Epidemiology

Study of intellectual performance of children in ordinary schools after certain serious complications of whooping cough

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Abstract

In a case-control study 27 index children from ordinary schools who had had convulsions or apnoea as a complication of whooping cough about eight years previously were compared with 27 children who had never had whooping cough and 15 who had had whooping cough without complications. Other factors likely to cause intellectual impairment after conception were considered. The index group had a significantly lower median intelligence quotient and poorer school attainment than either of the control groups.

The results support the hypothesis that convulsions or apnoea as a complication of whooping cough may be associated with subsequent intellectual impairment.

Introduction

A large epidemic of whooping cough in West Glamorgan, south Wales, during 1977-9 was studied.[1] Subsequently follow up studies were carried out on children who were under 5 years of age at the onset of whooping cough during this epidemic.[2] The purpose of the present follow up study, seven to eight years later, was to investigate the hypothesis that certain serious complications of whooping cough may be associated with subsequent intellectual impairment in some children. Of 1500 children who were under 5 when they had whooping cough in the epidemic, 34 (2%) had apnoea, convulsions, or encephalopathy as a complication. One of the two children with encephalopathy died during the illness, and the other developed a complete tetraplegia and severe mental retardation; he was not included in this study. A child who had apnoea had left the country, leaving 31 children for possible inclusion in the index group.

Methods

We defined whooping cough as severe and distressing paroxysms of coughing, each occurring in the same breath and often ending in a characteristic whoop or vomiting, or both. The attacks are usually worse at night and the illness lasts from three to 12 weeks or more. Apnoea may follow a severe paroxysm of coughing when the child would normally be expected to take a deep breath, often accompanied by the characteristic whoop. Instead, the child stops breathing for periods lasting one minute or longer and becomes deeply cyanosed.

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Of the 31 children, 27 had had apnoea and four had had convulsions for the first time during the attack of whooping cough. Each child was matched with two others by age, sex, and social class[3] and the same class in school, one control having never had whooping cough (control group 1) and the other having had whooping cough but none of the named complications (control group 2). The age of each control did not differ by more than four months from that of the index child.

As a result of our strict method of matching, in only 27 cases could we obtain a matched control who had not had whooping cough (control group 1) and in only 15 cases a control who had had whooping cough but none of the complications (control group 2), leaving a total of 69 children studied. The four children for whom no controls could be obtained were excluded from the study. Two were severely mentally subnormal and two came from such small schools that an age match was not possible. The final index sample thus comprised 27 children. Although this may seem a small sample it included nearly all the possible cases among the 1500 children who had had whooping cough; 17 of the 27 (63%) had bacteriological confirmation of the diagnosis.

Parents of an index or control child were first visited by the two researchers, a doctor (WOW) and an educational psychologist (BJ). One questionnaire was completed about the health of the child and the family and another about the child's education and behaviour.

Other possible causes of intellectual impairment that had occurred since conception were also considered. Details of the mother's pregnancy, her confinement, and the condition of the child at birth (including birth weight and Apgar score) were obtained from the relevant hospitals. A detailed medical examination was carried out at school followed by a comprehensive examination of the current psychological and educational state of each child. This was carried out with carefully selected tests and questionnaires appropriate for use with children in the age range of the sample (6 years 8 months to 11 years). Wilcoxon's matched pairs signed ranking test was used to examine the hypothesis that no significant differences would be found in intelligence quotient (IQ), educational attainment, or behaviour between the index cases and control group 1 (27 pairs) and the index cases and control group 2 (15 pairs). In all analyses the two tailed significance values are quoted because it was thought that a prediction of direction was not justified. The British ability scales were used to calculate IQs.

Results

The mean age of the total sample of 69 was 8 years 4 months, with 43 of the children (62%) in the range 7 years to 8 years 11 months. More children in control group 1 (12; 44%) than in the index (3; 11%) group were first born. The groups were well matched for household size. Most (85%) of the parents had left school at the minimum school leaving age.

PREGNANCY AND CONFINEMENT

The mean age of the mothers at the time of confinement was 26 years (range 16-34 years), and there were no significant differences among the three groups.

There were no apparent differences between the index children and control group 1 in the number of mothers who had suffered from any illnesses during pregnancy (table I). None of the illnesses were serious, and they were not of types known to affect the fetus. Twenty (74%) of the index children had been born at full term compared with 23 (85%) in control group

1. The confinement had been normal in 24 (89%) of the index children and 21 (78%) in control group 1. Four in the index group (12%) and three (11%) in the control group 1 had been born prematurely. The Apgar scores (all measured at about five minutes after birth) of the premature children in these groups were 7 or over. The only breech delivery was a child in the index group who had an Apgar score of 6 and was now normal in intelligence and school attainment. Six children had been born by caesarean section, all with Apgar scores of 7 or above, except for one child in control group 2 who had had a score of 5 but who was now functioning at a level appropriate for age.

CLINICAL HISTORY

There was no evidence of any serious reaction to any vaccine given to the children. Only three (11%) of the index children and two (13%) in control group 2 had been fully vaccinated against diphtheria, pertussis, and tetanus compared with 11 (41%) in control group 1. The average age at the onset of whooping cough was lower in the index cases (1 year 5 months, range 2 weeks to 3 years) than in control group 2 (3 years 3 months, range 12 weeks to 7 years) (p=0·0001).

Table II shows the past illnesses; a history of serious cerebral damage was not found in any child. All the children with asthma were in the two groups who had had whooping cough—seven in the index group (26%) and five in control group 2 (33%)—(p<0·05).[4] There were 16 (59%) with a history of recurrent bronchitis in the index group, four (27%) in control group 2, and only one in control group 1 (p<0·05).[4] These figures, though significant, are small and should be interpreted with caution. There were 17 children (63%) with recurrent ear infections in the index group, two (13%) in control group 2, and seven (26%) in control group 1. Children with minor hearing difficulties were commoner in the index group, but the numbers were too small for statistical comparison. It was difficult to ascertain how many of the children had had these problems before they had had whooping cough because almost half of them were under 12 months old when they had the illness. More children had a history of measles in the index group (21, 68%) than in control group 1 (17, 63%), but only five (19%) in the index group had been vaccinated compared with 15 (56%) in control group 1.

Nine children in the index group had a history of convulsions (five before the episode of whooping cough), but two of these had further convulsions during the attack. The remaining four children had convulsions for the first time during the attack of whooping cough and one continued to have fits for 12 months afterwards; this was the only child of the nine who received anticonvulsant drugs. Of the three children who had not had convulsions during the attack of whooping cough, one had a fit during an attack of meningitis and the two others had convulsions associated with fever. Two cases of febrile convulsions occurred in control group 2 and two in control group 1, one after a "breath holding attack" and the other associated with measles. All the convulsions were generalised, and none suggested petit mal or jacksonian epilepsy.

TABLE I—*Details of pregnancy and confinement in index group, control group 1 (children who had not had whooping cough), and control group 2 (children who had had whooping cough without complications). Figures are numbers (percentages) of children*

	Index cases (n=27)	Group 1 (n=27)	Group 2 (n=15)
Pregnancy:			
Toxaemia	3 (11)	5 (19)	2 (13)
Illness during pregnancy	2 (7)	4 (15)	3 (20)
Gestation:			
Premature	4 (15)	3 (11)	4 (27)
Full term	20 (74)	23 (85)	8 (53)
Postmature	3 (11)	1 (4)	3 (20)
Delivery:			
Normal	20 (74)	23 (85)	10 (67)
Forceps	4 (15)	3 (11)	1 (7)
Breech	1 (4)	0	0
Caesarean	2 (7)	1 (4)	4 (27)
Anxiety about survival at birth:			
None	25 (93)	23 (85)	13 (87)
Badly jaundiced	1 (4)	2 (7)	1 (7)
Baby in incubator	1 (4)	2 (7)	1 (7)
Birth injury	0	0	0
Mean Apgar score (about five minutes after birth)	9	9	8

TABLE II—*Details of previous diseases suffered by index children compared with those in control groups 1 and 2. Figures are numbers (percentages) of children*

Disease	Index cases (n=27)	Group 1 (n=27)	Group 2 (n=15)	p Value
Asthma	7 (26)	0	5 (33)	<0·05*
Recurrent bronchitis	13 (48)	1 (4)	4 (27)	<0·05*
Recurrent ear infection	12 (44)	7 (26)	2 (13)	<0·05*
Hard of hearing	9 (33)	2 (7)	0	
Convulsions	9 (33)	2 (7)	2 (13)	
Measles	21 (78)	17 (63)	10 (67)	
Chickenpox	18 (67)	15 (56)	8 (53)	
Eczema	7 (26)	2 (7)	4 (27)	
Hay fever	2 (7)	0	0	

*χ^2 Test was used to test the three groups simultaneously.

CLINICAL EXAMINATION

There were no significant differences in the mean height, weight, or head circumference among the three groups. The central nervous system was normal in all 69 children. Although eight of the 27 index children had a history of asthma, only one had evidence of asthma at the time of clinical examination; several of the children had, however, received treatment before attending school. The cardiovascular system was normal in all the children except one boy who had operation scars from Mustard's operation for congenital tranposition of the great vessels. He was perfectly fit, was no longer breathless or cyanosed, and played games like other children. Any defects of vision or hearing were minor, and there were no cases of nerve deafness.

PSYCHOLOGICAL ASSESSMENT

There was a distinct trend in the results of psychological assessment, with the index group achieving lower scores on most of the aspects of development studied. Control group 1 had a significantly higher median IQ than the index group (p=0·018). Control group 2 also achieved a higher median score than the index group, but this difference was not significant. Table III shows the results of IQ testing with those from index cases matched

TABLE III—*Median IQ scores for index children and control groups 1 and 2 with results of Wilcoxon's matched pairs signed ranking test*

	Median scores				Index cases (n=27) / Group 1 (n=27)			Index cases (n=15) / Group 2 (n=15)		
	Index cases (n=27)	Group 1 (n=27)	Index cases (n=15)	Group 2 (n=15)	Sum of positive ranks (W)	Normalised test statistic (Z)	p Value	Sum of positive ranks (W)	Normalised test statistic (Z)	p Value
IQ	90	96	94	97	287	2·355	<0·05	71	1·162	NS
Speed	50	50	52	45	163	0·013	NS	44	0·979	NS
Matrices	46	54	46	55	187	2·488	<0·05	65	2·845	<0·01
Similarities	46	48	46	53	166	1·286	NS	58	1·493	NS
Block design (L)	42	43	43	44	182	0·915	NS	66	1·435	NS
Block design (P)	51	49	53	55	223	1·207	NS	55·5	0·699	NS
Immediate visual recall	46	46	48	46	161·5	0·329	NS	53·5	0·559	NS
Delayed visual recall	42	49	42	46	203·5	0·712	NS	69	0·511	NS
Recall of digits	42	48	42	47	162	1·617	NS	48	0·708	NS
Recall of designs	47	54	48	53	221·5	2·541	<0·05	86	2·104	<0·05
Word definitions	43	48	39	47	314	3·005	<0·01	58	1·493	NS

TABLE IV—*Median scores for attainment for index children and control groups 1 and 2 with results of Wilcoxon's matched pairs signed ranking test*

	Median scores				Index cases (n=27) / Group 1 (n=27)			Index cases (n=15) / Group 2 (n=15)		
	Index cases (n=27)	Group 1 (n=27)	Index cases (n=15)	Group 2 (n=15)	Sum of positive ranks (W)	Normalised test statistic (Z)	p Value	Sum of positive ranks (W)	Normalised test statistic (Z)	p Value
Neale reading	25	38	25	39	299·5	2·656	<0·01	97	2·102	<0·05
Neale comprehension	11	14	10	15	274·5	3·017	<0·01	87	2·167	<0·05
Vernon spelling	12	17	15	20	246·0	2·248	<0·05	67·5	1·542	NS
Vernon mathematics	11	14	12	16	239·5	1·630	NS	84·5	1·396	NS
British picture vocabulary	86	84	86	99	169·5	0·959	NS	88	1·591	NS

TABLE V—*Discrepancies between attainment ages and chronological ages on reading and spelling tests for index cases and control group 1*

	Neale reading		Neale comprehension		Vernon spelling	
	Index cases	Group 1	Index cases	Group 1	Index cases	Group 1
Attainment age less than chronological age:						
>2 Years	3	1	2	2	4	2
19 Months-2 years	2	1	3	1	1	3
13-18 Months	4	4	2	1	8	1
7-12 Months	5	2	3		3	4
≤6 Months	3	2	6	2	4	5
Attainment age=chronological age	1		2			
Attainment age greater than chronological age:						
≤6 Months	3	6	4	8	2	3
7-12 Months	3	3		3	3	3
13-18 Months	2	4	1	3	1	1
19 Months-2 years	1	4	3	3	1	2
>2 Years			1	4		3

against control groups 1 and 2 separately, and table IV shows the attainment scores set out in the same way. In all individual scales of the British ability scales the index group had lower median scores than control group 1, but the differences were significant for only three of the 10 scales used: the non-verbal reasoning scale (p=0·013), the recall of designs scale (p=0·011), and the word definitions scale (p=0·003) (table III). The index group achieved significantly lower median scores than control group 1 for reading (p=0·008), comprehension (p=0·002), and spelling (p=0·025). The median score for the index group was lower on the arithmetic test (p=0·103), but this result was not significant. The median scores of control group 2 were also higher than those of the index group, but reached significance only for reading (p=0·036) and comprehension (p=0·030) (table IV). In both the vocabulary and arithmetic tests all the groups' median scores were below the normal for their chronological age, but the index group's scores were below the normal for chronological age in all the tests (table V). In the Bender gestalt test control group 1 achieved a higher mean score (p=0·021) and a higher test age score than the index group (p=0·010). Analysis of the overall scores using the Bristol social adjustment guide showed no significant behavioural differences among the groups. No differences were identified in IQ or attainment between children with and without asthma. The Mann-Whitney test was used for this analysis because of the wide variance of individual scores.

Analysis of the mean scores for those with and without a history of convulsions showed no significant difference in IQ (p=0·114, Mann-Whitney test), but the children with no history of convulsions had higher scores for attainment and the results were significant for reading (p=0·011), comprehension (p=0·040), mathematics (p=0·028), and spelling (p=0·035). The result was not significant for vocabulary (p=0·331).

Apnoea had occurred in 23 of the index children, one of whom had also had a convulsion at the end of an attack. Nine (39%) of these children achieved IQs of less than 90 compared with an expected 25% in the normal population.[5] The remainder of the apnoeic children (61%) achieved IQs between 90 and 110, compared with an expected 50% in the normal population. None of the apnoeic children reached an IQ above 110, however, the expected proportion in the normal population being 25%.

SCHOOL FACTORS

Of the 27 index children, 13 (48%) were either receiving or about to receive remedial help at school, compared with three (20%) in control group 2 and three (11%) in control group 1. Attendance records in the schools showed no significant differences among the three groups, although a higher number of absences was recorded for the index group; the differences were not significant. The parents of 37% of the children in the index group thought that their child was performing below average compared with 20% in control group 2 and none in control group 1.

Discussion

The possible adverse effects of the complications of whooping cough, particularly the occurrence of long term respiratory or neurological sequelae, have been widely reported.[6-14] None of the studies, however, are contemporary, and all predate the widespread use of vaccine and antibiotics. The most up to date studies are those of Butler *et al* in 1982[15] and Johnston *et al* in 1985.[16] Butler *et al* used data from the 1970 child health and education study and found that children who had been admitted to hospital with whooping cough had lower scores in a range of educational tests at 5 years of age.[15] Johnston *et al* found no evidence in IQ or reading attainment in a case-control study of 316 children who had had whooping cough and 711 controls who had not.[16] In our study of children who had either apnoea or convulsions after an attack of whooping cough the index group had a significantly lower median IQ and poorer attainment score than the children who had not had whooping cough, although no significant behavioural differences were identified.

These differences may have been due to apnoea or fits, or both, or to some other factors. Possible causes during the mother's pregnancy and confinement have already been excluded. There were many more first born children in the group who had not had whooping cough (control group 1), and educational studies have shown that first born children have a socioeducational advantage over later siblings. First born children, however, have less opportunity of getting whooping cough because they have no siblings to bring the infection home. We would expect caring parents of whatever social class to have had their children immunised, but the opposite may have been the case with pertussis. Some caring parents may have taken notice of the adverse publicity given to the vaccine in the media after 1974 and decided not to have

their children vaccinated. A survey carried out by this unit in 1976 showed that among a national sample of 100 general practitioners a third were advising parents against pertussis vaccination. This change in the attitudes of doctors and parents resulted in a drop not only in pertussis vaccination but also in vaccinations against other diseases, including measles.

Recurrent otitis media can interfere with a child's schooling either by causing absenteeism or because of difficulties with hearing. In a study of the respiratory sequelae of whooping cough children who had had whooping cough were compared with those who had not. Hospital admissions for otitis media, deafness, and removal of tonsils and adenoids were the same in the two groups before the attack of whooping cough but were significantly more common in the index group after the attack.[2] Although more patients in the index group gave a history of hearing difficulties, we did not find evidence of any hearing difficulties that might seriously have affected the child's schooling either in the history or on clinical examination.

Convulsions were more common in the index group before the attack of whooping cough than in control group 2, but the numbers were too small for statistical comparison and should be interpreted with caution. Only one of the children in the three groups had recurrent convulsions needing anticonvulsant drugs. This child started having convulsions for the first time during the attack of whooping cough and continued having fits for a year after recovery from the illness. At 10 years of age he was functioning intellectually at only the 5½-6 year range. Recurrent convulsions would be more likely to result in intellectual impairment than one isolated febrile convulsion. Two other children who had convulsions for the first time during the attack of whooping cough were also functioning below average in intelligence and attainment, though another child seemed to be of average ability. It is difficult to be certain with such small numbers whether a child with a history of convulsions is more likely to get a worse attack of whooping cough. Two children not included in this study, however, who had a history of recurrent convulsions had an encephalopathy during the attack of whooping cough; one died and the other survived, but with a complete tetraplegia. The child who died had been born with a meningocele.

Some of the children who had whooping cough and who also had other factors may have been born with genetic disadvantages, but this should not obscure the fact that convulsions and apnoea in themselves are serious complications that may result in brain damage due to cerebral anoxia. Such injury to the central nervous system may lead to intellectual impairment and learning difficulties.[17-21] Some children may develop more minor degrees of cerebral damage that will be recognised only at school. A convulsion during an attack of whooping cough could be due to cerebral damage caused by fever, anoxia, or cerebral haemorrhage; true encephalitis is probably rare. Electroencephalography carried out on 31 infants in a Leningrad hospital, all except five of whom had moderate to severe whooping cough without clinical evidence of disease of the central nervous system, showed that three of the children had focal changes that persisted after recovery from the whooping cough.[22] Apnoea in particular is a common cause of cerebral anoxia in whooping cough, and the seriousness of the condition is reflected in the descriptions given by the parents.

Parents often panicked when the attacks occurred, fearing that the child would not breathe again unless someone took urgent action. The father of one child gave mouth to mouth resuscitation on two occasions because he thought his child was going to die. Seven of the mothers held their children upside down by the ankles. Five others said they had beaten the children on the back, and two had put their fingers down their children's throats. Two children had lost consciousness and one, according to the mother, had been "semiconscious for several hours." The mother of another child said that she was unable to feel the pulse or heart beat during the attack but that the heart beat returned when the child breathed again; when she panicked, though, she may not have felt for the heart beat properly. The frequency of attacks varied from six during the whole illness to three to eight attacks daily for 14 days. In only one case was the attack followed by a convulsion.

Are children with asthma more likely to get apnoea? In a recent study of the respiratory sequelae of whooping cough 85 of 813 children (11%) who had had whooping cough four and a half years earlier suffered from asthma.[2] Of these 85, six (7%) had apnoea compared with 21 (3%) of the remaining 728. The proportions differ significantly ($p<0.05$). This suggests that these children were more susceptible than others to both asthma and apnoea. Was apnoea being mistaken for asthma and vice versa? This is unlikely because the descriptions of apnoea given by the parents were so consistent that it should be regarded as a condition in itself. We have no evidence in this study to show that children of low intelligence had more severe whooping cough. It is now generally accepted that both genetic and environmental factors influence intelligence.[23-25] To make an exact comparison between the study children and their parents and siblings would have entailed carrying out a similar range of psychoeducational tests on the whole family. Comparison would not have been valid across such a wide age range even had such extensive testing been practicable.

We conclude that prolonged apnoea or seizures, or both, after an attack of whooping cough greatly increase the risk of later learning difficulties at school.

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References

1 Swansea Research Unit of the Royal College of General Practitioners. Effect of a low pertussis vaccination uptake on a large community. *Br Med J* 1981;282:1-10.
2 Swansea Research Unit of the Royal College of General Practitioners. Respiratory sequelae of whooping cough. *Br Med J* 1985;290:1937-40.
3 Office of Population Censuses and Surveys. *Classification of occupations*. London: HMSO, 1970.
4 Nass CAG. The χ^2 test for small expectations in contingency tables, special reference to accidents and absenteeism. *Biometrika* 1959;46:365.
5 Eysenck HJ. *Know your own IQ*. Harmondsworth: Penguin, 1962.
6 Byers RK, Rizzo ND. A follow up study of pertussis in infancy. *N Engl J Med* 1950;242:887-91.
7 Berg JM. Neurological sequelae of pertussis with particular reference to mental defect. *Arch Dis Child* 1959;34:322-4.
8 Christie AB. *Infectious diseases: epidemiology and practice*. Edinburgh: Churchill Livingstone, 1980.
9 Creighton C. *History of epidemics in Britain, AD 1666-1893*. Cambridge: Cambridge University Press, 1894:666-77.
10 Sears WG. The nervous complications of whooping cough. *British Journal of Children's Diseases* 1929;26:178-93.
11 Nelson RL. The neurological complications of whooping cough. *J Pediatr* 1939;14:39-47.
12 Dolgopol VB. Changes in the brain in pertussis with convulsions. *Archives of Neurology and Psychiatry* 1941;46:477-503.
13 Levy S, Perry H. Pertussis as a cause of mental deficiency. *Am J Ment Defic* 1948;52:217-26.
14 Rosenfield GB, Bradley C. Childhood behavior sequelae of asphyxia in infancy. *Pediatrics* 1948;2:74-84.
15 Butler NR, Golding J, Haslum M, Stewart-Brown S. Recent findings from the 1970 child health and education study: preliminary communication. *J R Soc Med* 1982;75:781-4.
16 Johnston IDA, Anderson HR, Lambert HP, Patel S. Reading attainment and physical development after whooping cough. *J Epidemiol Community Health* 1985;39:314-9.
17 Luria AR. *Higher cortical functions in man*. New York: Basic Books, 1966.
18 Tarnopol L, Tarnopol M, eds. *Brain function and reading disabilities*. New York: University Park Press, 1977.
19 Dinnage R. *The handicapped child*. Vol I. London: William Clowes and Sons Ltd, 1970.
20 Pirozzolo FJ, Wittrock MC. *Neuropsychological and cognitive processes in reading*. London: Academic Press, 1981.
21 Ross EM, Peckham CS, West PB, Butler NR. Epilepsy in childhood: findings from the national child development study. *Br Med J* 1980;280:207-10.
22 Stepanov AI, Shvalko AD. Electroencephalographic changes in whooping cough. *Pediatriya* 1969;48:21-4.
23 Douglas JWB. *The home and the school*. London: Panther Modern Society, 1971.
24 Mussen PH, Conger JJ, Kagan J. *Child development and personality*. New York: Harper and Row, 1979.
25 Vernon PE. *Intelligence: heredity and environment*. San Francisco: Freeman, 1979.

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