at age 36, and educational status. Note that ordinal regression derives single odds ratio describing increased risk of having outcome in abdominal pain group compared with "no pain" group, independent of level of severity of outcome.

nal pain had more absence from school between the ages of 6 and 10 years, but only a modest non-significant increase in absence was evident at 13 years.

The outcome of children with pain is shown in table 3. Persistent abdominal pain in childhood was associated with psychiatric disorder, and this association remained after correction for potential confounders in an ordinal regression model. Childhood pain was only very weakly associated with abdominal pain and headache at 36 years but was associated with increasing numbers of physical symptoms at this age. Because there is a strong association between psychiatric disorder and physical symptoms, psychiatric disorder was added to the model, and this led to the association between persistent abdominal pain and physical symptoms in adulthood failing to reach significance. None of the children with persistent abdominal pain developed inflammatory bowel disease during the period of follow up. Only one subject with abdominal pain in childhood died over the follow up period, and this was lower than the rate for the rest of the cohort (hazard ratio (controlled for sex and social class) 0.15; 0.02 to 1.06).

Discussion

This study used population based data to follow up a group of children with persistent abdominal pain over a period of 20 years. There were three main findings. Firstly, persistent abdominal pain in childhood was associated with physical ill health in the parents. Secondly, persistent abdominal pain in childhood did not predict abdominal pain in adulthood but was modestly associated with other common physical symptoms in adulthood. Thirdly, persistent abdominal

pain in childhood was a predictor of psychiatric disorder in adulthood.

Methodological concerns

We were not able to define recurrent abdominal pain in the conventional manner. We believe, however, that our sample of children was likely to be symptomatic for much of childhood and to reflect clinical samples of children with recurrent abdominal pain. They were somewhat more likely to have been absent from school for long periods during middle childhood. The population base of this sample and the lack of differences in follow up rates for children with abdominal pain and those without make it unlikely that these results are due to selection bias. The results reported here compare those with persistent abdominal pain with children who never experienced pain. When those who had experienced pain once or twice in childhood were included in the control group the results were not substantially altered, although some of the odds ratios were slightly reduced (results not shown).

Family ill health and symptoms

The relation between sickness in the family and medically unexplained symptoms in adulthood has been reported in several retrospective studies. The relation between persistent abdominal pain present in childhood and ill health in the parents suggests that the parental anxiety and preoccupations with physical health may reinforce the child's concern about physiological and minor medical bodily sensations. From the clinical viewpoint this suggests that in the treatment of children with persistent abdominal pain it is important to understand parental beliefs and experiences and to avoid behaviours that might reinforce pain behaviour in the child. This is a component of treatments which have been shown to be effective.^{4 21}

While the parents of children with persistent abdominal pain were more likely to have psychiatric disorders, the children themselves did not seem especially maladjusted. They did not score especially high on neuroticism but were more likely to be "day dreamers" and there was a non-significant trend for them to be lacking in energy. These behaviours may be akin to inhibited traits (such as shyness, fearfulness, and being easily upset), which are recognised to be predictors of adult depression.²²

So far as we know, this is the largest and longest follow up of abdominal pain in children to date. The survey members were growing up in the 1950s, and it is interesting to speculate whether the same associations would have been detected in a modern sample. With an increasingly health conscious population the parents of children with abdominal pain may be less readily reassured than they were 40 years ago. Modern medical advances may mean that these children would be more extensively investigated today than previously and that a proportion may avoid unnecessary operations, but it may also reinforce illness beliefs.

Overall the results suggest that the outcome in terms of symptoms of persistent pain is good. Though there is some evidence that persistent abdominal pain in childhood is associated with medically unexplained physical symptoms in adult life it is a more powerful predictor of adult psychiatric disorder. Apley's "little

Key messages

- Persistent abdominal pain in childhood is more common in families with high rates of reported physical illness and psychological symptoms
- The outcome for persistent abdominal pain is good in terms of mortality
- Children with persistent abdominal pain are not at greatly increased risk of developing physical symptoms in adulthood
- Abdominal pain in childhood is associated with considerably increased risk of psychiatric disorders in adulthood

belly-achers¹³ do not grow up to be big belly achers but do grow up to suffer from anxiety or depression.

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Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India

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Abstract

Objectives: To assess the efficacy and tolerability of aminosidine compared with sodium stibogluconate for treating visceral leishmaniasis.

Design: Randomised, unblinded, controlled trial with 180 day follow up.

Setting: Kala-Azar Research Centre, Brahmpura, Muzaffarpur, Bihar, India.

Subjects: People of either sex aged 6-50 years with symptoms and signs suggestive of visceral leishmaniasis (fever, loss of appetite, enlarged spleen) with leishmania amastigotes detected in Giemsa stained aspirates of spleen or bone marrow.

Interventions: Aminosidine at three daily doses (12, 16, and 20 mg/kg) for 21 days and sodium stibogluconate 20 mg/kg/day for 30 days.

Main outcome measures: Laboratory measures of efficacy: parasite count, haemoglobin concentration,

white cell count, platelet count, serum albumin concentration. Clinical measures of efficacy: spleen size, fever, body weight, and liver size. Measures of safety: liver and renal function tests, reports of adverse events.

Results: Of the 120 patients enrolled (30 per treatment arm), 119 completed treatment and follow up. Cure at end of follow up was achieved in 23 (77%), 28 (93%), and 29 (97%) patients treated with 12, 16, and 20 mg aminosidine/kg/day respectively, and in 19 (63%) patients given sodium stibogluconate. At 16 and 20 mg/kg/day, aminosidine was significantly more active than sodium stibogluconate in both clinical and laboratory measures of efficacy. No significant clinical or laboratory toxicity occurred in any treatment group.

Conclusions: A 21 day course of aminosidine 16 or 20 mg/kg/day should be considered as first line treatment for visceral leishmaniasis in Bihar.