Papers

Clinical course of untreated tonic-clonic seizures in childhood: prospective, hospital based study

C A van Donselaar, O F Brouwer, A T Geerts, W F M Arts, H Stroink, A C B Peters

Abstract

Objective: To assess decleration and acceleration in the disease process in the initial phase of epsilepsy in children with new onset tonic-clonic seizures.
Study design: Hospital based follow up study.
Setting: Two university hospitals, a general hospital, and a children's hospital in the Netherlands.
Patients: 204 children aged 1 month to 16 years with idiopathic or remote symptomatic, newly diagnosed, tonic-clonic seizures, of whom 123 were enrolled at time of their first ever seizure; all children were followed until the start of drug treatment (78 children), the occurrence of the fourth untreated seizure (41 children), or the end of the follow up period of two years (85 untreated children).
Main outcome measures: Analyis of disease pattern from first ever seizure. The pattern was categorised as decelerating if the child became free of seizures despite treatment being withheld. In cases with four seizures, the pattern was categorised as decelerating if successive intervals increased or as accelerating if intervals decreased. Patterns in the remaining children were classified as uncertain.
Results: A decelerating pattern was found in 83 of 85 children who became free of seizures without treatment. Three of the 41 children with four or more untreated seizures showed a decelerating pattern and eight an accelerating pattern. In 110 children the disease process could not be classified, mostly because drug treatment was started after the first, second, or third seizure. The proportion of children with a decelerating pattern (42%, 95% confidence interval 35% to 49%) may be a minimum estimate because of the large number of patients with an uncertain disease pattern.
Conclusions: Though untreated epilepsy is commonly considered to be a progressive disorder with decreasing intervals between seizures, a large proportion of children with newly diagnosed, unprovoked tonic-clonic seizures have a decelerating disease process. The fear that tonic-clonic seizures commonly evolve into a progressive disease should not be used as an argument in favour of early drug treatment in children with epilepsy.

Introduction

Untreated epilepsy may be thought of as a progressive disorder. Such a view has emerged from the observation by Elwes *et al* that untreated epilepsy shows an accelerating pattern.[1] They found that intervals between successive untreated seizures decreased in many patients. In addition, a larger number of seizures before starting treatment seemed to be associated with a poorer control of seizures.[2] If these observations are correct, an aggressive approach may be appropriate, as has been advocated by Reynolds *et al*, who advised starting treatment as soon as possible, preferably after the first seizure, to prevent the development of intractable epilepsy.[3-5] Early treatment for all patients with newly diagnosed seizures has considerable consequences, however, as all antiepileptic drugs have side effects. A randomised trial comparing early and delayed treatment, the multicentre study of epilepsy and single seizures, is being conducted by D Chadwick.

Intervals between seizures may vary. Patients with accelerating patterns—shortening intervals between seizures—may be more likely to be referred and treated. The retrospective study by Elwes *et al*[1] was confined to patients for whom the decision to start treatment had already been made. Patients with accelerating seizure patterns may have been overrepresented, and it is doubtful that these findings could be applied to newly diagnosed patients.

The uncertainty about the clinical course of epilepsy and the possible clinical consequences of early treatment of all patients prompted us to study the pattern of seizures in a cohort of children with newly diagnosed, unprovoked tonic-clonic seizures.

Methods

This study is part of the prospective, multicentre Dutch study of epilepsy in childhood, which started in 1988. We enrolled all children aged 1 month to 16 years with newly diagnosed single seizures or epilepsy who had been referred to two university hospitals, a general hospital, and a children's hospital in the Netherlands up to August 1992. The main aims were to study the prognosis of single seizures, the prognosis of newly diagnosed epilepsy, and the consequences of early withdrawal of antiepileptic drugs in children who responded well to treatment. The study was approved

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Table 1 Main characteristics of 563 children with newly diagnosed seizures and those with tonic-clonic seizures. Figures are number (percentage) of patients unless stated otherwise

	Original cohort (n=563)	Tonic-clonic seizures only	
		Intervals known (n=204)	Intervals not known (n=57)
No (%) of boys	271 (48)	104 (51)	24 (42)
Mean (median) age at intake (years)	6.0 (5.6)	6.6 (6.3)	5.4 (3.8)
Interval from first seizure to intake:			
<3 Months	377 (67)	181 (89)	28 (49)
3-6 Months	70 (12)	7 (3)	5 (9)
6 Months-1 year	56 (10)	14 (7)	7 (12)
≥1 Year	55 (10)	2 (1)	15 (26)
Not known	5 (1)	2 (4)	
Mean interval (months)	4.5	1.4	9.2
No of seizures before intake:			
1	174 (31)	123 (60)	7 (12)
2	76 (14)	41 (20)	8 (14)
3	46 (8)	19 (9)	10 (18)
≥4	90 (16)	21 (10)	20 (35)
Unknown	177 (31)		
Aetiology:			
Idiopathic including mental retardation	456 (81)	183 (89)	49 (86)
Remote symptomatic	107 (19)	21 (11)	8 (14)
Type of epilepsy:			
Generalised	329 (58)	135 (66)	38 (67)
Partial	202 (36)	62 (30)	17 (30)
Not classifiable	32 (6)	7 (3)	2 (3)

by the medical ethical committees of the participating hospitals. Most children were referred directly by their general practitioners; some were seen in casualty departments, and some were referred by paediatricians.

A committee of three child neurologists judged whether the description of the ictal events fulfilled the predefined descriptive diagnostic criteria adapted from van Donselaar *et al*.[6] Children with neonatal, febrile or other acute symptomatic seizures were excluded, as were children who were referred from other hospitals. The panel assessed the diagnosis of epilepsy, classified the seizures according to the revised classification of the International League Against Epilepsy,[7] and categorised the epilepsies according to the criteria proposed by Gastaut.[8] Etiology was classified as remote symptomatic or idiopathic.[9] Children with single seizures were not treated with antiepileptic drugs, but the attending child neurologists were free to start or to delay treatment in children presenting with a status epilepticus or in children who had suffered two seizures or more.

Of the 563 children who were enrolled between 1 August 1988 and 1 August 1992, 261 children had seizures of only the tonic-clonic type, including seizures with partial onset. We excluded 57 of these patients because no accurate data on numbers and dates of all seizures could be obtained. The remaining 204 children formed our study group; table 1 presents their main characteristics. Children enrolled in this study were seen at an early stage of their disease. The mean interval between the first ever seizure and time of recruitment was 4.5 months for all 563 patients, 1.4 months for the study population, and 9.2 months for the 57 children excluded because accurate data were lacking. All children were followed until the occurrence of the fourth untreated seizure, the start of drug treatment, or the end of the follow up period of two years, whichever came first.

Multiple seizures within 24 hours were considered as separate events and a status epilepticus as a single event. Disease pattern was categorised as uncertain if the child was given drug treatment after the first, second, or third seizure. We classified the pattern as decelerating if the child became free of seizures without drugs. In cases with four seizures or more the pattern was classified as decelerating if the time intervals from the first ever seizure successively increased and as accelerating if the time intervals successively decreased. The patterns in all remaining children were classified as uncertain.

Results

We enrolled 123 children after their first seizure, 41 after two seizures, 19 after three seizures, and 21 after four or more seizures. Drug treatment was started in 10, 19, 9, and 20 patients, respectively, at time of intake. Table 2 presents the number of seizures before intake and during follow up.

Table 3 shows seizure patterns as from the first ever seizure. We classified the disease pattern as decelerating in 83 patients because they became free of seizures without medication: 60 had only one seizure, 15 had only two, and eight had only three. In two additional untreated children, whose last seizure occurred too close to the end of the follow up period to assess the disease pattern, we classified the disease pattern as uncertain. The pattern could not be assessed in an additional 78 children who were treated after their first seizure (10 children presenting with a status epilepticus) or their second (46 children) or third seizure (22 children). Of the 22 children treated after their third seizure, the intervals had decreased in 14 and increased in eight. Of the 41 patients with four or more untreated seizures, three showed a decelerating pattern, 30 an erratic pattern (classified as uncertain), and eight an accelerating pattern. In summary, the pat-

Table 2 Seizures and recurrences in a cohort of 204 children with epilepsy

	Recurrence during follow up							
	No recurrence		1 Recurrence		2 Recurrences		3 Recurrences	
Number of seizures at time of intake	No of children (n=131)	No given drugs (n=58)	No of children (n=50)	No given drugs (n=38)	No of children (n=14)	No given drugs (n=11)	No of children (n=9)	No given drugs (n=6)
1 Seizure (n=123)	70	10	35	27	9	8	9	6
2 Seizures (n=41)	27	19	9	5	5	3		
3 Seizures (n=19)	13	9	6	6				
≥4 Seizures (n=21)	21	20						

tern was decelerating in 86 children (42%, 95% confidence interval 35-49%), uncertain in 110 (54%), and accelerating in eight (4%).

Discussion

The possibility that untreated epilepsy is a progressive disorder is of major importance in balancing the pros and cons of early treatment with antiepileptic drugs. Our study shows that in a large proportion of children with newly diagnosed, untreated tonic-clonic seizures the intervals between successive seizures become longer. This proportion may be a low estimate because we could not classify the pattern in the substantial number of patients who were given drug treatment after the first or subsequent seizures.

Ideally, the clinical course of epilepsy would be studied in an unselected, untreated group of children enrolled at the onset of the disease and followed for a long time without treatment, but such a study design is ethically not acceptable at this time. Our study reflects clinical practice. We enrolled the patients at an early stage of their disease and were rather reluctant to start treatment with antiepileptic drugs. On the basis of the catchment area of the participating hospitals and the incidence figures from epidemiological studies we estimate that we have enrolled about 75% of the children with new onset epilepsy.

Study design

The design of our study has some limitations. We confined ourselves to children with tonic-clonic seizures (including seizures with partial onset). We expected to get accurate data on the number and dates of these events only in this group of children. We excluded 57 of the 261 eligible patients because accurate data on some seizures were lacking; the mean interval between the first ever seizure and enrolment was much longer in these children. If none of these 57 patients had a decelerating pattern (which is highly unlikely), the proportion of children with a decelerating pattern would decrease to 33%. We thus think that excluding these children did not have a profound impact on our main conclusion.

We included patients enrolled after a single seizure, because some doctors recommend treating these patients as soon as possible.[5] Moreover, these children can be followed prospectively from the onset of their "epilepsy." Had we confined our study to patients with at least two seizures (excluding the 60 patients with a first seizure who did not have a recurrence without treatment and the 10 patients who were treated after their first seizure), the proportion of patients with a decelerating pattern would be much lower (19%) but would still be greater than the proportion with an accelerating pattern.

We defined the occurrence of the fourth untreated tonic-clonic seizure as an end point. By that time most children will be receiving treatment with antiepileptic drugs. Moreover, the timing of seizures in the early phase will be one of the deciding factors in starting or delaying treatment. Determining the proportion of children with an erratic seizure pattern would require delaying the start of treatment much longer so that a larger number of successive time intervals could be evaluated in each patient—an approach that was ethically not acceptable at the time of this study. We believe that our data give a fair approximation of the lower limit of the proportion of children with a decelerating pattern.

Table 3 Timing of seizure patterns in 204 children with epilepsy

Recurrence of seizures	No of patients	Classification of pattern
First seizure (n=204):		
No recurrences, no drugs	60	Slowing
Drug treatment	10	Uncertain
Second seizure (n=134):		
No recurrence, no drugs	15	Slowing
No recurrence, no drugs	1	Uncertain (follow up too short)
Drug treatment	46	Uncertain
Third seizure (n=72):		
No recurrence, no drugs	8	Slowing
No recurrence, no drugs	1	Uncertain (follow up too short)
Drug treatment	22	Uncertain
Fourth seizure (n=41):		
Increasing intervals	3	Slowing
Varied intervals	30	Uncertain
Decreasing intervals	8	Accelerating

Study results

Our results contradict the results of Elwes *et al*,[1] who found an accelerating seizure pattern in "many" (59%) patients with untreated tonic-clonic seizures. The group of patients that we studied was younger than Elwes *et al*'s cohort. Also, that retrospective study was confined to patients in whom the decision to start treatment had already been made. The researchers classified the temporal pattern as accelerating if successive intervals decreased even if the patient had had only three seizures. With similar selection and analysis, 22 of 57 children (39%) in our study had an accelerating pattern. This clearly shows that studies using only patients already allocated to treatment are biased towards exclusion of patients with decelerating seizure patterns.

Length of intervals between seizures may fluctuate. The policy to treat all patients immediately may obscure the fact that the interval between subsequent seizures may be longer, even without drug treatment. Had we treated all our patients at the time of recruitment, we would have missed the favourable outcome of a substantial proportion of children who became free of seizures without drugs. We might even have been convinced that lack of seizures was due to the drugs instead of to the course of their epilepsy.

Key messages

- Untreated epilepsy is commonly thought to be a progressive disease
- Early treatment, preferably after the first seizure, has been advocated
- In at least 42% of children with newly diagnosed tonic-clonic seizures, the disease has a decelerating pattern, with successively longer intervals between seizures
- The fear that tonic-clonic seizures commonly evolve into a progressive disorder should not be used as an argument in favour of early treatment of these children

Elwes *et al* probably missed the favourable prognosis in a substantial proportion of patients by treating them all at the time of enrollment.

We believe our findings are a fair approximation of the clinical course of idiopathic or remote symptomatic, newly diagnosed, tonic-clonic seizures in childhood. The fear that early untreated epilepsy commonly evolves into a progressive disease should not be used as an argument in favour of early treatment of these children.

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Neonatal risk factors for cerebral palsy in very preterm babies: case-control study

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Abstract

Objective: To identify neonatal risk factors for cerebral palsy among very preterm babies and in particular the associations independent of the coexistence of antenatal and intrapartum factors.
Design: Case-control study.
Setting: Oxford health region.
Subjects: Singleton babies born between 1984 and 1990 at less than 32 weeks' gestation who survived to discharge from hospital: 59 with cerebral palsy and 234 randomly selected controls without cerebral palsy.
Main outcome measures: Adverse neonatal factors expressed as odds ratios and 95% confidence intervals.
Results: Factors associated with an increased risk of cerebral palsy after adjustment for gestational age and the presence of previously identified antenatal and intrapartum risk factors were patent ductus arteriosus (odds ratio 2.3; 95% confidence interval 1.2 to 4.5), hypotension (2.3; 1.3 to 4.7), blood transfusion (4.8; 2.5 to 9.3), prolonged ventilation (4.8; 2.5 to 9.0), pneumothorax (3.5; 1.6 to 7.6), sepsis (3.6; 1.8 to 7.4), hyponatraemia (7.9; 2.1 to 29.6) and total parenteral nutrition (5.5; 2.8 to 10.5). Seizures were associated with an increased risk of cerebral palsy (10.0; 4.1 to 24.7), as were parenchymal damage (32; 12.4 to 84.4) and appreciable ventricular dilatation (5.4; 3.0 to 9.8) detected by cerebral ultrasound.
Conclusion: A reduction in the rate of cerebral palsy in very preterm babies requires an integrated approach to management throughout the antenatal, intrapartum, and neonatal periods.

Introduction

Preterm birth is associated with a clear increase in risk of cerebral palsy.[1-5] During the early 1980s there was an increase in the survival of very preterm babies which was accompanied by a sharp increase in the rate of cerebral palsy in this group. The aetiology of the cerebral damage has been the focus of considerable attention, and emphasis has recently shifted from intrapartum and neonatal factors to antenatal and prenatal events.[6-9] Several hypotheses have been proposed to explain the origins of cerebral palsy in very preterm babies. Firstly, it may be the result of an ischaemic insult in utero leading to both preterm birth and damage to the white matter.[1] This damage may be manifest later as cerebral palsy. Secondly, it may be that immature babies who are particularly vulnerable to cerebral haemorrhage and ischaemia sustain injury as a result of intrapartum and neonatal complications.[10] A third possibility is that cerebral palsy represents the endpoint of a continuum of adverse events which occur throughout the period when the brain is especially vulnerable to ischaemia. These events may occur before, during, and after birth.

A better understanding of the aetiology of preterm cerebral palsy is necessary for preventive strategies and treatments to be developed. In efforts to understand aetiological factors, however, an attempt must be made to disentangle neonatal factors that are causes of cerebral palsy from those that are consequences of earlier disturbances. In a recent case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm babies we found associations between chorioamnionitis, prolonged rupture of membranes, and maternal infection and an increased risk of cerebral palsy.[8] We also found associations between pre-eclampsia and delivery without labour and a decreased risk of cerebral palsy. Although adverse antenatal events seem to be important to our understanding of the origins of cerebral palsy, it is likely that these events contribute only to some of the cases of preterm cerebral palsy and that others have their origins in adverse neonatal events or as a result of a continuum of adverse effects throughout antenatal and early neonatal life. To investigate this further we

carried out a case-control study on our original study population of singletons born before 32 weeks of gestation that was designed to identify neonatal risk factors for cerebral palsy in very preterm babies and, in particular, the associations independent of the coexistence of previously identified antenatal and intrapartum factors.

Subjects and methods

Selection of subjects

All the selected babies were singletons of less than 32 completed weeks of gestation who survived to hospital discharge, born to mothers resident in Oxfordshire and West Berkshire between 1984 and 1990. Multiple births were excluded from this study as current evidence suggests that the risk factors for cerebral palsy in this group may differ from those in singleton births.[11]

Gestational age for all groups was estimated by using a combination of menstrual dates and an ultrasound scan performed before 20 weeks' gestation. The scan date was preferred if the menstrual date was uncertain or there was a discrepancy of more than 14 days between the menstrual date and the scan estimate.

Cases—Fifty nine children with cerebral palsy were identified from the Oxford region register of early childhood impairments.[12] The definition of cerebral palsy used by the register is that of a permanent impairment of voluntary movement or posture presumed to be due to permanent damage to the immature brain. The register includes children of mothers who were resident within the former Oxford health region at the time of delivery. Multiple sources of ascertainment are used to compile the register, and the condition of the children is determined at the age of 3 and 5 years.

Controls—A total of 474 babies who survived to discharge and did not develop cerebral palsy were identified from two sources to ensure maximum ascertainment: the hospital admission registers and the Oxford record linkage study. On the basis of an audit of preterm birth at the John Radcliffe Hospital (unpublished data) we estimated that an adverse neonatal factor would be present in 25-30% of controls. We predicted that a study population of 59 cases of cerebral palsy with four controls for each case would be large enough to detect for each neonatal factor an odds ratio of 2.5 with 80% power and an α level of 0.05. We wished, therefore, to select approximately half of the potential controls, and 235 controls were thus randomly selected. Controls were selected from the entire geographical population of very preterm babies (<32 completed weeks' gestation) but were not matched with the cases for gestational age. An unmatched case-control study design allowed us to investigate the relation between gestational age and cerebral palsy among very preterm babies.

Data sources

The neonatal notes of babies included in the study were reviewed by a researcher unaware of the children's outcomes. A detailed dataset was completed, encompassing 52 variables including characteristics at birth; cardiovascular, respiratory, systemic, and metabolic complications; neurological sequelae; and cerebral ultrasound findings. Patent ductus arteriosus (clinical diagnosis supported by cardiac ultrasonography, requiring indomethacin or surgical ligation), hypotension (mean blood pressure <30 mm Hg on at least two occasions), blood transfusion for either anaemia or hypotension, prolonged mechanical ventilation (duration of at least seven days), pneumothorax (diagnosis confirmed by chest *x* ray, requiring insertion of chest drain), and sepsis (clinical diagnosis confirmed with microbiology, requiring antimicrobial therapy) were of special interest. Details of diagnosis, onset, duration, and management were recorded. Birth trauma referred to severe bruising or *x* ray evidence of a fracture.

Ultrasound data were included if at least two scans were available, the first recorded during the first week of life and the second as near as possible to six weeks after birth. This approach was likely to identify lesions developing in both the early and late neonatal periods. In fact most babies had daily scans for the first week and weekly scans thereafter, with additional scans if clinically indicated. Ultrasound scanners (Advanced Technical Laboratories) used were the ATL 300C until 1988 and the UM4 thereafter with 7.5 MHZ transducer heads. The findings were described by using a classification modified from a data sheet used in a neonatal trial (OSIRIS).[13] The right and left cerebral hemispheres were described separately in terms of germinal layer or intraventricular haemorrhage, ventricular dilatation, parenchyma echodensity, and parenchyma cysts. Moderate ventricular dilatation was assigned where the ventricular index was above the 97th centile and hydrocephalus was assigned when the dilatation was more than 4 mm above the 97th centile, using a centile chart from an unpublished study by M Levene *et al*. Parenchyma cyst was an umbrella term used for any parenchymal echolucency suggesting a cavity. For the purposes of this study parenchymal echodensities and echolucencies were grouped together and termed parenchyma damage.

Antenatal and intrapartum data had been recorded from the obstetric notes of the mothers; these data were available from our earlier study.[8] Factors included in the logistic regression model as potentially important confounders were antepartum haemorrhage, maternal infection, chorioamnionitis, prolonged rupture of membranes, pre-eclampsia, and the mode of delivery.

Ethical approval

The approval of the Oxfordshire and West Berkshire ethics committees was obtained before the start of the study.

Statistical methods

The odds ratio associated with a given factor estimates the risk of cerebral palsy given the factor relative to the risk of cerebral palsy without the factor. The 95% confidence intervals for crude odds ratios were calculated with the programme CIA.[14] The odds ratios with adjustment for potential confounders were calculated by logistic regression, using the statistical package for the social sciences.[15] As the study populations were unmatched for gestational age, in the first instance an odds ratio was calculated for each neonatal factor with adjustment for gestational age. Biologically plausible interactions of neonatal factors were investigated by entering variables into a logistic regression model in a forward conditional fashion. Only variables with a strong association with cerebral palsy remained significant ($P<0.05$) independent of the other variables. We

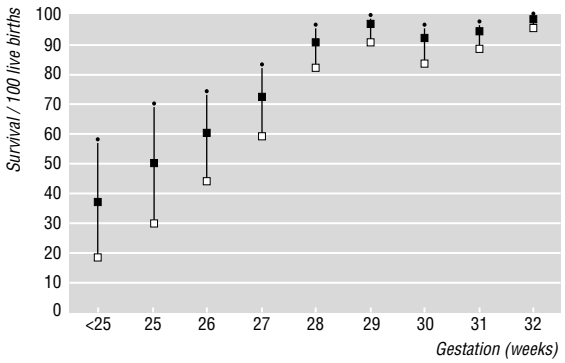

Fig 1 Survival of very preterm infants in relation to gestational age. Bars are 95% confidence intervals

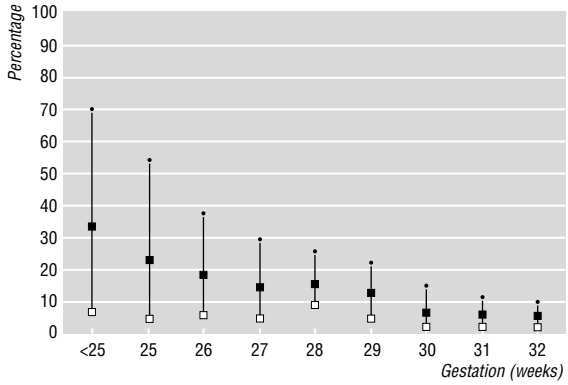

Fig 2 Percentage of surviving very preterm infants with cerebral palsy. Bars are 95% confidence intervals

included these factors in further regression models, looking for relations between neonatal factors and cerebral palsy independent of the presence of adverse antenatal factors and the delivery mode. There were no more than six variables in a logistic regression model at any one time. Trends in the rates of survival and cerebral palsy among survivors by gestational age were tested by χ^2 tests for trend.

Results

Of 638 singleton babies born alive at less than 32 completed weeks' gestation to mothers resident in Oxford district and West Berkshire during 1984-90, 105 died before discharge. The survival rate increased with increasing gestational age ($P<0.0001$; fig 1) and the incidence of cerebral palsy among survivors decreased with increasing gestational age ($P<0.0001$; fig 2).

Neonatal notes were available for all 59 children with cerebral palsy and 234 controls, a total of 293 babies. Mean gestational age at birth for children with cerebral palsy was 1.3 (95% confidence interval 0.7 to 1.9) weeks less than for the controls (mean 28.6 (SD 2.3; range 24-32) weeks *v* 29.9 (1.9; 23-32) weeks; $P<0.0001$). As this difference in gestational age confounds any comparison between cases and controls, odds ratio estimates were adjusted for gestational age. Further adjustment for birth weight did not affect the results; hence odds ratios are reported without this adjustment.

Table 1 Characteristics at birth in very preterm babies with and without cerebral palsy

Characteristics	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Male sex	37 (63)	133 (57)	1.3 (0.7 to 2.3)
Small for gestational age†:			
Birth weight	4 (7)	30 (13)	0.5 (0.2 to 1.5)
Head circumference	3 (5)	31 (13)	0.3 (0.1 to 1.1)
Apgar score at 5 minutes ≤3	5 (8)	4 (2)	5.3 (1.4 to 21)
Cord blood available	24 (41)	128 (55)	0.6 (0.3 to 1.1)
pH umbilical artery ≤7.10‡	6/24 (25)	16/123 (13)	2.3 (0.8 to 6.8)
Birth trauma	13 (22)	35 (15)	1.1 (0.5 to 1.6)

*Adjusted for gestational age; gestational age entered as a continuous variable.
†More than 2 SD below the mean Oxford centile charts.
‡Samples not available for some babies.

Neonatal factors

An Apgar score of ≤3 at 5 minutes was significantly associated with an increased risk of cerebral palsy (odds ratio 5.3 (1.4 to 21) (table 1). Otherwise the two groups did not differ significantly in characteristics of the babies or condition at birth.

Cardiovascular and respiratory complications were common among these babies: 232 (79%) had at least one complication. Patent ductus arteriosus, hypotension, transfusion, prolonged ventilation, and pneumothorax were associated with cerebral palsy after gestational age was adjusted for (table 2). On forward conditional logistic regression of the cardiovascular and respiratory factors described, transfusion and pneumothorax were independently associated with cerebral palsy (odds ratios 2.2 (1.1 to 4.7) and 4.8 (2.2 to 10.8) respectively).

Sepsis, total parenteral nutrition, and hyponatraemia were associated with an increased risk of cerebral palsy (table 3). The numbers with hyponatraemia were small, however, and this association could be a chance finding. The association with sepsis was independent of other systemic, cardiovascular, or respiratory complications (odds ratio 3.3 (1.6 to 6.8)). The sequence of antenatal infection and neonatal sepsis was strongly associated with cerebral palsy, but this occurred in only a few subjects (table 4).

Neonatal seizures occurred in 28 (9.6%) babies and were associated with a highly significant increased risk of cerebral palsy (table 5). Cerebral ultrasound scans were available for a total of 239 (82%) babies, with a similar proportion for cases and controls. Isolated intraventricular haemorrhage was not associated with an increased risk of cerebral palsy, but there was a strong association between cerebral palsy and parenchymal lesions and ventricular dilatation. Retinopathy of prematurity (all grades) occurred more frequently among cases than controls, but the difference was not significant at the 5% level.

Neonatal factors controlled for antenatal and intrapartum events

Patent ductus arteriosus, hypotension, transfusion, prolonged ventilation, pneumothorax, sepsis, hyponatraemia, and total parenteral nutrition were associated with an increased risk of cerebral palsy after adjustment by logistic regression for gestational age, antenatal complications, and the mode of delivery (table 6). The only antenatal factors of importance in the logistic regression model were chorioamnionitis, any maternal infection, and mode of delivery.

Discussion

Neonatal complications

Several cardiovascular, respiratory, and systemic factors investigated in this study of very preterm babies were associated with an increased risk of cerebral palsy. In earlier studies, hypotension, transfusion, and patent ductus arteriosus have been associated with periventricular leukomalacia,[16-19] an ultrasound finding which predicts later handicap (especially cerebral palsy) more accurately than any other antecedent.[20-29] Pneumothorax and prolonged ventilation have been associated with both periventricular leukomalacia[17 19 30] and cerebral palsy.[31 32] The findings in this study are consistent with these observations, supporting the hypothesis that cardiovascular and respiratory disturbances have a role in the aetiology of cerebral ischaemia in very preterm babies.

A second hypothesis concerns infection, and several studies have shown associations between neonatal sepsis and both periventricular leukomalacia[17-19] and cerebral palsy.[32] Our results support this hypothesis as neonatal sepsis and cerebral palsy were strongly associated even after other potentially confounding neonatal complications were adjusted for.

These findings suggest a role for several neonatal complications in the aetiology of cerebral palsy in preterm babies. The difficulty in interpreting these findings, however, lies in determining which neonatal factors are causes of cerebral palsy and which are consequences of earlier disturbances in the antenatal and intrapartum periods and already part of the outcome. Some neonatal factors, such as transfusion, may be markers of severity of neonatal illness or may be the consequence of a disabling cerebral haemorrhage. Our previous study of antenatal and intrapartum risk factors for cerebral palsy in very preterm babies found a strong association between maternal infection and, in particular, chorioamnionitis and an increased risk of cerebral palsy. Maternal infection occurred, however, in only 37% of cases and 17% of controls and is likely to explain only a proportion of cases of preterm cerebral palsy. It is possible, therefore, that the origins of cerebral palsy lie in the neonatal period for a large proportion of very preterm babies. In addition, because of the design of a case-control study it is not possible to predict the timing of cerebral damage in relation to the insult and it is possible that the ischaemia associated with chorioamnionitis is not manifest until the neonatal period and may occur only if the baby suffers an additional further insult in the neonatal period. Our finding that the sequence of maternal infection followed by neonatal sepsis was strongly associated with cerebral palsy lends some strength to the theory of a continuum of insults in the pathogenesis of preterm cerebral palsy. However, this sequence of events affected only a small proportion of the study population.

Timing of brain injury

The question of the timing of cerebral damage was addressed in a study of the ultrasound findings and clinical events of preterm babies with cerebral palsy.[4] Although antenatal complications were common, only a small proportion of babies (2/18) had evidence of antenatal cerebral damage; most had evidence of parenchymal damage of neonatal onset. These

Table 2 Cardiovascular and respiratory factors in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Patent ductus arteriosus	28 (48)	56 (24)	2.0 (1.1 to 3.7)
Cardiac disease	3 (5)	4 (2)	3.1 (0.6 to 15.3)
Hypotension	21 (36)	33 (14)	2.2 (1.1 to 4.5)
Transfusion	45 (76)	96 (41)	3.2 (1.6 to 6.7)
Thrombocytopenia	2 (3)	11 (5)	0.5 (0.1 to 2.4)
Prolonged ventilation	36 (61)	65 (28)	2.7 (1.3 to 5.7)
Hyaline membrane disease	48 (81)	151 (65)	1.5 (0.7 to 3.1)
Pneumonia	7 (12)	21 (9)	1.0 (0.4 to 2.7)
Recurrent apnoeas	28 (48)	84 (36)	1.0 (0.5 to 1.9)
Pneumothorax	19 (32)	21 (9)	3.4 (1.6 to 7.2)
Bronchopulmonary dysplasia	7 (12)	8 (3)	1.6 (0.5 to 5.1)

*Adjusted for gestational age; gestational age entered as a continuous variable.

Table 3 Systemic and metabolic neonatal factors in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Renal disease	5 (9)	15 (6)	1.5 (0.5 to 4.4)
Metabolic acidosis	19 (32)	42 (18)	1.7 (0.9 to 3.3)
Sepsis	27 (46)	41 (18)	2.8 (1.5 to 5.5)
Necrotising enterocolitis	8 (14)	16 (7)	1.6 (0.6 to 4.1)
Total parenteral nutrition	29 (49)	42 (18)	3.0 (1.5 to 6.0)
Hyponatraemia	9 (15)	4 (2)	6.8 (1.9 to 24.2)
Hypocalcaemia	6 (10)	14 (6)	1.0 (0.3 to 3.0)
Hypoglycaemia	7 (12)	26 (11)	0.9 (0.3 to 2.2)
Hypothermia	0 (0)	14 (6)	
Umbilical artery catheter	37 (63)	95 (41)	1.6 (0.9 to 3.1)

Table 4 Antenatal infection and neonatal sepsis in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Chorioamnionitis and neonatal sepsis	5 (8)	2 (1)	7.1 (1.2 to 40.6)
Any maternal infection and neonatal sepsis	11 (19)	9 (4)	4.2 (1.6 to 11.2)

*Adjusted for gestational age; gestational age entered as a continuous variable.

Table 5 Neurological neonatal factors in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Seizures	20 (34)	8 (3)	10.0 (4.1 to 24.7)
Cerebral ultrasound scan performed	50 (85)	189 (81)	1.3 (0.6 to 2.9)
Intraventricular haemorrhage	13 (26)	48 (25)	1.0 (0.5 to 2.1)
Parenchymal damage†	30/50 (60)	7/190 (4)	32 (12.4 to 84.4)
Ventricular dilatation†	28/50 (56)	19/190 (10)	5.4 (3.0 to 9.8)
Retinopathy	7 (12)	5 (2)	3.1 (0.9 to 11.2)

*Adjusted for gestational age; gestational age entered as a continuous variable.
†Samples not available for some babies.

Table 6 Neonatal factors adjusted for gestational age, antenatal factors, and intrapartum factors in very preterm babies with and without cerebral palsy

Factors	No (%) cases (n=59)	No (%) controls (n=234)	Odds ratio* (95% CI)
Patent ductus arteriosus	28 (48)	56 (24)	2.3 (1.2 to 4.5)
Hypotension	21 (36)	33 (14)	2.3 (1.3 to 4.7)
Transfusion	45 (76)	96 (41)	4.8 (2.5 to 9.3)
Prolonged ventilation	36 (61)	65 (28)	4.8 (2.5 to 9.0)
Pneumothorax	19 (32)	21 (9)	3.5 (1.6 to 7.6)
Sepsis	27 (46)	41 (18)	3.6 (1.8 to 7.4)
Hyponatraemia	9 (15)	4 (2)	7.9 (2.1 to 29.6)
Total parenteral nutrition	29 (49)	42 (18)	5.5 (2.8 to 10.5)

Key messages

- Preterm birth is associated with an increased risk of cerebral palsy
- Antenatal, intrapartum, and neonatal factors have all been associated with cerebral palsy in preterm babies
- Neonatal pneumothorax, sepsis, and transfusion are associated with preterm cerebral palsy independently of adverse antenatal factors and mode of delivery
- Intrauterine infection followed by neonatal sepsis is associated with a very high risk of cerebral palsy among preterm babies
- The prevention of cerebral palsy among very preterm babies requires an integrated approach throughout the antenatal, intrapartum, and neonatal periods

observations suggest a role for neonatal complications in the pathogenesis of preterm cerebral palsy.

Grether *et al*,[9] in a recent study of prenatal and perinatal factors and cerebral palsy in very low birthweight infants, considered the interaction between prenatal and neonatal events and found chorioamnionitis to be associated with cerebral palsy only when seizures occurred in the neonatal period. With our previous study we had a full dataset of antenatal, intrapartum, and neonatal factors and could examine the independent associations between neonatal complications and cerebral palsy by controlling for the presence of antenatal and intrapartum factors. Transfusion, prolonged ventilation, pneumothorax, and sepsis had strong associations with cerebral palsy, adding further support to the hypothesis that cardiorespiratory disturbances and infection contribute to the aetiology of cerebral palsy in at least a proportion of cases and, more particularly, that this contribution can be independent of antenatal and intrapartum disturbances.

Cerebral lesions

As in previous studies of periventricular leukomalacia and cerebral palsy, we found strong associations between neonatal seizures, ultrasonically diagnosed parenchymal damage and ventricular dilatation, and preterm cerebral palsy. It is possible, of course, that cerebral ultrasound lesions arise incidentally as a result of severe physiological disturbances which in themselves cause cerebral palsy. This is unlikely, though, because ultrasound findings are so much more predictive of cerebral palsy than are cardiorespiratory complications. The statistical power of this study was limited for assessment of the complex interaction of these neurological factors and antenatal, intrapartum and neonatal events, and the results of multivariate analyses could be misleading. These interrelationships could be evaluated, however, with combined data from multiple sources.

In conclusion, we suspect that cerebral palsy has multiple risk factors, both causes and modifiers, but that a proportion of cases of cerebral palsy among very preterm singletons have their origins in the neonatal period. It would seem, therefore, that a major reduction in cerebral palsy among very preterm babies will arise only from an integrated approach throughout the antenatal, intrapartum, and neonatal periods to the management of any baby at risk. The possibility that new neonatal interventions may lead to a reduction or an increase in the frequency of cerebral palsy among very preterm babies can be tested by well designed randomised controlled trials.

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Survival after diagnosis of AIDS: a prospective observational study of 2625 patients

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Abstract

Objective: To estimate median survival and changes in survival in patients diagnosed as having AIDS.
Design: Prospective observational study.
Setting: Clinics in two large London hospitals.
Subjects: 2625 patients with AIDS seen between 1982 and July 1995.
Main outcome measures: Survival, estimated using lifetable analyses, and factors associated with survival, identified from Cox proportional hazards models.
Results: Median survival (20 months) was longer than previous estimates. The CD4 lymphocyte count at or before initial AIDS defining illness decreased significantly over time from 90×10^6/l during 1987 or earlier to 40×10^6/l during 1994 and 1995 ($P<0.0001$). In the first three months after diagnosis, patients in whom AIDS was diagnosed after 1987 had a much lower risk of death (relative risk 0.44, 95% confidence interval 0.22 to 0.86; $P=0.017$) than patients diagnosed before 1987. When the diagnosis was based on oesophageal candidiasis or Kaposi's sarcoma, patients had a lower risk of death than when the diagnosis was based on *Pneumocystis carinii* pneumonia (0.21 (0.07 to 0.59), $P=0.0030$ and 0.37 (0.16 to 0.83), $P=0.016$). Three months after AIDS diagnosis, the risk of death was similar in patients whose diagnosis was made after and before 1987 (1.02 (0.79 to 1.31), $P=0.91$). There were no differences in survival between patients diagnosed during 1988-90, 1991-3, or 1994-5.
Conclusions: In later years, patients were much more likely to survive their initial illness, but long term survival has remained poor. The decrease in CD4 lymphocyte count at AIDS diagnosis indicates that patients are being diagnosed as having AIDS at ever more advanced stages of immunodeficiency.

Introduction

Although much has been published about the survival of patients with AIDS, large studies tend to be based on surveillance data from the United States.[1-4] Although data from surveillance studies can estimate survival in large numbers of patients, such studies are limited to basic data collection and follow up. A large British study based on surveillance data that were published in 1993 reported the bias that can occur as a result of reporting delays and underreporting, which are common problems with surveillance data.[5] The estimates of median survival from this study may well have changed because of improvements in treatment or the change, in 1993, of the definition of AIDS used in surveillance.[6] Rogers *et al* have more recently published a study based on British surveillance data describing the influence of covariates such as age and calendar year of diagnosis.[7] A current estimate of the prognosis of patients with AIDS would help in planning future research and allocation of resources.

A total of 12 565 cases of AIDS were reported between 1982 and March 1996 in England and Wales; 8713 of these patients (69%) are known to have died.[8] Our two hospitals have dedicated HIV units that, between them, have seen 2625 patients with AIDS—over a fifth of those in Britain—between 1982 and July 1995, the end date of the present study. Data were collected prospectively on patients throughout this period, and therefore the aim of our study was to provide an up to date estimate of survival in a large, unselected group of patients, and to identify whether survival has improved over time.

Patients and methods

We included all patients from the Chelsea and Westminster Hospital diagnosed as having AIDS between January 1982 and July 1995 and all patients from the Royal Free Hospital (RFH) diagnosed with AIDS between January 1986 and August 1994. AIDS was diagnosed according to the definition in use at the time. For example, patients receiving a diagnosis of pulmonary tuberculosis in 1994 would be classified as AIDS patients, but if the diagnosis had been made in 1991, before the revision of the surveillance definition,[6] they would not be classified as AIDS patients. Demographic data, details of all AIDS defining illnesses, treatment, and immunological data are prospectively collected and maintained on a separate database at each site. Prospective data collection began in 1986 at the Chelsea and Westminster and 1990 at the Royal Free Hospital; retrospective data for all patients with HIV who had ever been seen at either clinic was added at this time. Only the factors known at the time of initial AIDS diagnosis were included in this analysis, and no adjustments were made for CD4 lymphocyte counts during follow up or further AIDS defining illnesses.

Statistical methods

Estimates of median survival were obtained by using a lifetable analysis.[9] Patient survival was measured from the month of diagnosis of initial AIDS defining illness until death. Patients who did not die during the study were censored at the time of their last clinic attendance. Some patients had been diagnosed as having AIDS before their first visit to either hospital. These patients were included in the study, but their survival was left-truncated (survival was calculated from the time of their initial AIDS defining illness, but they were not included in the risk set until the date they were first seen at either hospital). The relative risks of death were obtained by using Cox propor-

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tional hazards models. With the exception of the lifetable analysis, all data were analysed with SAS[10]; all P values are two sided.

To compare survival in different years, patients diagnosed in 1987 or earlier were placed in one group, representing those to whom treatment was not generally available when AIDS was diagnosed; those whose illness was diagnosed after 1987 were placed in a separate group. Patients whose illness was diagnosed after 1987 were split into further groups, but as survival within each group was similar these were combined. Tests of the proportional hazards assumption showed that the effect of year of diagnosis decreased with time. From the lifetable analysis it was clear that the risk of death in the first three months after AIDS diagnosis for patients diagnosed after 1987 was much lower than that of patients diagnosed before 1987. Therefore the relative risk of death in the first three months after AIDS diagnosis was compared with the risk of death after three months. This was modelled by two separate Cox proportional hazards models. The first estimated the relative risk of death in the first three months of follow up; thus patients who were followed up for more than three months were censored at three months. The second model estimated the relative risk of death after three months. In this model patient follow up started three months after a diagnosis of AIDS, so patients who survived for less than three months or who were lost to follow up within three months were not included. There was no evidence that the proportional hazards assumption did not hold in either model (P = 0.15 and P = 0.78 respectively).

Table 1 Characteristics of patients with AIDS seen at the Royal Free and Chelsea and Westminster Hospitals

	No (%) of patients	No (%) of deaths	Survival	
			Median (months)	P value
All patients	2625 (100)	1613 (61.5)	20	
Centre:				
Royal Free Hospital	385 (14.7)	204 (53.0)	21	0.92
Chelsea and Westminster Hospital	2240 (85.3)	1409 (62.9)	20	
Sex:				
Male	2497 (95.2)	1552 (62.2)	19	0.80
Female	125 (4.8)	58 (46.4)	21	
Exposure category:				
Homosexual/bisexual	2206 (84.0)	1356 (61.5)	21	
Heterosexual	92 (3.5)	64 (69.6)	13	
Intravenous drug users	94 (3.6)	45 (47.9)	23	0.0001
Other	184 (7.0)	114 (62.0)	20	
Unknown	49 (1.9)	34 (69.4)	7	
Age at diagnosis of AIDS:				
≤25 years	118 (4.5)	64 (54.2)	28	
26-35 years	1105 (42.1)	638 (57.7)	24	
36-45 years	917 (34.9)	582 (63.5)	20	0.0001
46-55 years	377 (14.4)	245 (65.0)	17	
>55 years	108 (4.1)	84 (77.8)	10	
Year of diagnosis:				
1987 or earlier	339 (12.9)	285 (84.1)	19	0.73
1988 or later	2286 (87.1)	1328 (58.1)	21	
CD4 count at diagnosis:				
Unknown	1002 (38.2)	633 (63.2)	20	
$<50\times10^6$/l	753 (28.7)	504 (66.9)	18	
$50\text{-}99\times10^6$/l	311 (11.8)	200 (64.3)	21	0.0001
$\leq100\times10^6$/l	359 (21.3)	279 (49.4)	18	
Initial AIDS defining illness:				
Oesophageal candida	382 (14.6)	206 (53.9)	24	
Kaposi's sarcoma	490 (18.7)	288 (58.8)	22	
Pneumocystis carinii pneumonia	802 (30.6)	509 (63.5)	22	0.0001
Other single disease	708 (27.0)	417 (58.9)	17	
2 Or more diseases consecutively	243 (9.3)	193 (79.4)	16	

Results

In total, 2625 patients were diagnosed as having AIDS during the study period: 385 (14.7%) from the Royal Free Hospital and 2240 (85.3%) from the Chelsea and Westminster Hospital (table 1). The median duration of follow up after diagnosis of AIDS was 15.4 (90% range 2.3-52.8) months, during which time 1613 patients (61.5%) died. The first diagnosis of AIDS was made at the Chelsea and Westminster Hospital in 1982; the first diagnosis at the Royal Free was in 1986.

The population was, on average, quite young; the median age at AIDS diagnosis was 35.7 (range 2.1-72.2) years. Male patients were significantly older than female patients (median age 35.9 *v* 30.2 years; P < 0.0001, Wilcoxon test). Patients from the homosexual/bisexual exposure category were the oldest patient group (median age 36.2 years) and intravenous drug users were the youngest (median age 31.7 years). In the Royal Free Hospital cohort the proportion of female patients was significantly higher than in Chelsea and Westminster Hospital cohort (45/382 (11.6%) *v* 81/2240 (3.6%); P < 0.0001, χ^2 test), and the proportion of patients in the homosexual/bisexual exposure category was significantly lower (252/385 (65.5%) *v* 1954/2240 (87.2%); P < 0.0001, χ^2 test). Overall, the proportion of female patients with AIDS increased over time, from 1.3% (four patients) before or during 1987 to 7% (31 patients) in 1994 and 1995 (P < 0.0001, χ^2 test).

The most common single initial AIDS defining illness was *Pneumocystis carinii* pneumonia (802 cases, 30.6%), followed by Kaposi's sarcoma (490 cases, 18.7%) and oesophageal candidiasis (382 cases, 14.6%). No other single illness was used for diagnosis in over 100 patients; 243 patients (9.3%) were diagnosed with two or more AIDS defining illnesses simultaneously. Kaposi's sarcoma was significantly more likely to be diagnosed in men than women (477/2497 (19.1%) *v* 12/125 (3.6%); P < 0.0001, χ^2 test), as was oesophageal candidiasis (370 (14.8%) *v* 12 (9.6%); P < 0.0001, χ^2 test). The median CD4 lymphocyte count within three months of the initial AIDS defining illness, available for 1623 (61.8%) patients, was 56×10^6/l (90% range 6×10^6/l-416×10^6/l), and was significantly higher among patients from the Royal Free Hospital (median 62×10^6/l *v* 54×10^6/l at Chelsea and Westminster; p = 0.0169; Wilcoxon test). The CD4 lymphocyte count at the initial AIDS defining illness decreased significantly over time, from 90×10^6/l in patients whose illness was diagnosed during 1987 or earlier to 61×10^6/l during 1988-90 (P < 0.0001, Wilcoxon test).

Median survival overall was 20 months (table 1); only one in 15 patients remained alive five years after diagnosis. Age was strongly related to survival after diagnosis (fig 1). Median survival in patients aged 25 or less at initial diagnosis was 28 months; in patients aged over 55 at diagnosis it was 10 months.

Figure 2 shows the relation between survival and year of diagnosis. In the first three months of follow up,

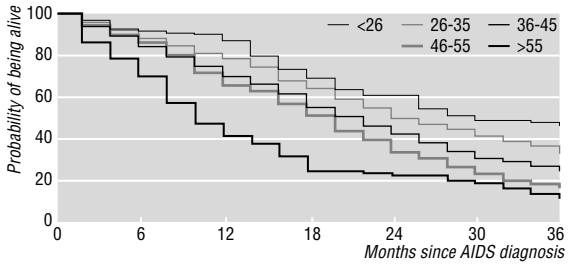

Fig 1 Lifetable progression rates: age at AIDS diagnosis

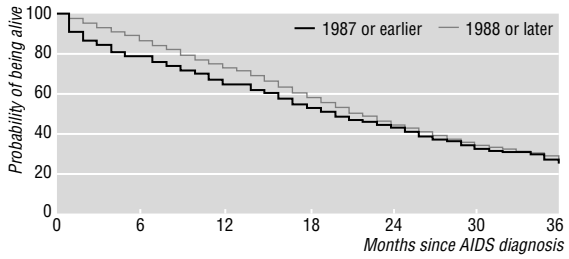

Fig 2 Lifetable progression rates: year of AIDS diagnosis

168 patients (6.4%) died and 127 (4.8%) were lost to follow up. The survival curves for those in whom AIDS was diagnosed before or during 1987 and after 1987 diverge rapidly; 15.9% of patients (54/339) in whom AIDS was diagnosed before or during 1987 had died within three months of diagnosis compared with 5.2% of patients (19/2286) in whom AIDS was diagnosed after this date. The survival curves converge as survival increases, and two years after diagnosis there is little difference in survival between patients in whom AIDS was diagnosed before or during 1987 and after 1987. As the survival curves converge, patients in whom AIDS was diagnosed after 1987 must be at a slightly higher risk of death after three months than those diagnosed before this time. When we broke the period after 1987 into three groups (1988-90, 1991-3, and 1994-5) we found no differences in survival between the groups either during the first three months or afterwards.

To overcome the problem of the converging survival curves, we divided follow up time into two distinct periods and obtained the relative risk of death in each period, as described in the methods. Table 2 shows the results of a multivariate analysis that included all cofactors in the model. We found no significant differences in survival in either time period according to the hospital of diagnosis or sex. Compared with the risk of death for homosexuals or bisexuals, only patients for whom exposure category could not be determined had a significantly greater risk of death. This increased risk was consistent in both time periods and may correspond to a later presentation in this group of patients (relative risk 3.75 during first three months after diagnosis (95% confidence interval 1.20 to 11.75), P = 0.024; relative risk 2.60 after first three months (1.41 to 4.79), P = 0.0021). The age effect was strong in both periods and CD4 lymphocyte count was strongly related to risk of death. The relative risk of death for a patient with a 50% lower CD4 count at baseline was 1.41 (1.22 to 1.64; P < 0.0001) during the first three months and 1.59 (1.50 to 1.68; P < 0.0001) after three months.

In the three months immediately after diagnosis of AIDS, patients whose defining illness was Kaposi's sarcoma or oesophageal candidiasis were at a significantly lower risk of death than those whose defining illness was *Pneumocystis carinii* pneumonia (0.21 (0.07 to 0.59), P = 0.003 and 0.37 (0.16 to 0.83), P = 0.016). After this time, patients with either of these diagnoses were at a similar risk of death to patients whose diagnosis was based on *Pneumocystis carinii* pneumonia. When diagnosis was based on a single disease other than oesophageal candidiasis, Kaposi's sarcoma, or *Pneumocystis carinii* pneumonia, patients had a higher risk of death in both time periods than did patients whose diagnosis was based on *Pneumocystis carinii* pneumonia (1.43, P = 0.11 and 1.30, P > 0.005). Risk of death was also higher, but not significantly higher, for patients whose diagnosis was based on two or more diseases.

In the three months after diagnosis of AIDS, patients in whom AIDS was diagnosed after 1987 had a significantly lower risk of death than patients in whom AIDS was diagnosed before this date (0.44; 0.22 to 0.86). As discussed above, when the diagnosis was made after 1987 the patients had a slightly higher risk of death after three months than when the diagnosis was made before 1987 (1.02; 0.79 to 1.31, P = 0.91). To further examine the differential effects in the two periods, we considered the interaction between the main covariates and duration of follow up time, modelled as time dependent covariates. This creates a binary variable that takes the value zero for a patient with less than three months' follow up and switches to a value of one after three months' follow up. The interaction with

Table 2 Multivariate analysis examining all cofactors relating to survival of patients with AIDS seen at two London clinics

	Within 3 months of diagnosis of AIDS		After 3 months	
	Relative risk of death (95% CI)	P value	Relative risk of death (95% CI)	P value
Centre:				
Royal Free Hospital	1.00		1.00	
Chelsea and Westminster Hospital	1.17 (0.67 to 2.01)	0.58	1.02 (0.84 to 1.24)	0.82
Sex:				
Male	1.00		1.00	
Female	1.49 (0.63 to 3.51)	0.36	0.81 (0.52 to 1.25)	0.34
Exposure category:				
Homosexual/bisexual	1.00		1.00	
Heterosexual	2.39 (0.96 to 5.62)	0.082	1.01 (0.64 to 1.59)	0.96
Intravenous drug users	0.97 (0.23 to 4.14)	0.96	1.22 (0.73 to 2.01)	0.45
Other	0.82 (0.39 to 1.74)	0.60	1.35 (0.74 to 1.74)	0.53
Unknown	3.75 (1.20 to 11.75)	0.024	2.60 (1.41 to 4.79)	0.0021
Age (per 10 year increase)	1.58 (1.30 to 1.92)	0.0001	1.41 (1.30 to 1.52)	0.0001
CD4 count (per 50% decrease)	1.41 (1.22 to 1.64)	0.0001	1.59 (1.50 to 1.68)	0.0001
AIDS defining illness:				
Pneumocystis carinii pneumonia	1.00		1.00	
Oesophageal candida	0.21 (0.07 to 0.59)	0.0030	0.91 (0.74 to 1.12)	0.37
Kaposi's sarcoma	0.37 (0.16 to 0.83)	0.020	1.09 (0.88 to 1.34)	0.43
Other single diagnosis	1.43 (0.92 to 2.22)	0.11	1.30 (1.08 to 1.57)	0.0050
2 Or more diseases	1.16 (0.60 to 2.24)	0.65	1.25 (0.98 to 1.59)	0.070
Year of diagnosis:				
1987 or earlier	1.00		1.00	
1988 or later	0.44 (0.22 to 0.86)	0.017	1.02 (0.79 to 1.31)	0.91

Table 3 Survival in published studies of patients with AIDS, including the present study

Study (year of publication)	Country of origin	No of subjects	Median survival (months)	% Alive at 12 months	% Alive at 24 months
Piette *et al* (1992)[11]	United States	43 795	12.7	49.1	18.4
Blum *et al* (1994)[2]	United States	23 324	13.7	54.7	31.9
Piette *et al* (1991)[1]	United States	23 271	11.5	NA	NA
Lundgren *et al* (1994)[12]	Europe	6578	17.0	NA	NA
Rothenberg *et al* (1987)[3]	United States	5833	11.4	48.8	28.2
Lemp *et al* (1990)[4]	United States	4233	12.5	51.6	20.2
Whitmore-Overton *et al* (1993)[5]	United Kingdom	3984	16.7	NA	NA
Chang *et al* (1993)[13]	United States	3699	11.5	48.8	29.0
Luo *et al* (1995)[14]	Australia	3204	14.3	57.2	26.4
Mocroft *et al* (1997)	United Kingdom	2625	20.0	70.8	40.5
Chequer *et al* (1992)[15]	Brazil	2135	5.1	32.0	21.0
Seage *et al* (1993)[16]	United States	1931	13.5	54.0	23.0
Payne *et al* (1990)[17]	United States	1015	17.0	65.4	35.1

NA=estimate not available.

year of diagnosis (after 1987 or before 1987) was highly significant ($P < 0.0001$), supporting the view that patients whose diagnosis was made after 1987 were at a lower risk of death in the three months after an AIDS diagnosis than were patients whose diagnosis was made after this date.

Discussion

This large cohort of patients with AIDS has helped to confirm cofactors of disease progression. Table 3 summarises published studies of more than 1000 patients with AIDS,[1-5 11-17] ranked by the number of patients studied. Our study is one of the largest studies based on data collected prospectively at a clinic rather than on surveillance data. The estimate of median survival is longer than has previously been suggested and the proportion of patients alive one and two years after diagnosis is considerably higher than that reported in other studies. In addition to the increase in median survival, the proportion of patients who survived for three years (21.8%; 19.6 to 24.0%) was higher than that found by Lundgren *et al* (16%) in a large observational study of AIDS patients diagnosed between 1979 and 1989 across Europe.[12] Changes in the surveillance definition of AIDS[6 18] and improvements in antiretroviral treatment and prophylaxis for *Pneumocystis carinii* pneumonia[19-21] are both likely to have contributed to the improved survival seen in this patient group.

Patients for whom exposure category was not known had an increased risk of death, even after confounding variables were adjusted for. These patients may form a unique group who were too ill at presentation to be questioned about risk behaviour. Such patients may present with a wide variety of serious medical problems, or may not be well enough to be offered standard treatment with its associated side effects.[22 23]

Survival and AIDS defining illnesses

In the three months after diagnosis of AIDS, patients whose diagnosis was based on Kaposi's sarcoma and oesophageal candidiasis were at a significantly lower risk of death than those whose diagnosis was based on *Pneumocystis carinii* pneumonia, which may suggest that these are milder diseases which can initially be treated and are less likely to be terminal when first diagnosed. This is consistent with results from other studies, where patients with these as the initial AIDS defining illness had the longest median survival.[12 14 24 25] After three months, patients with other single AIDS defining illnesses had a significantly higher risk of death. Diseases in this category included lymphomas, toxoplasmosis, cytomegalovirus disease, and infection with non-tuberculosis mycobacterium, all of which have a poor prognosis[12 14 15 24] and, with the exception of lymphomas, tend to be diagnosed at lower CD4 lymphocyte counts.

Improvements in survival in later years

Many studies have indicated that survival in AIDS patients has improved over time.[2 4 5 12 13 25] Our results do not directly show an increase in survival in later years, but they show that in the first three months after diagnosis, patients whose diagnosis was made in later years had a significantly lower risk of death, and this may be due to improvements in treating the initial AIDS defining illness.[26] In 1987 and before, patients often died of their initial AIDS defining illness, and a significant proportion of patients would die within three months. Rothenberg *et al*[3] stated in 1987 that almost 12% of patients died within a month of their initial AIDS diagnosis[3]; this compares with 3.3% in our patients in whom AIDS was diagnosed after 1987. A later study showed that, before 1987, almost one quarter of patients died within three months of their initial AIDS defining illness; during 1987-90 this proportion had dropped to 14%.[5] In our study, from three months after diagnosis there was no difference in the risk of death according to year of diagnosis. Lundgren *et al* showed that although short term survival was improving during the 1980s, the long term prognosis of patients with AIDS was poor.[12]

Declining CD4 lymphocyte count at diagnosis of AIDS

In this as in other studies[12 27-29] the average CD4 lymphocyte count at the initial AIDS defining illness has declined over time, suggesting that AIDS is now being diagnosed later and patients are more immunocompromised when AIDS is diagnosed. In addition, the

Key messages

- Estimates of the prognosis of AIDS patients help with allocation of resources and future research
- Historically, surveillance data have been used to estimate survival in large patient groups
- In an unselected group of 2625 patients with AIDS, median survival (20 months) was longer than previously estimated; the CD4 count at diagnosis decreased significantly over time
- After 1987, patients were much more likely to survive an initial AIDS defining illness, but long term prognosis remained poor
- There has been little change in prognosis since 1987; this may be due to AIDS being diagnosed at ever more advanced stages of immunodeficiency

pattern of AIDS defining illnesses has been changing: Kaposi's sarcoma and *Pneumocystis carinii* pneumonia have become less common as AIDS defining illnesses, and diseases associated with more advanced immunosuppression, such as cytomegalovirus diseases, have become more common.[29 30] This has been attributed to the widespread use of antiretroviral therapy and prophylaxis against *Pneumocystis carinii* pneumonia,[28 29] which has been shown to delay the initial AIDS defining condition.[19 20 31] If the onset of AIDS has been delayed substantially then survival after a diagnosis of AIDS may be expected to decrease. Survival after diagnosis of aids was longer in our study than previously reported, which may indicate that the time between seroconversion and death is increasing.

Measuring survival after diagnosis of AIDS depends on recognition of the disease, and improvements in survival over recent years have been attributed to an increased awareness and support for patients with AIDS[5] and earlier detection of disease.[29] An alternative approach to identify possible improvements in survival time is to monitor survival after a given CD4 lymphocyte count—200×10^6/l, for example—is reached. Issues such as treatment, AIDS defining illnesses, and the role of potential cofactors in improving survival can also be addressed. This has been discussed in part by the recent study by Enger *et al*[31] and will be further investigated in our cohort of patients.

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ONE HUNDRED YEARS AGO

Found drunk

When the police in Denmark find anyone in the streets drunk and incapable they take him in a cab to the station, where he gets sober under a surgeon's care. On recovering sobriety the police take him home. A bill for the services of the cabman, the surgeon, and the police agents for special duty is then presented to the host of the establishment where the patient took his last drink. In Turkey if a Turk falls down in the street while intoxicated and is arrested, he is sentenced to the bastinado, which punishment is repeated as far as the third offence. After the third bastinadoing he is considered to be incorrigible, and is called "Imperial," or "privileged" drunkard. If arrested after that he has only to give his name and address, and state that he is a "privileged" drunkard, when he is released and conducted home, the bill for these kindnesses being rendered to him for payment next day. (*BMJ* 1897;i:35.)

Young people, alcohol, and designer drinks: quantitative and qualitative study

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Abstract

Objective: To examine the appeal of "designer drinks" to young people.
Design: Qualitative and quantitative research comprising group discussions and questionnaire led interviews with young people accompanied by a self completion questionnaire.
Settings: Argyll and Clyde Health Board area, west Scotland.
Subjects: Eight groups aged 12-17 years; 824 aged 12-17 recruited by multistage cluster probability sample from the community health index.
Results: Young people were familiar with designer drinks, especially MD 20/20 and leading brands of strong white cider. Attitudes towards these drinks varied quite distinctly with age, clearly reflecting their attitudes towards and motivations for drinking in general. The brand imagery of designer drinks—in contrast with that of more mainstream drinks—matched many 14 and 15 year olds' perceptions and expectations of drinking. Popularity of designer drinks peaked between the ages of 13 and 16 while more conventional drinks showed a consistent increase in popularity with age. Consumption of designer drinks tended to be in less controlled circumstances and was associated with heavier alcohol intake and greater drunkenness.
Conclusions: Designer drinks are a cause for concern. They appeal to young people, often more so than conventional drinks, and are particularly attractive to 14-16 year olds. Consumption of designer drinks is also associated with drinking in less controlled environments, heavier drinking, and greater drunkenness. There is a need for policy debate to assess the desirability of these drinks and the extent to which further controls on their marketing are required.

Introduction

In recent years a new range of fortified wines, such as MD 20/20 or "Mad Dog" and strong white ciders, such as White Lightning and Ice Dragon, has emerged: so called "designer drinks." The fortified wines have sweet, fruity flavours (for example, cherry, banana, and strawberry), a concentration of alcohol by volume of between 13% and 21%, and, in 1994, sales of at least £40m.[1] The white ciders are, according to industry sources, filtered to remove colour and some flavours to make them more appealing to younger consumers[2 3] and usually have an alcohol by volume of between 8% and 9%. The appeal of these drinks to people under the age of 18 has been the focus of mounting public concern.[4 5]

We reviewed the literature on young people's drinking to assess the main health concerns that have been expressed and the impact that designer drinks are claimed to have on these. We also describe the first major primary research that has been done to test these claims.

Adolescent drinking behaviour

Drinking alcohol in adolescence is a normative behaviour. Most people have their first taste of alcohol around the age of 10 (although Casswell *et al* report it to be at age 7[6]) and are introduced to it by their parents, usually to celebrate a special occasion.[7-9] By 16, about 90% have tasted alcohol.[10-13] Alcohol is thought to be important in adolescent development and socialisation as it helps young people to integrate with their peers and to negotiate their passage into the adult world.[14 15]

Although most adolescents drink moderately and sensibly,[9 16 17] many, however, have experience of intoxication,[10] and a considerable minority drink heavily. Adolescent intoxication is associated (although not necessarily causally linked) with the occurrence of accidents, certain crimes, and risky behaviour, including unsafe sexual encounters.[18-20] Heavy drinking, while not a predictor of alcohol problems in later life,[12] is associated with the use of illicit substances[9 21] and poor performance at school.[22]

Under age drinking has not increased in recent years,[23 24] but the quantity of alcohol being consumed on a typical drinking occasion is increasing.[25] In addition, NHS information and statistics data (table 1) show a significant increase in the number of discharges for "non-dependent abuse of alcohol" among 11 to 17 year olds between 1990 and 1995, suggesting an increase in the occurrence of intoxication in young people. It is also clear that the amount of alcohol consumed and the frequency of drinking by teenagers increases with age,[26] as does the tendency for drinking to move out of the parental home and into more public places where it is often done in the company of friends.[10 27] Furthermore, these phenomena are correlated.[28]

The impact of designer drinks on this picture is uncertain, but concern has been expressed that they may be reinforcing the tendency to drink more on single occasions,[25] with concomitant increases in the risks associated with intoxication. There is also concern that these drinks might have a particular appeal for teenagers[4 5 29] and that the marketing of them is legitimising an illicit activity.

Subjects and methods

We examined whether or not designer drinks appeal to young people; the nature of any such appeal and how it correlates with age; and whether or not the consumption of designer drinks is associated with greater alcohol intake per drinking session or greater loss of control, or both.

We conducted both qualitative and quantitative research. The qualitative research comprised focus group discussions. This procedure entails bringing together six to eight respondents, who are carefully selected in social demographic terms, in an informal setting under the direction of a skilled moderator to discuss the subject of interest in depth. The method has been more fully described in a previous article published in this journal.[30] The quantitative research used conventional methods based on questionnaires to collect statistically reliable data from a large representative sample of the population.

Table 1 Discharges from hospital in Scotland with diagnosis of "non-dependent abuse of alcohol" for 11-17 year olds, 1990-5

Age group	1990	1991	1992	1993	1994	1995
11	4	8	8	11	21	12
12	27	23	33	37	52	50
13	49	68	76	89	131	107
14	115	111	114	109	141	190
15	110	109	128	140	150	161
16	105	115	121	123	148	175
17	113	97	127	125	149	147
Total	523	531	607	634	792	842
Rate per 100 000 population	116.3	119.7	136.6	142.5	176.9	190.0

Source: Information and Statistics Division (ISD), Common Services Agency.

Qualitative research

Fifty six children and young adults were interviewed in eight groups. These varied in terms of age (12-13; 14-15; 16-17 years), sex, social class (A, B, C1 and C2, D, E), and drinking behaviour (tried/not tried drinking) (table 2). Subjects were recruited door to door by professional interviewers and invited to attend discussions about their spare time activities at a prearranged venue. Respondents were paid a standard fee for attending, and fieldwork took place in the west of Scotland during the summer of 1995. Each discussion lasted about two hours, during which respondents were shown a wide range of alcohol products and related promotional material. They were encouraged to talk openly and informally about their drinking and their thoughts about the different products. Projective questioning procedures were used to tap emotional responses. All the discussions were tape recorded and then transcribed.

Quantitative research

A multistage cluster probability sample of 12-17 year olds was drawn from the community health index (a listing of names and addresses of people registered with a general practitioner within the health board area) for Argyll and Clyde Health Board. The initial sample frame comprised a list of all postcode sectors, but those covering the most rural parts (that is, islands and sectors with fewer than 500 households) were excluded for reasons of cost. A random sample of 30 postcode sectors was then drawn, stratified by district and Carstairs score[31] (a measure of affluence or deprivation within an area) across the board. Within each of the 30 postcode sectors 40 people aged 12-17 years inclusive were selected from the index by using a random procedure stratified by age and sex.

A total sample of 824 respondents was achieved, equivalent to a response rate of 78% after allowance for ineligible contacts. The achieved sample under-represented males and similarly under-represented 16 and 17 year olds and was therefore reweighted with census data.

The qualitative research informed the development of a two part questionnaire that then underwent detailed piloting. The first part of the questionnaire was completed in a face to face interview; the second, seeking more sensitive information, was completed by the respondent in confidence.

Results

Qualitative research

Most of the young people were familiar with designer drinks, especially MD 20/20 and the leading brands of strong white cider. Their attitudes towards them varied quite distinctly with age, clearly reflecting their attitudes towards and motivations for drinking in general.

Children aged 12 and 13 years used alcohol to experience the adult world and to satisfy their curiosity. It also enabled many of them to socialise and to say that they had tried drinking. Those aged 14 and 15 were testing out their own limits and having fun. They enjoyed losing control every once in a while. For them drinking to get drunk was important, as was sharing the experience with others. Those aged 16 and 17 were anxious to show their maturity and experience with alcohol, drinking more like adults.

The drinks consumed matched these attitudes and motivations: 12 and 13 year olds experimented with any available drinks; 14 and 15 year olds consumed a wider range of drinks and wanted these to be relatively strong, inexpensive, and pleasant tasting (typically sweet)—all characteristics of designer drinks. On an emotional level they enjoyed drinking for fun, getting drunk, and losing control—again values offered by designer drinks. The characteristics and brand imagery of designer drinks, in contrast with those of more mainstream products, were thought to meet these requirements admirably.

Young adults aged 16 and 17 years had started to establish tastes for more "mature" drinks, including a wider range of spirits and bottled beers. They went to pubs and clubs, were keen to establish relationships with the opposite sex, and wanted to appear adult and sophisticated. For them many designer drinks signalled

> "You can't remember what you did...but you can laugh at it."
>
> "Everyone tells you what you've done and it's a class night."
>
> (Girls; 14 to 15; C2, D, E; drinkers; Paisley)

> "I'd go out for 'a pint'...just a pint and I wouldn't get drunk off it. But I still go out and get leathered sometimes."
>
> "If you down Mad Dog (MD 20/20) dead quick, you get steaming then you throw up but if you're in pubs you can take your time. You drink to socialise as well."
>
> (Boys; 16 to 17; A, B, C1; drinkers; Port Glasgow)

"Because it's called Mad Dog (MD 20/20), you think you'll go mad."
(Boy; 14 to 15; C2, D, E; drinker; Paisley)

"It (TNT—a brand of white cider) makes you think about blowing your mind."
(Girl; 14 to 15; C2, D, E; drinker; Paisley)

"It's (TNT) a pure novelty...that's blatantly made to get (the) young. Nobody over 18 would ever dream of drinking that kind of thing."

"You'd look stupid if you went to a nightclub and sat with a bottle of Mad Dog (MD 20/20), 'cos everybody is sitting drinking pints and stuff."
(Boys; 16 to 17; A, B, C1; drinkers; Port Glasgow)

immaturity and the under age drinker and were rejected as a result.

Quantitative research

The quantitative research showed that over two thirds (577/824; 70%) of 12-17 year olds drank alcohol and that of these, more than half (295/577; 51%) had tried MD 20/20 and more than two fifths (244/577; 42%) had tried one of four brands of strong cider. As with the qualitative findings, however, there were considerable variations with age.

The frequency of drinking, amount consumed, and the extent of drunkenness increased with age (table 3). For example, while only 2% of 12 year olds drank every week, 4% of 12 year old drinkers had consumed 15 units or more on their last drinking occasion and 19% of those who had drunk in the previous 6 months claimed to have been really drunk. The equivalent figures for 17 year olds were 57%, 26%, and 69%, respectively. The drinking environment also varied with age, with 14-15 year olds drinking mainly in the open air (table 4).

Turning specifically to designer drinks we looked in detail at how the subjects perceived the market leader, MD 20/20. The 577 young drinkers perceived it to have several appealing attributes, including a sweet taste (482), pleasant taste (336), affordability (247), and being well known (410). It was also thought to be popular with people of their age (384); unpopular with people of their parents' age (420); a drink for the inexperienced drinker (261), and easy to drink outside (304). It scored better on many of these attributes than conventional beer (for example, Budweiser; table 5).

When we gave the subjects a hypothetical choice of drinks (table 6), including a range of soft, energy, and alcoholic drinks, the appeal of MD 20/20 was strongest among 13-15 year old drinkers but declined among 16-17 year olds. In contrast, beer consistently increased in popularity with age.

Turning to actual consumption, beer and spirits seemed to be the main drinks consumed, although designer drinks were also popular with all 12-17 year olds. The popularity of designer drinks, however, peaked between the ages of 13 and 16. In contrast, more conventional drinks such as spirits showed a consistent increase in popularity with age (table 7). For example, strong white ciders were more popular among 13-14 year olds than other age groups, with almost a quarter having consumed these drinks, but much weaker conventional ciders, such as Strongbow or Woodpecker (alcohol by volume 4.5-4%), showed no variation in consumption by age. Similarly, the appeal of the recent arrival MD 20/20 decreased after age 16, but the appeal of the more traditional Buckfast did not.

Designer drinks tended to be consumed in less controlled circumstances. For example, while just over a quarter (27%) of all drinkers had had their last drink in the open air, this figure increased to over half (53%) for those who had drunk strong white cider and 65% for those who had drunk fortified wines (table 8).

Finally, the survey showed that an interest in designer drinks was associated with heavier alcohol consumption and greater loss of control. Strong cider and fortified or tonic wines accounted for the highest alcohol consumption, with an average intake on one drinking occasion of 6.8 units and 6.0 units,

Table 2 Sample for qualitative research

Group	Sex	Age	Social class	Drinking behaviour	Location
1	Male	12-13	A, B, C1	Tried drinking	Dumbarton
2	Female	12-13	C2, D, E	Tried drinking	Port Glasgow
3	Male	14-15	C2, D, E	Tried drinking	Paisley
4	Female	14-15	C2, D, E	Tried drinking	Paisley
5	Female	14-15	A, B, C1	Non-drinker	Inverary
6	Male	16-17	A, B, C1	Tried drinking	Port Glasgow
7	Male	16-17	C2, D, E	Non-drinker	Dumbarton
8	Female	16-17	C2, D, E	Tried drinking	Inverary

Table 3 Drinking behaviour by age

Age group	Ever drank alcohol (all; n = 824, weighted)	Drink weekly (all; n = 824, weighted)	Consumption of ≥15 units on last drinking occasion (all consuming ≤30 units on last occasion; n = 548, weighted)	Proportion claiming to have been really drunk (all drinking in previous 6 months; n = 540, weighted)	Drinking in open air on last occasion of drinking (all who drink; n = 577, weighted)
12	62/137	3/137	2/61	9/49	15/62
13	70/137	10/137	2/68	19/65	24/70
14	95/138	18/138	4/88	34/88	31/95
15	109/137	29/137	13/105	47/103	31/109
16	118/137	45/137	17/112	65/115	29/118
17	123/137	79/137	30/115	82/119	24/123

Table 4 Places where young people* drank alcohol in past six months by age

Age group	Main drinking environments				
	Open air (such as street or park)	Own home	Friend's home	Pub, hotel, or nightclub	Special occasion (such as party or wedding)
12 (n = 62)	13	16	8	3	24
13 (n = 70)	22	21	14	4	26
14 (n = 95)	47	29	28	14	31
15 (n = 109)	51	31	53	25	44
16 (n = 118)	55	47	61	65	60
17 (n = 123)	53	69	79	94	73

*Base: all drinkers (n = 577, weighted).

Table 5 Perceptions of MD 20/20 and Budweiser beer among teenage drinkers*

Semantic scale		Mean score		Paired differences		
Score = 1	Score = 5	MD 20/20	Budweiser	Mean difference (MD score – beer score) (95% CI)	*t*	P value
Sweet taste	Not sweet taste	1.78	3.78	–1.99 (–2.11 to –1.87)	–33.23	<0.001
Pleasant taste	Unpleasant taste	2.39	3.05	–0.67 (–0.81 to 0.53)	–9.34	<0.001
Expensive	Cheap	3.22	2.94	0.28 (0.15 to 0.42)	4.2	<0.001
Well known	Less well known	2.13	1.26	0.86 (0.74 to 0.99)	13.7	<0.001
Popular with people their age	Unpopular with people their age	2.14	2.58	–0.44 (–0.58 to –0.29)	–6.05	<0.001
Popular with people their parents' age	Unpopular with people their parents' age	4.07	2.33	1.74 (1.61 to 1.87)	26.77	<0.001
For the experienced drinker	For the inexperienced drinker	3.40	2.91	0.49 (0.36 to 0.62)	7.36	<0.001
Easy to drink outside	Difficult to drink outside	2.42	2.45	–0.03 (–0.17 to 0.11)	–0.4	0.693

*Base: all drinkers (n = 577, weighted).

Table 6 Preferred drink of young people* according to age

Drink	All ages (n = 577)	12 (n = 62)	13 (n = 70)	14 (n = 95)	15 (n = 109)	16 (n = 118)	17 (n = 123)	P value†
Budweiser	106	1	5	16	19	31	34	<0.001
MD 20/20	56	3	11	15	14	8	4	<0.01
Irn Bru	104	11	19	17	23	18	16	0.181
Cola drink	55	15	7	12	9	11	1	<0.001

*Base: all drinkers (n = 577, weighted).
†χ^2 tests for age differences.

Table 7 Numbers of young people who had drunk designer and conventional drinks by age*

Type of drink	All ages (n = 548)	12 (n = 61)	13 (n = 68)	14 (n = 88)	15 (n = 105)	16 (n = 112)	17 (n = 115)	P value†
Beer	267	22	29	44	51	64	57	<0.05
Non-fortified/non-tonic wine	89	17	19	15	18	12	8	<0.0001
Strong white cider	83	10	16	20	16	12	10	<0.01
Conventional cider	91	9	14	16	18	14	20	0.621
Spirits	166	8	13	22	26	41	56	<0.0001
Fortified/tonic wines	68	11	10	11	15	12	8	<0.05
MD 20/20	35	7	7	6	10	6	0	<0.01
Buckfast	24	4	3	4	4	4	6	0.578
Liqueurs	38	2	3	4	5	9	15	<0.01

*Base: all consuming ≤30 units on last occasion (n = 548, weighted) .
†χ^2 test for trend.

respectively, from these drinks alone. By contrast, the lowest average intake was observed for conventional wines, with a mean consumption of 2.1 units. Similarly, those who had drunk strong cider and fortified wines on their last occasion of drinking reported greater sociability, greater loss of control, and greater aggressiveness or antisocial behaviour from their general drinking than drinkers who had not consumed such drinks.

Discussion

This research provides the first systematic evidence that designer drinks—a new range of fortified fruit wines and strong white ciders—are a cause for concern. They do seem to have both tangible and emotional qualities that make them appealing to young people, often more so than conventional drinks. They are also being consumed by many youngsters. Furthermore, this appeal and the level of consumption seems to peak before adulthood, suggesting that these drinks are particularly attractive to 14-16 year olds. It is also clear that their consumption is associated with drinking in a less controlled environment, heavier drinking, and greater drunkenness.

There is a need for a thorough policy debate, particularly concerning the extent to which these

Table 8 Places where young people* drank alcohol on latest occasion by type of drink consumed

	Main drinking environments				
Type of drink consumed	**Open air (such as street or park)**	**Own home**	**Friend's home**	**Pub, hotel, or nightclub**	**Special occasion (such as party or wedding)**
Any alcohol (n = 577)	155	111	111	139	126
Beer (n = 288)	69	58	59	90	70
Conventional cider (n = 103)	36	30	20	18	25
Strong cider (n = 96)	51	4	25	15	15
Fortified wine (n = 64)	42	11	14	14	14
Non-fortified/non-tonic wine (n = 94)	8	36	15	10	28
Spirits (n = 182)	45	25	38	74	35

*Base: all drinkers (n = 577, weighted).

Key messages

- There has been concern that designer drinks might have a particular appeal for teenagers and be legitimising under age drinking
- Young people aged 14 and 15 years want drinks to be relatively strong, inexpensive, and pleasant tasting
- Designer drinks are seen by 14 and 15 year olds to have these qualities and as a result are particularly appealing
- By contrast, for 16 and 17 year olds many designer drinks signal under age drinking and immaturity
- Consumption of designer drinks is associated with heavier alcohol consumption, drinking in less controlled environments, and greater drunkenness

products should be freely marketed and whether further controls are required.

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ONE HUNDRED YEARS AGO

Hospitals at Christmas time

Mr Burdett has given a most pleasant account of Christmas Day at the London hospitals. His profound knowledge of their administration does not hinder him from comprehending the lighter side of the life within their walls, and he praises above all the devotion of the nursing staff, the residents, and the students—their determination to fill the whole place with happiness. Christmas Day lifts to their zenith the sympathy and good fellowship that illumine our hospitals—every ward is made home, every patient receives assurance that goodwill among men is a solid fact. We are, indeed, in some risk of overdoing our festivities—bewildering those who are seriously ill, and upsetting their temperatures. So long as we avoid this excess of hospitality our Christmas entertainments, being of the quality of mercy, are twice blessed; and it is just because of the sombre shadows that hang over hospitals that when festivities come there they have a brightness and a beauty far above the pleasures of a placid and self-centred life. (*BMJ* 1897;i:38.)

Impotence after sclerotherapy of haemorrhoids: case reports

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Sclerotherapy for haemorrhoids has been practised in the United Kingdom for almost a century.[1] Urological complications due to a misplaced injection are rare and seem to occur in men only after injection of haemorrhoids at right anterior sites.[2] I report on three patients who developed urinary symptoms and impotence after such an injection.

Case reports

Case 1—A 67 year old man underwent proctoscopic injection of grade I haemorrhoids with 3 ml of 5% phenol in arachis oil into each of the primary haemorrhoidal sites. He immediately felt rectal pain; four hours later he developed dysuria, frequency, and frank haematuria. His urinary symptoms settled after a two week course of ciprofloxacin and diclofenac. He was unable to achieve either spontaneous or waking erections after the injections and remained unable to achieve any form of erection one year later.

Case 2—A 52 year old man underwent proctoscopic injection of grade I haemorrhoids with 3 ml of 5% phenol in arachis oil into each of the primary haemorrhoidal sites. He immediately experienced rectal and pelvic discomfort and later the same day developed frequency, dysuria, pelvic pain, and frank haematuria. His symptoms slowly settled during a two month course of norfloxacin, and cystoscopy performed two months after his injections showed no important abnormality apart from benign prostatic enlargement. Six months after the injections he remained unable to achieve spontaneous or waking erections.

Case 3—A 46 year old man underwent proctoscopic injection of grade II haemorrhoids with 4 ml of 5% phenol in arachis oil into each of the primary haemorrhoidal sites. He developed acute pelvic discomfort at the time of injection, followed by urgency, dysuria, fever, and aching in the left testis. His symptoms persisted after two months of treatment with norfloxacin and diclofenac, and cystoscopy performed four months after the injections showed only benign prostatic enlargement. He remained unable to achieve spontaneous or waking erections one year after the injection. He continued to take tamsulosin for persistent symptoms of bladder outflow obstruction, with good relief of symptoms.

Comment

All three patients had normal spontaneous, night time, and waking erections before their haemorrhoidal injections. The development of pelvic pain at the time of injection and urinary symptoms within a few hours was highly suggestive of a misplaced injection into the prostatic or periprostatic tissue.

Haematuria, haematospermia, prostatic abscess, epididymitis, urethral stricture, chronic cystitis, urolithiasis, seminal vesicle abscess, and urinary perineal fistula have all been reported after sclerotherapy for haemorrhoids,[2] but impotence has not been recognised.

With the development of radical prostatectomy for early prostate cancer, urologists now have a better understanding of the anatomy of the cavernous plexuses which innervate the erectile tissue of the penis and, in particular, their close relation to the posterolateral border of the prostate and seminal vesicles.[3] Impotence due to cavernous plexus damage can be caused by subtrigonal injection of phenol in men for a hypersensitive bladder,[4] but it has not been reported after haemorrhoidal injection. Coloproctologists should be aware that if the typical "striation sign" indicating a well sited, submucosal injection is not seen at the time of haemorrhoidal injection or if the patient develops immediate, acute pain, it is likely that the injection has been given too deeply.[5] Such injections may not only cause urinary symptoms but could also damage the cavernous plexuses, resulting in erectile impotence.

Although the urinary symptoms caused by intraprostatic or periprostatic injection of sclerosant can usually be resolved by antibiotics and anti-inflammatory analgesics, the oily nature of the sclerosant solution, which limits its diffusion, encourages the sclerosant to remain in the region of the cavernous plexus and may cause irreversible nerve damage, resulting in permanent impotence.

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