Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database

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Abstract

Objectives To assess whether children with autism are more likely to have a history of gastrointestinal disorders than children without autism.
Design Nested case-control study.
Setting UK General Practice Research Database.
Subjects Children born after 1 January 1988 and registered with the General Practice Research Database within 6 months of birth.
Outcome measures Chronic inflammation of the gastrointestinal tract, coeliac disease, food intolerance, and recurrent gastrointestinal symptoms recorded by the general practitioner.
Results 9 of 96 (9%) children with a diagnosis of autism (cases) and 41 of 449 (9%) children without autism (matched controls) had a history of gastrointestinal disorders before the index date (the date of first recorded diagnosis of autism in the cases and the same date for controls). The estimated odds ratio for a history of gastrointestinal disorders among children with autism compared with children without autism was 1.0 (95% confidence interval 0.5 to 2.2).
Conclusions No evidence was found that children with autism were more likely than children without autism to have had defined gastrointestinal disorders at any time before their diagnosis of autism.

Introduction

Autism is a spectrum of developmental disorders characterised by impaired social interaction and communication.[1] Several studies have shown that the prevalence and incidence of autism have risen steeply over the past decade.[2 3]

Wakefield and colleagues suggested an association between chronic inflammatory intestinal disease and autism in 1998.[4] They described 12 children with autism and gastrointestinal symptoms, including diarrhoea, pain, and food intolerance. Colonoscopy and biopsy showed ileal-lymphoid-nodular hyperplasia and non-specific colitis. The authors hypothesised that chronic intestinal disease and malabsorption may be causal factors in the development of autism. This has raised concerns about gastrointestinal disease as a risk factor for autism. Using a nested case-control design we assessed the frequency of chronic inflammation of the gastrointestinal tract, coeliac disease, food intolerance, and recurrent gastrointestinal symptoms among children with a diagnosis of autism compared with children without autism. We used anonymised data from the UK General Practice Research Database.

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Methods

Since 1987 more than 3 million residents of the United Kingdom registered with selected UK general practitioners who record details of patient characteristics, drugs dispensed, diagnoses, and hospital referrals for the General Practice Research Database. Diagnoses were recorded according to a modified version of the Oxford Medical Information Systems coding system.[5] The high quality of data recording has been validated in many studies carried out by the Boston Collaborative Drug Surveillance Program.[6–15]

We included as the base population all children born after 1 January 1988 and registered within 6 months of birth (n=211 480). From the computer records we identified all children in the study population with a first recorded diagnosis of autism (ICD code 307.0) between 1 January 1988 and 31 December 1999. We requested hospital and referral records, including letters from psychiatrists, neurologists, and consultant paediatricians, for all potential cases. We reviewed them for evidence of the spectrum of autistic disorders, including Asperger's syndrome. If the diagnosis of autism was confirmed by additional documentation then we considered the child to be a case. If the case records indicated that the diagnosis was not an autistic spectrum disorder, we excluded the child from further analysis. We considered children with inconclusive or unobtainable records to be "possible" cases. We took the first recorded diagnosis of autism in the computer record as the index date for that case.

To encompass the condition reported by Wakefield and colleagues,[4] we identified children with inflammatory bowel disease (ulcerative colitis, regional enteritis), chronic gastroenteritis, food intolerance (including coeliac disease), and recurrent gastrointestinal symptoms—for example, diarrhoea, colic, or vomiting on three separate occasions within 6 months of one another—in the computer records at any time before the index date. We requested recorded details of hospi-

Table 1 Characteristics of children with autism and matched controls. Values are numbers (percentages) unless stated otherwise

	Cases (n=96)	Controls (n=449)
Boys	84 (88)	394 (88)
Girls	12 (13)	55 (12)
Mean age (months):		
Boys	51.0	49.8
Girls	49.4	49.4
Gastrointestinal disorder:		
Coeliac disease	0	1 (0.3)
Chronic gastroenteritis	2 (2)	0
Regional enteritis	0	0
Malabsorption	0	1 (0.3)
Ulcerative colitis	0	0
Food intolerance	3 (3)	11 (2)
Symptoms three times in 6 months	4 (4)	28 (6)
Referred to hospital for disorders	6 (6)	18 (4)

tal admissions and consultations. No further information was available for the less severe conditions of food intolerance and recurrent gastrointestinal symptoms, other than the general practitioner's record.

We matched up to five controls to each case by birth date (within 2 months), sex, and practice. We assigned the index date for each case as the index date for the matched controls, thereby ensuring close matching of age and controlling for calendar time of diagnosis. By using conditional logistic regression we estimated the relative risk of a history of the defined gastrointestinal disorders at any time before the index date among children with autism compared with children without autism. We also considered the time relation between measles, mumps, and rubella vaccination and the onset of gastrointestinal symptoms among the cases.

Our study protocol was approved by the Scientific and Ethical Advisory Group of the General Practice Research Database. To protect confidentiality, all data provided were anonymised.

Results

Overall, 103 children were identified with a first time computer record of autism. The case records for 83 children were received, and after review 66 (80%) were considered to have autism. Seven children were excluded because their records indicated that the diagnosis was not autism. Case records were inconclusive for 10 children and unavailable for 20; these children were considered to be "possible" cases.

Overall, 96 cases were included in further analysis and were matched to 449 controls. Table 1 shows the distribution of age, sex, and gastrointestinal disorders among the cases and controls.

Nine (9%) cases and 41 (9%) controls had gastrointestinal disorders before the index date. No child had Crohn's disease or ulcerative colitis. Two cases had chronic gastroenteritis: a premature triplet with necrotising enterocolitis at 3 months old and a child with chronic diarrhoea despite normal endoscopy. One control was diagnosed with coeliac disease, and one with Down's syndrome had malabsorption with normal endoscopy. Three cases and 12 controls had food intolerances; 10 (83%) were due to milk. No case developed gastrointestinal symptoms within 1 month of measles, mumps, and rubella vaccination and only three had gastrointestinal symptoms beginning within 3 months of the vaccination (two with milk intolerance at 6 and 8 weeks after vaccination and one with the first of three episodes of diarrhoea at 6 weeks after vaccination).

The estimated odds ratio for a history of gastrointestinal disorders among children with autism compared with children without autism was 1.0 (95% confidence interval 0.5 to 2.2; table 2). The odds ratio among boys was 0.8 (0.3 to 1.9). Among girls, only two cases and two controls had any gastrointestinal disorders; therefore no useful odds ratio could be estimated.

No material difference was found in the overall odds ratio if only children with case records confirming the diagnosis of autism were considered (n=66). The odds ratio for a history of serious gastrointestinal disease (coeliac disease, chronic gastroenteritis, malabsorption, and food intolerance) among children with autism compared with those without autism did not differ substantially from the odds ratio estimated with inclusion of all gastrointestinal disease.

Table 2 Odds ratio for a history of gastrointestinal disease among children with autism (cases) compared with children without autism (controls)

	Cases (n=96)	Controls (n=449)	Odds ratio* (95% CI)
No (%) with no gastrointestinal disease	87 (91)	408 (91)	Reference group
No (%) with gastrointestinal disease	9 (9)	41 (9)	1.0 (0.5 to 2.2)

*Controls matched to cases by age (within 2 months), sex, general practice, and index date.

Discussion

In 1995 Thompson and colleagues proposed that measles vaccination might be a risk factor for inflammatory bowel disease.[16] Although this was refuted, Wakefield and colleagues later expanded the hypothesis to include the subsequent development of autism and related developmental disorders after exposure to the measles, mumps, and rubella vaccine.[4 17] Under this hypothesis gastrointestinal symptoms sufficient to bring children to medical attention were considered to be intermediate in a proposed causal pathway from the vaccine to autism. This form of autism, which was apparently associated with behavioural regression soon after vaccination, was considered to be a new variant developmental disorder. The series of children evaluated by Wakefield and colleagues with this disorder, who were reported to have "ileal-lymphoid-nodular hyperplasia" on endoscopy, had chronic gastrointestinal symptoms that began at various times after vaccination.[4]

Recently, Fombonne and colleagues reported that their group found no evidence for a "new variant" autism with regression and gastrointestinal symptoms such as hypothesised by Wakefield and colleagues.[18] They analysed data from a recent UK health survey and two previously studied clinical series of cases in which a standardised interview was conducted to establish the diagnosis of autism. They found no increase in the prevalence of childhood disintegrative disorder, no shift toward an earlier age of first parental concern, and no increase in the rate of developmental regression since the introduction of the measles, mumps, and rubella vaccine. No cases of autism had inflammatory bowel disorders, and there was no association between regression and the occurrence of

What is already known on this topic

Gastrointestinal disease with a characteristic endoscopic and pathological appearance has been reported among a case series of children with autism and hypothesised to be related to measles, mumps, and rubella vaccination

The incidence of autism has been rising over the past decade despite a stable rate for measles, mumps, and rubella vaccination among the same population

What this study adds

Children with autism are no more likely than children without autism to have had gastrointestinal disorders at any time before the diagnosis of autism

Less than 10% of children diagnosed with autism have a history of gastrointestinal disorders, and for most the symptoms are mild

No temporal association was found between measles, mumps, and rubella vaccination and the onset of gastrointestinal symptoms in children with autism

gastrointestinal symptoms. Too few cases with any particular gastrointestinal disorder were present to estimate separate odds ratios for individual disorders.

Subsequently, Taylor and colleagues carried out a population based study, with data from five health districts in north east London. This study also provided no support for a hypothesised measles, mumps, and rubella associated new variant form of autism characterised by developmental regression and bowel problems. The proportions of 473 autistic children with regression or with bowel symptoms did not change significantly over the 20 year period that spanned the introduction of the measles, mumps, and rubella vaccine in 1988.[19]

Here we report the results of a population based study of the relation between gastrointestinal symptoms and diagnosed autism using data from general practices located throughout the United Kingdom. In a case-control analysis matching on age at index date, calendar time, and general practice, we found no increase in a history of chronic gastrointestinal inflammation, coeliac disease, food intolerance, or recurrent gastrointestinal symptoms among children with autism compared with those without autism. Because it may take years before a diagnosis of autism is apparent, we reviewed computer recorded histories for cases and controls from birth to include all potentially relevant gastrointestinal symptoms. By requiring all children to have been registered with their general practitioner within 6 months of birth and by matching on the index date, we ensured that early histories were complete and that the duration of follow up was similar among cases and their controls.

We cannot exclude the possibility that some children in our study had subclinical gastrointestinal symptoms before their presentation with autistic behaviour. However, the children described by Wakefield and colleagues had symptomatic gastrointestinal disease.[4] We also cannot exclude the possibility that severe gastrointestinal disease may be associated with the development of autism in certain individuals. However, our results indicate that if this occurs, it is likely to be uncommon. A strength in the design of our study is that symptoms were recorded at the time they were reported to the general practitioners rather than being recalled retrospectively by parents or caregivers. The lack of structured interviews to ensure uniformity in the diagnosis of autism, however, is a potential limitation. Still, the high proportion of cases diagnosed by general practitioners that we were able to confirm by reviewing additional documentation, including hospital discharge summaries and consultants' letters, indicates that our cases are a valid subgroup of children in the general UK population who are diagnosed with autism. Our results are consistent with those of other studies in providing evidence against a substantial association between gastrointestinal illness in children and the later development of autism.[18 19]

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