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Accuracy of the clinical diagnosis of Down Syndrome

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SUMMARY

Objectives – to determine the accuracy of clinical diagnosis of Down syndrome, identify problems in reaching a diagnosis, to provide recommendations for improvement and estimate a minimum prevalence for all types of Down syndrome.

***Design* – A retrospective observational study was carried out over a five-year period. Genesis, a database located in the Department of Medical genetics, was used to identify the number of Down syndrome karyotypes including trisomy, translocation, and mosaic sample variants. Age of diagnosis was determined using date of receipt. Karyotyping requests for a clinical diagnosis of Down syndrome were also identified. Patient notes and cytogenetic laboratory reports were used to identify clinical indication for karyotyping.**

***Setting* – Regional Genetics Centre, covering all cytogenetic analyses for referrals within the entire Northern Ireland population.**

***Results* – 208 postnatal cases of Down syndrome were identified, 197 (94.7%) trisomy, 3 (1.45%) translocation, and 8 (3.85%) mosaic variants. 112 (54.8%) were male and 96 (46.2%) female. 268 samples were taken to confirm or exclude a clinical diagnosis of Down syndrome. 185 of these had Down syndrome, 77 were normal, and 6 had another abnormality. 90% and 100% of trisomy and translocation Down syndrome respectively were diagnosed on the basis of clinical features. This fell to 37.5% of mosaic Down syndrome patients being diagnosed clinically ($p<0.001$). Simian crease, sandal gap, epicanthic folds, hypotonia, upslanting palpebral fissures, and protruding tongue are the most frequent characteristic features seen. Similarly epicanthic folds, protruding tongue, simian crease and sandal gap, hypotonia, and upslanting palpebral fissures are also described in a significant proportion of karyotypically normal individuals, thus arousing a suspicion of Down syndrome. 89.4% of patients were diagnosed between day 1 and 7 of life. Of 10.6% patients diagnosed after day 7 of life, 7.6% were adults and 3% children. The minimum prevalence was estimated at 167.9 per 100,000, or 1 in 595 births.**

***Conclusion* – In a defined population, with a prevalence of around 1 in 600 births, accurate clinical diagnosis occurred in 90%, 100%, and 37.5% of trisomy, translocation, and mosaic patients. 49.5% of patients had one or more of the following phenotypic findings: Simian crease, sandal gap, epicanthic folds, hypotonia, upslanting palpebral fissures, and protruding tongue. However, the same six features aroused a suspicion of Down syndrome in individuals with normal karyotyping, thus causing undue stress and worry to parents.**

Mosaic cases may be more common than previously recognised, and often do not have dysmorphic features. It is therefore a diagnosis that should always be considered in those who are educationally subnormal without a definitive diagnosis.

INTRODUCTION

Down syndrome is one of the most common and the best known of all malformation syndromes,[1] with an estimated prevalence of 1/600 - 1/800.[2] Numerous clinical features have been recognised the accurate prevalence of the condition. Chromosomal analysis is time consuming, and delay leads to anxiety amongst parents whilst the diagnosis is unsure. Undue worry is caused to parents of karyotypically normal children being

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investigated for Down syndrome on the basis of a few clinical features.

Earlier clinical diagnosis allows parents to begin to accept the diagnosis at an earlier stage, and in some instances, make medical decisions about life threatening events.[4]

The objectives of this study were to determine accuracy of, and time taken to reach a clinical diagnosis, to identify problems in reaching a clinical diagnosis and provide some recommendations for improvement, whilst estimating the prevalence of the condition in a well defined population.

METHODS/STUDY DESIGN

A retrospective observational study was carried out over a five-year period from 01/01/97 – 31/12/01. Genesis, a genetic clinical and laboratory records database in the Department of Medical Genetics that covers the entire Northern Ireland population of 1.7 million, was used to collect data on the following: number of Down syndrome patients, including trisomy, translocation and mosaic variants, the clinical indication for karyotyping request, the ratio of male to female Down syndrome patients, age at diagnosis (using date of receipt), and number of karyotyping requests for a clinical suspicion of Down syndrome. A separate card index of all chromosome disorders from 1971 was also utilised, along with a search of the clinical records from the Northern Ireland genetics service (dating back to 1969), and cross checking these with the genesis records to achieve as complete an ascertainment as possible within the defined population of 1.7 million.

Patient notes and cytogenetic laboratory records were then used to identify clinical features of those who had undergone karyotyping for a clinical suspicion of Down syndrome, and reason for late diagnosis.

RESULTS

We identified 210 cases of Down syndrome. Two samples were from (prenatal) cordocentesis and therefore excluded from further analysis.

Of 208 cases included in our study 197 (94.7%) had full trisomy 21, three (1.45%) were translocation, and 8 (3.85%) were mosaic Down syndrome (Fig. 1). 112 (54.8%) were male and 96 (46.2%) female.

268 samples underwent karyotyping to confirm or exclude a clinical diagnosis of Down syndrome. 185 of these had Down syndrome, 77 were normal and 6 had another abnormality (Fig. 2.).

Clinical indication for karyotyping of 208 Down syndrome samples was recorded, including the breakdown for trisomy, translocation, and mosaic patients – Table I, 90% of trisomy Down syndrome and 100% of translocation Down syndrome were diagnosed on the basis of clinical features. This fell to 37.5% in mosaic Down syndrome patients. Statistical analysis using Fishers exact test showed a highly significant difference between mosaic group and the other two groups combined, in that mosaic Down syndrome is more difficult to detect clinically ($p<0.001$).

As well as indication for karyotyping, individual clinical features of each child with Down syndrome were identified using karyotyping request forms and patient notes. In 29% of patients it was only stated that the patient had Down syndrome and individual clinical features were not noted. Of the remaining 71% who had clinical features described, the frequency of each feature was recorded and these were expressed as a percentage. The majority of patients had numerous features described. The results are therefore cumulative (Fig. 3).

Trisomy, Translocation and Mosaic Down syndrome

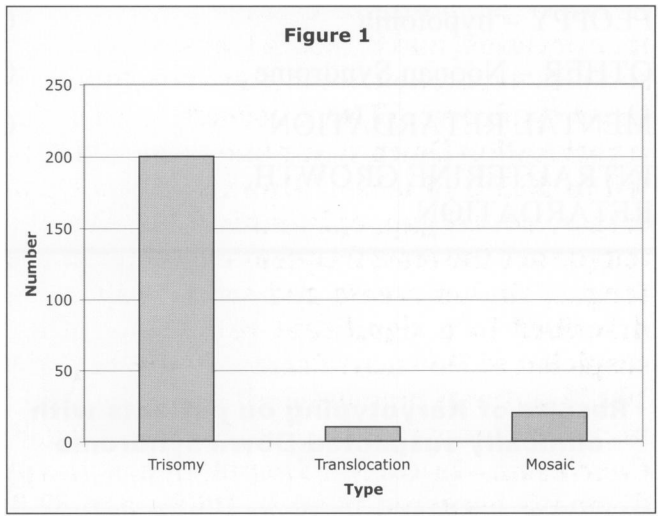

Fig 1. Number and type of Down syndrome

We analysed the 77 patients with a normal karyotyping result to see if we could identify clinical features that may have been suggestive of Down syndrome. In 13% no clinical features were described and Down syndrome only was

TABLE I

Trisomy, Translocation, and Mosaic Down Syndrome - Clinical Indication for Karyotyping

Clinical Indication for Karyotyping	*Total (208)*		*Trisomy (197)*		*Translocation (3)*		*Mosaic (8)*	
	%	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*
DOWN SYNDROME – clinical suspicion of Down Syndrome	88	183	90	177	100	3	37.5	3
DYSMORPHIC/MCA – two or more dysmorphic features or multiple congenital abnormalities	7	15	7	14	0	0	12.5	1
DEVELOPMENTAL DELAY	0.5	1	0	0	0	0	12.5	1
CHECK – repeat sample. Previous sample identified Down Syndrome	1.5	3	1	2	0	0	12.5	1
CABNFH – chromosomal abnormality, family history of	0.5	1	0.5	1	0	0	0	0
FLOPPY – hypotonia	0.5	1	0.5	1	0	0	0	0
OTHER – Noonan Syndrome	0.5	1	0	0	0	0	12.5	1
MENTAL RETARDATION	0.5	1	0	0	0	0	12.5	1
INTRAUTERINE GROWTH RETARDATION	1	2	1	2	0	0	0	0

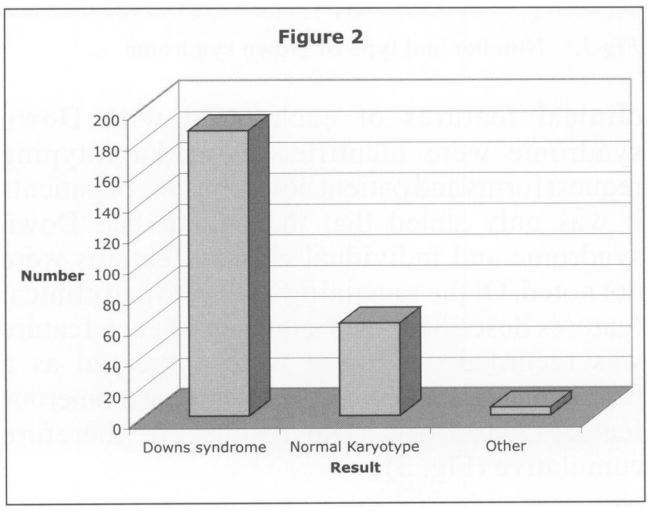

Fig 2. Results of karyotyping on patients with clinically suspected Down syndrome.

stated. In the remaining 86% the clinical features described were recorded and expressed as a percentage of frequency (Fig. 4).

Age at diagnosis was calculated using date of receipt of sample to the Cytogenetic Laboratory. 186 patients were diagnosed between day 1 and 7

Frequency of Clinical Features found in patients with Down syndrome – expressed as a percentage

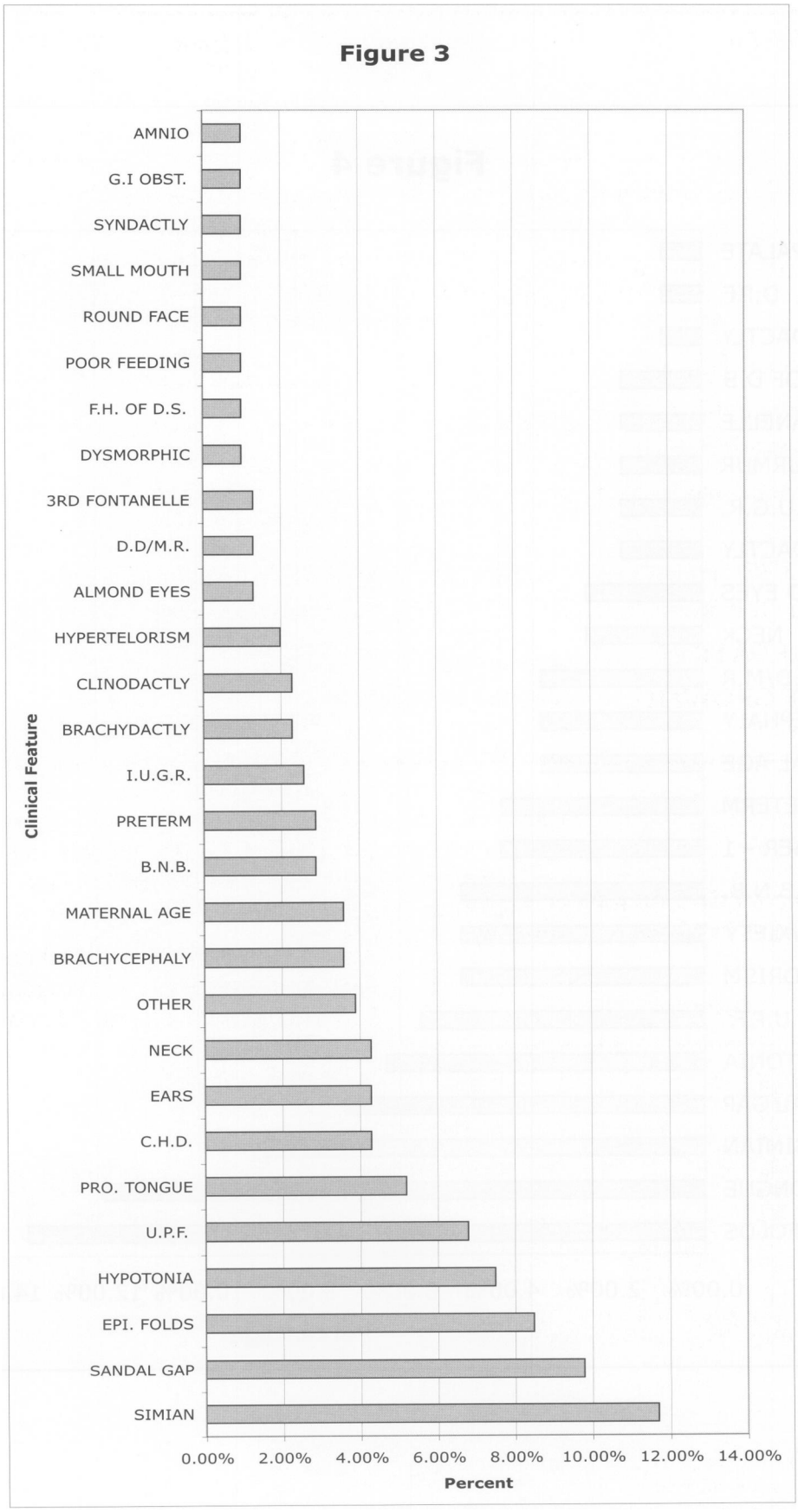

Fig 3. Frequency of clinical features found from records of patients with Down syndrome – expressed as a percentage

Frequency of Clinical Features suggestive of Down syndrome in patients with normal Karyotyping – expressed as a percentage

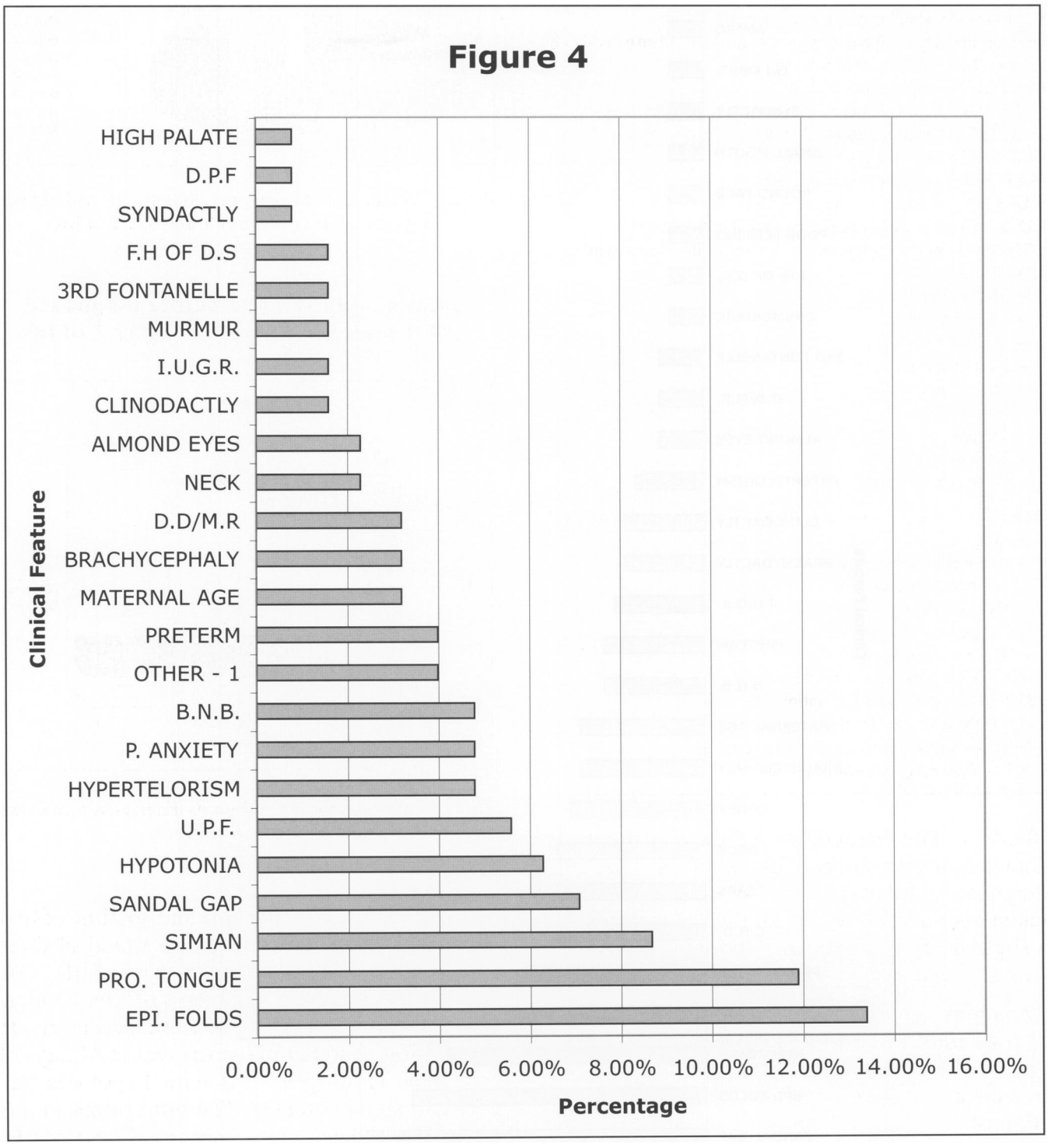

Fig 4. Frequency of clinical features suggestive of Down syndrome from records of patients with normal karyotyping – expressed as a percentage.

ABBREVIATIONS

AMNIO – Previously diagnosed with Down syndrome on amniocentesis
B.N.B – Broad nasal bridge
CH.D – Congenital heart disease
D.D/M.R – Developmental delay / Mental retardation
D.P.F – Down slanting palpebral fissures
Dysmorphic – Dysmorphic features noted, not described individually
EARS – Low set or dysmorphic ears
EPI. FOLDS – Epicanthic folds
F.H of D.S – Family history of Down syndrome (1st degree)
G.I OBST. – Gastrointestinal obstruction
I.U.G.R – Intrauterine growth retardation
MATERNAL AGE – Maternal age >30
MURMUR – Undiagnosed cardiac murmur
NECK – Short neck / increased nuchal skin thickness
OTHER – Other abnormality / diagnosis in the Down syndrome group including:
- Macrocephaly
- Microcephaly
- Noonan Syndrome
- Renal abnormalities
- Short stature
- Swollen feet
- Talipes
- Umbilical hernia
- Wide spaced nipples

OTHER 1 – Other abnormality in group with normal karyotype including:
- Atrioventricular septal defect
- Duodenal Atresia
- Hydrops Fetalis
- Talipes
- Tracheoesophageal fistula

P. ANXIETY – Parental Anxiety
PRETERM – < 37 weeks gestation
PRO. TONGUE – Protruding tongue
SIMIAN – Simian crease, unilateral/bilateral.
U.P.F – Upslanting palpebral fissures

(89.4%). The breakdown of these patients is shown as a percentage (Fig. 5). Of the 7 patients diagnosed on day 6, two of these samples were taken over a holiday period, thus accounting for a slight delay in diagnosis. One sample on day 7 was also taken over a holiday period.

22 patients were diagnosed after day 7 of life. 16 (7.6%) adults and 6 (3%) children. These were further sub-divided into trisomy (15), translocation (1) and mosaic (6) Down Syndrome (Fig. 6).

Three patients in the mosaic group were diagnosed in childhood. One was diagnosed at 6 months of life and was clinically felt to be Noonan Syndrome. A second child in this group was diagnosed at 19 months and presented with developmental delay. The third child had a sample sent at 7.5 years of

Percentage of patients diagnosed with Down syndrome between day 1 and day 7 of life

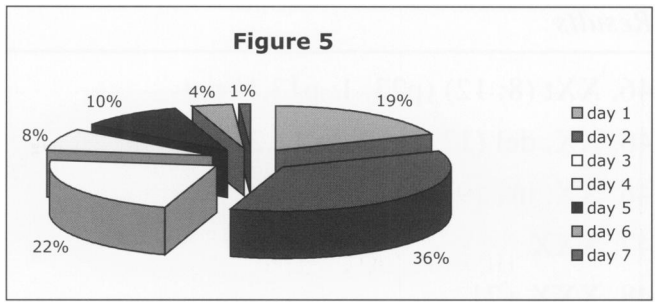

Fig 5. Percentage of patients diagnosed with Down syndrome between day 1 and day 7 of life.

Infants, children and adults diagnosed with Down syndrome after day 7 of life

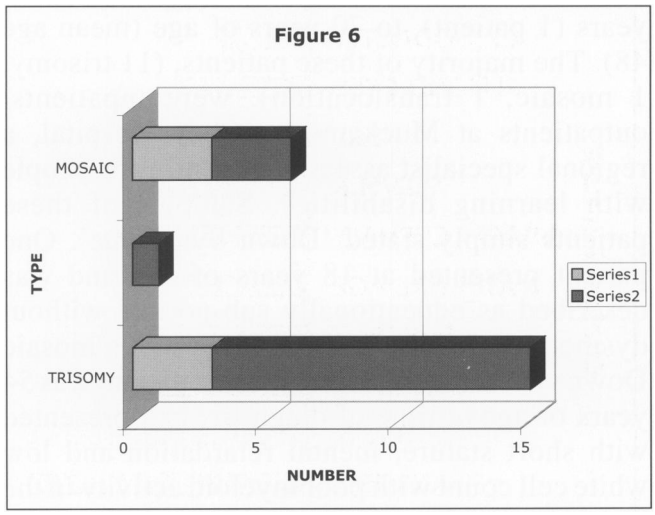

Fig 6. Infants, children and adults diagnosed with Down syndrome after day 7 of life.

age. This was a check sample and not time of first diagnosis. In the trisomy group a total of three children were diagnosed after day 7 of life. One infant was diagnosed at 23 days of life. Clinical indication for karyotyping was intrauterine growth retardation. Another diagnosis was at 31 days of life. This child presented with hypotonia and bilateral simian creases. The third infant in this group was a check sample sent at 37 days of life. All six children with a diagnosis later than day 7 of life were from different hospitals around the Northern Ireland region, including the regional neonatal centre. Baby checks are carried out by different specialities and different grades of staff in various hospitals.

TABLE II

Abnormal results and their clinical interpretation

Results	*Clinical Interpretation*
46, XXt (8; 12) (p23, 1; p13.1) pat	Balanced translocation
46, XX, del (12) (p12.2p 11.23)	Partial deletion of chromosome 12
46, XX, inv (9) (p11q13)	Normal female with variant
47, XXX	Triple X
48, XXX +21	Triple X and trisomy 21
47, XX, +mar.ish	Small bisatellited dicentric derivative 15

Of those diagnosed as adults, there were 12 trisomies, 3 mosaics, and 1 translocation Down syndrome. Age in this group ranged from 18 years (1 patient), to 70 years of age (mean age 48). The majority of these patients, (11 trisomy, 1 mosaic, 1 translocation), were inpatients/ outpatients at Muckamore Abbey Hospital, a regional specialist assessment centre for people with learning disabilities. Samples of these patients simply stated 'Down Syndrome'. One patient presented at 18 years of life and was described as educationally sub-normal without dysmorphic features. This patient was a mosaic Down syndrome. A further mosaic patient was 54 years of age at time of diagnosis and presented with short stature, mental retardation and low white cell count with poor myeloid activity in the bone marrow. One trisomy patient was diagnosed at 54 years of age. Notes were unavailable. History on the request form stated that there was a family history of translocation.

Six karyotyping samples were found to be abnormal but not Down syndrome Table 2. In the sample group that was felt to be clinically Down syndrome, two samples were unsuccessfully karyotyped. One sample was in the wrong bottle and the second was an unbanded analysis from poor growth.

DISCUSSION

Based on the 5-year period having identified 192 births in the neonatal period, in a population total of 114,307 live births, a minimum prevalence of 167.9 per 100,000 (or 1 in 595 births) was calculated. This compares closely to previous (lower) estimates of the prevalence of Down syndrome and is an accurate minimum prevalence figure, taking into account the number of mosaic Down syndrome cases which are difficult to calculate in the population which may not be reflected in other less accurate prevalence figures. If we include the cases diagnosed in adulthood as a proxy for missed cases of mosaic Down syndrome yet to be recognised, (208), the figure increases to 181.9 per 100,000 (or approximately 1 in 550 births).

Over the study period, 208 postnatal cases of Down syndrome were identified. 94.7% trisomy, 1.45% translocation, and 3.85% mosaic variants. Expected ratios are 94% trisomy, 5% translocation, and 1% mosaic variants.[2] The detection rate of mosaic variants is higher than the standard quoted rates of 1-3%. Our study includes a complete population, and newly diagnosed adult cases, which may account for this. Often mosaic variants do not have dysmorphic features, and it is therefore worthwhile to carry out a chromosomal analysis on those who are educationally sub-normal without dysmorphic features.

46% of our Down syndrome cases were female and 54% male. The diagnosis was suspected clinically in 88% of patients – 90% of trisomy Down syndrome, 100% of translocation Down syndrome, and only 37.5% of mosaic Down syndrome. Using Fishers exact test this is a highly significant result ($p < 0.001$) proving that mosaic Down syndrome is more difficult to detect leading to a late diagnosis.

In patients with Down syndrome, simian crease, sandal gap, epicanthic folds, hypotonia, upslanting palpebral fissures, and protruding tongue are the most frequent characteristics seen

and one or more are found in 49.5% of patients in our study. Hall [5] described ten cardinal features of trisomy 21 in the newborn. These included hypotonia, poor Moro reflex, hyper extensibility of joints, excess skin on back of neck, slanted palpebral fissures, and a flat facial profile. Hall looked at trisomy 21 only, without including mosaic or translocation Down syndrome. Our study includes translocation and mosaic Down syndrome and this may have accounted for the difference in results. Interestingly, epicanthic folds, protruding tongue, simian crease, sandal gap, hypotonia, and upslanting palpebral fissures are also described in 53% of karyotypically normal individuals thus arousing a suspicion of Down syndrome, and 28.7% of all karyotyping requests for clinically suspected Down syndrome were normal.

The prevalence of Down syndrome in this study compares well with other figures published previously and is higher. Two reasons are firstly, that this study figure is consistent with a more accurate figure inclusive of mosaic Down syndrome rates and consistent with the higher reported incidence of mosaic Down syndrome of around 4% in this study, when compared to older studies where rates are around 1-2%, and secondly, a reflection of the trend for increasing prevalence of Down syndrome over the last 10 years due to the tendency for couples to have their babies later in life.[6]

Recently, Hindley and Medakkar [7] looked at which criteria are being used to reach a diagnostic suspicion of Down syndrome in neonates using a questionnaire to cytogenetics laboratories in the United Kingdom. They found poor recording of characteristics of Down syndrome and almost one third of possible diagnoses were negative on karyotype.

Karyotyping request forms are not a completely accurate method of ascertaining the clinical features identified, or indeed present and not identified, on the patient. Many forms simply stated 'Down Syndrome' or 'clinical features of Down Syndrome'. Some requests may have only stated a few features elicited on the patient. The forms however give an indication of the reasons why samples are sent in or why the diagnosis of Down syndrome may be suspected and allow accuracy and referral reasons to be compared.

Age at diagnosis was determined using date of receipt of sample to the laboratory. We considered early diagnosis to be within 7 days and felt that this was sufficient to account for delay in sample to arrive in the laboratory due to weekends or holiday periods. After day 7 the earliest diagnosis was 23 days of life. A more accurate method may have been to use date of sampling. 89.4% of patients were diagnosed in the early period. Of those diagnosed after day seven, 7.6% were adults and only 3% children. Two children in this group were check samples meaning that only 6 children were diagnosed after day 7 of life. All 6 children were from different hospitals, thus baby checks were being carried out by different grades of staff. Numbers are not large enough to see any difference in outcome of time to diagnosis depending on who is carrying out the baby check.

The details in the patient notes held in the regional genetics centre, and request forms of the majority of those diagnosed as adults 13 were insufficient to determine whether they were a check sample or a first diagnosis. They may well have had a clinical diagnosis, but chromosomal analysis was not readily available at the time of first diagnosis.

CONCLUSION

49.5% of patients had one or more of six phenotypic findings: simian crease, sandal gap, epicanthic folds, hypotonia, upslanting palpebral fissures, and protruding tongue. Checking for these six features will heighten suspicion of a diagnosis of Down syndrome and the chances of abnormal karyotype. The overall minimum prevalence in the population is around 1 in 600 births. Mosaic cases are more common than previously recognised, and often do not have dysmorphic features, resulting in a later diagnosis Mosaic Down syndrome should always be considered in those who are educationally subnormal but have no definitive diagnosis

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