GENETIC COUNSELING, Vol. 18, No 2, 2007, pp 189-199

CHILDREN WITH 4q-SYNDROME: THE PARENTS' PERSPECTIVE

BY E.M. STREHLE AND P.M. MIDDLEMISS

Summary: *Children with 4q-syndrome: the parents' perspective:* A questionnaire survey was conducted among the parents of 32 not previously described children with 4q-syndrome, and 4 affected adult relatives. The questions related to the medical condition of the individual child and the interactions between parents and health professionals. The response rate of the survey was 58 %, and the mean age of the patients was 11.2 years. Thirty eight percent of children were diagnosed within the 1st month of life. Most parents felt severely distressed at the time of diagnosis and 66 % complained about a lack of medical information made available to them. However, parental understanding of the genetic aetiology responsible for the 4q-syndrome was overall good. Apart from a multidisciplinary team of healthcare workers, the internet and religion were named as sources of support. In all, 86 % of parents valued the experience of having a child with 4q-syndrome highly despite the difficulties involved.

Key-words: 4q-syndrome – 4q deletion – Questionnaire survey - Parents

INTRODUCTION

The term 4q-syndrome has been used to describe children who have a deletion of the long arm of chromosome 4 detectable by standard karyotyping (Fig. 1, Fig. 2) (7). We have shown that these children have certain features in common despite variations in the position and size of their deleted chromosomal segment (18, 19). This approach has been helpful in the counseling of parents of affected children, as individual deletions may be so rare that very little information can be collated from published case reports and standard medical textbooks. The Rare Chromosome Disorder Support Group Unique was founded in 1984 as a parent support group for trisomy 9p and initially only had 5 member families (16). Since then the group has grown to ca. 5,000 members and advises affected families and professionals on approximately 1000 different numerical and structural chromosomal abnormalities stored on its database (www.rarechromo.org). It is a well known fact that many parents of chronically ill children become experts in relation to their child's specific medical condition. On the other hand, not enough knowledge is available on how doctors are perceived by parents, for instance when giving a serious diagnosis (5, 11). We therefore designed an anonymous, cross-sectional survey, in which all parents of children with 4q-syndrome registered on the database of Unique were included.

Figure 1: Newborn with interstitial 4q-sydrome (patient No. 4, courtesy of parents)

Unique, Rare Chromosome Disorder Support Group, Caterham, Surrey, UK.

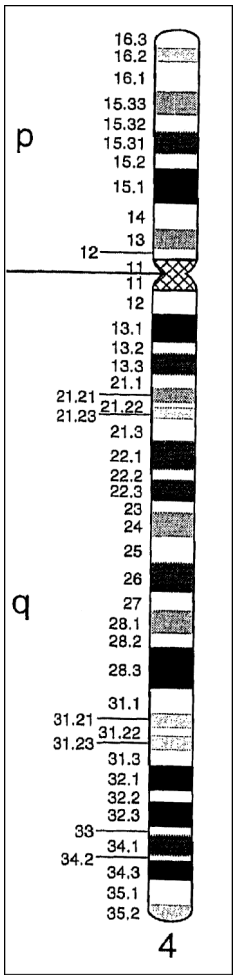

Figure 2: Human chromosome 4 ideogram from Francke (7)

The prime objective of the study was to gain insight into the views and feelings of parents who were unexpectedly confronted with a diagnosis of 4q-syndrome in their child, how they dealt with this information and how their attitudes changed with time. Of interest was also the level and quality of information and support made available to them by their health care providers. A further aim of the survey was the delineation of the 4q-syndrome and its natural course.

METHODS

In order to collect relevant and accurate information on children with 4q-syndrome and their parents' views and attitudes, an 8-page structured questionnaire was designed. The questionnaire contained 19 main questions and several sub-questions in an open and closed format (1). It was anticipated that completion should take between 20 and 30 minutes. Nine questions related to the physical characteristics and skills, the general health and the behaviour of each affected child. Eight questions focused on the relationship between parents and health care professionals, their way and efficiency of communication, and the accessibility of health services. Two questions covered demographic details. A total of 55 questionnaires and cover letters explaining the aims of the survey were sent to the parents; this was followed by a reminder letter 4 weeks later. Addressed, stamped envelopes were provided for families living in the UK. An abbreviated version of the questionnaire was sent to 5 adult relatives with 4q-syndrome. The study was approved by the research and ethics committee of the parent support group Unique.

RESULTS

PATIENT CHARACTERISTICS

The Unique database contained the details of 68 children with a pure 4q deletion; of these 13 had either passed away or their postal address could not be verified. A total of 55 paper questionnaires were sent to the parents; after 2 months 32 questionnaires were returned, giving a response rate of 58 %. Four out of 5 adults with 4q-syndrome replied to the abbreviated questionnaire. The majority of participants (63 %) were resident in the United Kingdom, where the parent support group Unique is based. The remaining families originated from other Anglophone countries (Table I). With one exception, the questionnaire was

completed by the mother of the child alone, and 8 of the mothers were single carers (25 %). Tables II and III list the karyotype, age and characteristic features for each child and his/her affected parent. Among the 16 interstitial and 20 terminal deletions of chromosome 4q there was 1 reciprocal balanced translocation (no. 8), 1 derivative chromosome (no. 19), 1 mosaic chromosome (no. 24) and 1 deletion defined by fluorescent in-situ hybridisation (no. 26). The male/female ratio of all patients was 0.8 (16/20). The youngest patient was 10 months and the oldest 47 years; their mean age was 11.24 years. A parent was affected in 16 % of families (5/32). All children had some degree of developmental delay or learning difficulties ranging from (very) mild (15) over moderate (10) to severe (7). Most of the older children received additional help at school or attended a special school. Two of the adult relatives had achieved higher qualifications. In 11 out of 29

Table I: Geographical distribution of 32 children with 4q-syndrome

Country/region	Questionnaires sent/returned
United Kingdom	25/20
Europe	4/2
United States	20/8
Canada	2/2
Australia	4/0

Table II: Adult relatives with 4q-syndrome

Relation to patient	Karyotype	Age (yr)	Health	Education
Mother of No. 9	46,XX,del(4)(q25q27)	28	Difficult pregnancy with affected child, otherwise well	Studying for psychology degree
Father of No. 29	46,XY,del(4)(q34qter)	47	Well, aggressive behaviour	Special school
Mother of No. 30	46,XX,del(4)(q34qter)	36	Cleft palate, hypermobility	Accounting technician
Father of No. 32	46,XY,del(4)(q35qter)	29	Well, dyspraxia, aggressiveness	Secondary school

Table III: Characteristics of 32 new patients with 4q-syndrome

No.	Karyotype	Age (mo)	Weight (kg), Height (cm)	DD LD	Phenotype
1	46,XX,del(4)(q12q21.1)	28	11.1, 83	I	Neonatal pulmonary hypertension and seizure, high forehead, slow growing hair, ear pit, squint, delayed tooth eruption, enamel defects, tantrums
2	46,XY,del(4)(q13.2q21.3)	61	16.3, 93	III	Fine hair, wide forehead, epilepsy, deafness, abnormal teeth, small chin, narrow airways, clinodactyly, hypotonia
3	46,XX,del(4)(q21.1q21.22)	26	12.5, 80	II	Large head, delayed white matter myelination, ptosis, squint, flat nasal bridge, irregular teeth, hypotonia
4	46,XX,del(4)(q21.1q21.3)	10	9.0, 72	I	Large head, frontal bossing, upwards slanting eyes, hypertelorism, low set ears, deafness, wide nasal bridge, clinodactyly, overlapping toes
5	46,XX,del(4)(q21.1q21.3)	46	9.0, 70	III	Fine hair, wide forehead, broad nasal bridge, low set ear, enamel defects, receding chin, impaired hearing and vision, short neck, clinodactyly
6	46,XX,del(4)(q21.1q21.3)	231	67.0, 158	III	Neonatal hypotonia, scoliosis, short fingers and toes, severe speech delay, behavioural difficulties
7	46,XY,del(4)(q21.3q23)	13	9.5, 76	I	Neonatal respiratory distress, large forehead, wears glasses, small chin, arc shaped finger and toe nails, toe webbing, hypotonia
8	46,XY,del(4)(q23q28) t(4;14)(p10q10)	46	13.6, -	II	Small and slanted eyes, short sighted, dented ear pinnae, wide nasal bridge, receding chin, heart defect, required gastrostomy, hypotonia, hyperactive
9	46,XY,del(4)(q25q27)mat	90	22.2, -	II	Macrocephaly, deafness, high arched palate, crowded teeth, Rieger anomaly, gastrostomy, constipation, autism
10	46,XY,del(4)(q25q28.2)	103	23.5, 119	II	Craniosynostosis, long sightedness, squint, low set ear, bifid uvula, high arched palate, double alveolar ridge, single palmar crease, overlapping toes, autism, ADHD, extension dystonia
11	46,XX,del(4)(q27q31.1)	64	12.7, 95	II	Thin hair, visual impairment, black spot on iris, small chin, thick finger and toe nails, obsessional behaviour
12	46,XX,del(4)(q27q31.22)	138	24.0, 130	III	Large forehead, hypotelorism, low set ears, deaf, small nose, crowded teeth, double alveolar ridge, pointed tongue, clinodactyly, overlapping toes, oxygen therapy, hyperactive, aggressive
13	46,XY,del(4)(q31q33)	200	82.6, 173	III	Slanted eyes, malaligned teeth, claw-like fingers, stiff 5th digits, hypoplastic 5th toes, double anus, epilepsy, aggressive
14	46,XY,del(4)(q32q33)	80	-, 118	II	Right ptosis, speech and language delay, autism, aggressive behaviour
15	46,XX,del(4)(q32q34)	101	25.4, 124	I	Brittle hair, visual impairment, bifid uvula, low set ears, complex cardiac defect, club feet, large toe nails, leg muscle cramps, aggressive behaviour
16	46,XX,del(4)(q32.2q34.2)	76	15.6, 104	I	Hypertelorism, anisocoria, high arched palate, protruding teeth, pointed tongue, cardiac defect, gastrostomy, clinodactyly, short fifth digits, overlapping toes, low tone
17	46,XX,del(4)(q32q35)	18	8.5, 72	I	Cleft palate, asymmetrical ears, hearing impairment, small chin, cardiac defect, apnoeas, kidney failure, gastrostomy, fundoplication, overlapping toes
18	46,XY,del(4)(q33q35.1)	23	12.0, 82	I	Twin, open anterior fontanelle, epicanthic folds, ptosis, optic nerve anomaly, mild hearing loss, upturned nose, small chin, hypothyroidism, heart defect, hypotonia
19	45,XX,-4,-21,+der(4) t(4;21)(q22q21)mat	188	88.9, 170	I	High forehead, ptosis, high arched palate, swallowing difficulties, deaf, long fingers, toe webbing, aggressive behaviour

20	46,XY,del(4)(q31qter)	287	65.3, 178	I	Pierre-Robin sequence, high forehead, astigmatism, deaf, crowded teeth, right 5th digit anomaly, slim fingers, 4th hammer toes, tracheostomy, oxygen therapy, orchidopexy, hypotonia, depression
21	46,XY,del(4)(q31qter)	269	36.3, 145	III	Low set ears, deaf, cleft lip and palate, delayed adult teeth, stiff 5th fingers with deformed nails, limited mobility of 2nd and 3rd digits, cryptorchidism, hyperactive
22	46,XX,del(4)(q31.3qter)	114	22.5, 114	III	Neonatal hypotonia, gastroesophageal reflux, stiff 5th fingers with overgrowing nails, overlapping toes, autism
23	46,XX,del(4)(q31.3qter)	67	16.3, 97	II	Wide forehead, hypertelorism, broad nose, large malformed ears, small ear canals, deaf, cleft palate, irregular teeth, long tongue, thin lips, small chin, 5th digit fused, overriding toes, depression
24	46,XY,del(4)(q32qter)[8]/ 46,XY[22]	193	54.4, 175	II	Squint, speckled iris, small nostrils and chin, deaf, cleft palate, pharyngoplasty, mastoidectomy, 5th finger hypoplastic with pointed nail, webbed and hammer toes, cryptorchidism
25	46,XX,del(4)(q32qter)	100	23.0, 122	I	Squint, vision and hearing impairment, small nose, receding chin, hypotonia
26	46,XX,del(4)(q33qter).ish del(4)(q33)(36P21+, DJ063k6-)	58	-, -	I	Hypertelorism, hearing loss, broad nasal bridge, pointed tongue, small teeth and chin, cleft palate, heart defect, double nail on 5th digit, clinodactyly, overlapping toes, hypotonia
27	46,XY,del(4)(q34qter)	119	41.3, 140	I	Large forehead, epilepsy, small nose, large cheeks and chin, long fingers and toes, hyperactive, aggressive behaviour
28	46,XX,del(4)(q34qter)	38	15.0, 92	I	Plagiocephaly, laryngotracheomalacia, apnoea, impaired hearing and vision, low set ears, left 5th finger tapered and stiff with double nail, overlapping toes, hypotonia, aggressive behaviour
29	46,XY,del(4)(q34qter)pat	151	65.8, 165	II	Long sightedness, chronic nasal obstruction, missing 5th toe nails, dyspraxia, autism, ADHD
30	46,XX,del(4)(q34qter)mat	60	╬	II	Swallowing difficulties, gastrostomy, small hands and feet, hip dysplasia, hypotonia, all milk teeth were extracted
31	46,XX,del(4)(q34.2q35.2)	80	-, -	I	Neonatal seizures, slow growing hair, iris coloboma, left ptosis, small teeth, dyspraxia, emotional difficulties
32	46,XY,del(4)(q35qter)pat	97	34.9, -	I	Big head, large ears, hearing loss, big cheeks, small hands and feet, ADHD, dyspraxia, aggressive behaviour

I = mild; II = moderate; III = severe; DD = developmental delay; LD = learning difficulties; ADHD = attention deficit hyperactivity disorder

patients (38 %) weight, height or both were on or below the 2nd centile indicating growth deficiency. Sixty five percent of children (20/31) had small hands and feet, the proportions being similar among interstitial and terminal deletions. Two thirds of children with a terminal deletion had an anomaly of the 5th digit and fingernail. Feeding and swallowing difficulties leading to vomiting, coughing, choking or aspiration were frequently seen in infants and also some older children (22/32 = 69 %). A significant number of these required long term nasogastric tube feeding, a gastrostomy and/or fundoplication. In older children a behavioural phenotype emerged with aggressive behaviour, autistic spectrum disorder or attention deficit hyperactivity disorder. Delayed

toilet training, sleep problems, dyspraxia or delayed puberty were other common features. The diagnosis of 4q deletion syndrome was given to the parents by a neonatologist, paediatrician, geneticist or general practitioner. The mean age at diagnosis was 21.3 months (range 1 week to 14 years, excluding the 5 affected adults). Thirty eight percent (12/32) were diagnosed within the 1st month of life.

PARENTAL PERCEPTIONS

Feelings at diagnosis of 4q-syndrome

The parents were asked what their feelings were at the time of diagnosis, what would have helped them most to adjust to the diagnosis, and how their feelings had changed since. For the majority of parents it was the worst experience ever, but it did not change the way they loved their child. They felt anguish, bitterness, confusion, despair, devastation, disbelief, distress, fear, grief, guilt, loneliness, numbness, sadness, shock or upset. One parent said "it knocked the wind out of me", another that "the baby she brought home had 'died' that day". Some parents felt relief that finally they had been given an explanation for their child's problems, particularly if he or she was older ("It gave our son's disabilities a title."). Having a diagnosis allowed the children to access health services more easily. It would have helped the parents, if the doctor had thoroughly researched the condition prior to breaking the news, and if the diagnosis had been given in a personal, sincere, sympathetic and timely fashion. They would also have appreciated if they had been made aware of other families with similarly affected children through parent support groups. Often there was a general information deficit due to the rarity of the deletion and a lack of specialist follow-up for children with 4q-syndrome. Some doctors gave incorrect information ("Your baby is going to die in 6 weeks. The mortality of this condition is 80 %.") or were insensitive ("So, you have a little retarded boy here. Put your child in residential care."). As the children grew older, their parents became more positive and hopeful, and they began to search independently for new information on their child's chromosomal disorder. Many parents assumed a more accepting attitude, learned to get on with life and took each day at a time. There still remained feelings of insecurity and uncertainty as they did not know what to expect from the future, for instance in relation to the degree of learning difficulties. Some parents felt a need to protect their children from medical professionals and developed a sceptical attitude towards them.

Understanding of 4q-syndrome

The parental knowledge of the basic mechanisms leading to their child's chromosomal abnormality was generally good. The information was usually passed on to them by a geneticist or they acquired it through their own studies. In the majority of cases a medical professional correctly pointed out that the chromosomal disorder was not hereditary, apart from rare exceptions, and could not have been prevented by anyone or anything. The spontaneous, random or *de novo* 4q deletion was understood to be caused by a mix up of chromosomes at the time of conception leading to the loss of certain bands/genes. Other terms used to describe the underlying pathology were "when egg and sperm met, this piece of chromosome went missing" or "the deletion was due to an accident of nature, when the embryo was formed". Doctors were on the whole cautious regarding the prognosis of 4q-syndrome, most likely due to the scarcity of similar published cases. The quality of the information given varied significantly, ranging from "there are no clear answers, wait and see" to "in the unlikely event of your daughter having children of her own, there is a 50:50 chance that they will have the same disorder". Most professionals stated that the child would have a degree of developmental delay/learning difficulties and might have short stature. The individual medical or surgical issues would affect day-to-day life and possibly lifespan. One geneticist said that the chromosomal deletion was in every cell of the child's body and that there would be no new physical problems ("What you see is what you get."). This was helpful to parents who attributed every acute illness to their child's chromosomal disorder. There was agreement among professionals as to the lack of a cure, instead symptomatic and supportive treatment was recommended depending on the specific needs of each child.

Professional and other support

The parents were asked which health professionals were involved in the regular care of their child and what other sources of support and information had helped them in coping with their child's illness. The professionals involved were geneticists, paediatricians and paediatric sub-specialists, orthopaedic, cardiothoracic and craniofacial surgeons, dentists, audiologists, physical, occupational and speech and language therapists, psychologists, health visitors, community nurses and school teachers. In many cases a multidisciplinary therapeutic approach was taken. Among other sources of support and inspiration parents mentioned their partners, friends and family, parent support groups, social

services, respite care, play groups, libraries, the internet and religion. A significant number were critical of their geneticist, who had given their son or daughter a diagnosis and prognosis, but not offered further support or follow-up appointments. Part of this disappointment may have been due to the fact that the geneticist was often the first person to break the "bad news". Two thirds of parents (21/32) felt that they had not been given enough (positive) information regarding their child's condition. A few parents did not receive any professional or other support. When asked how their situation could be improved, they suggested better data collection on children with 4q-syndrome, freeing up access to medical journals, provision of relevant leaflets, more local support groups and regular genetic reviews. They felt that communication between professionals was sometimes sub-optimal and resulted in a fragmentation of care ("No one was interested in the whole child".).

Positive experiences

As a final question parents were asked how their child had contributed most to their lives. A majority of 86 % (24/28) replied that caring for and bringing up a child with 4q-syndrome had enriched their lives and given them new perspectives despite all the difficulties encountered and the years of hard work. The phrases used were "he is our gift", "she taught me patience", "the best thing that ever happened to me", "she adds pure joy to my life", "the most loving individual I have ever met", "she is the sunshine of our life", "he made me realise I can cope with anything" and "he is a constant reminder of what is important in life". A significant number of children surpassed the predictions made by doctors and progressed further than expected. Several parents were impressed by the level of care that had been offered to them and felt that the health professionals had gone beyond the call of duty to help their son or daughter. They acquired detailed medical knowledge on their child's condition and were proud of what they achieved. Many parents were grateful to be able to participate in the questionnaire survey and other research. They were interested to be informed of the study results as they hoped to receive new answers regarding their child's future. One geneticist aptly conveyed a positive message by saying "the baby would be her own person just like any other child" and a mother commented "he made us laugh, worry and cry just like any child would".

DISCUSSION

Few paediatric case series have relied solely on information provided by parents, and therefore it is conceivable that the genetic description of the patients reported here is incomplete in parts. However, upon registration with Unique parents have to supply evidence of their child's karyotype and other relevant details. Most parents keep comprehensive records of their child's chromosomal disorder in the form of doctor's letters, copies of medical articles, school reports or similar. The good response rate of this survey (over 50 %) demonstrates the willingness of parents to contribute to medical research, and participating families expressed a keen interest for the study results to be shared with them. Several studies involving relatives of children and adults with a chromosomal abnormality have been published. Howlin and Udwin carried out a questionnaire survey among 239 parents who had an adult son or daughter with Williams syndrome (8). They found a high morbidity in these patients and increasing rates of mental health problems. At a mean age of 30.6 years 62 % lived with their parents and one third were employed. Steinhausen et al. studied the behaviour profile of 58 German or Swiss subjects with Prader-Willi syndrome (PWS) ranging from 3 to 29 years of age (17). Their parents were asked to complete the Developmental Behaviour Checklist which assesses behavioural and emotional disturbance in children and adolescents with intellectual disability. The results of this study revealed that during adolescence PWS patients are at an increased risk of developing psychological or psychiatric illness. Twelve Turkish mothers of children with Down syndrome were interviewed in a study with the aim to explore their experiences (14). A reduction of social contacts was observed in these families due to negative reactions from other community members. Almost all mothers showed great affection for their child with Down syndrome, which is similar to the findings in our survey. Cotton and Richdale investigated the sleep pattern of children with Prader-Willi syndrome, Down syndrome, familial learning disability and autism. Their parents reported between 4 and 7 times higher rates of sleeping difficulties compared to control children (3). Other studies examined the quality of oral health care in adults with Down syndrome and the prevalence of taurodontism, a dental anomaly, in patients with Klinefelter syndrome (9, 15).

A significant number of children with 4q-syndrome in our large case series displayed aggressive behaviour with increasing age, suggesting that this type of behaviour is part of the behavioural phenotype present in children with 4q-syndrome. There was also an increased incidence of autistic spectrum disorder and attention deficit hyperactivity dis-

order. Three recent studies support these findings. Ramanathan *et al.* identified several candidate genes for autism in an 11-year old boy child with del(4)(q31.3q33) encoding neurotransmitter receptor subunits and neuropeptide receptors (12). Pickard and co-workers found a subtelomeric deletion of chromosome 4q in an adult with mild learning disability and psychosis (10). In a genetic linkage analysis of families where attention deficit hyperactivity disorder was more prevalent a locus was identified on chromosome 4q13.2 which may contain susceptibility genes for ADHD (2).

Parents participating in this study frequently asked why this 4q deletion had occurred in their child, and apart from metaphysical explanations recent articles on aneuploidy induction and aneuploidy screening in human embryos provide some answers (20, 4, 6). Chromosomal errors are common in human reproduction and most of them lead to a loss of the embryo. It is estimated that only 25 - 30 % of fertilised eggs develop beyond the first trimester of a pregnancy. A partial monosomy of chromosome 4 (4q deletion) is a rare form of aneuploidy that can occur before, during or after meiosis (reproductive cell division). Deletions which affect no more than 3 % of the haploid autosomal complement are usually compatible with life. Factors predisposing to aneuploidy are parental ageing, significant exposure to chemicals or radiation, mutations of genes controlling cell division and disturbances of cell homoeostasis. However, none of the above has been proven to be a causative factor in any of the cases investigated here.

The results of our survey support the existence of a common somatic and behavioural phenotype in children with deletions of the long arm of chromosome 4, as predicted by Sandler and Hecht (13). We believe that this phenomenon can partly be explained by epigenetics. Our findings can assist health professionals in giving more comprehensive information to patients and relatives at the time of diagnosis. It is now possible to make a reasonably accurate prognosis in children with 4q-syndrome irrespective of the exact chromosomal breakpoint(s) of individual patients. We strongly encourage the publication in journals subject to peer-review of anonymised information from professionally-run, patient-led databases to amplify the information already available on the natural history of specific rare chromosome disorders.

ACKNOWLEDGEMENTS

We are grateful to the parents and children for participating in the study and for providing such detailed information.

REFERENCES

1. *ABRAMSON J.H., ABRAMSON Z.H.: Survey Methods in Community Medicine: Epidemiological Research, Programme Evaluation, Clinical Trials.* 5th Ed. Edinburgh, Churchill Livingstone, 1999.
2. *ARCOS-BURGOS M., CASTELLANOS F.X., PINEDA D., LOPERA F., PALACIO J.D., PALACIO L.G., RAPOPORT J.L., BERG K., BAILEY-WILSON J.E., MUENKE M.:* Attention-deficit/hyperactivity disorder in a population isolate: linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11. *Am. J. Hum. Genet.,* 2004, *75(6),* 998-1014.
3. *COTTON S., RICHDALE A.:* Brief report: parental descriptions of sleep problems in children with autism, Down syndrome and Prader-Willi syndrome. *Res. Dev. Disabil.,* 2006, *27(2),* 151-161.
4. *DELHANTY J.D.:* Mechanisms of aneuploidy induction in human oogenesis and early embryogenesis. *Cytogenet. Genome Res.,* 2005, *111(3-4),* 237-244.
5. *DUBE C.E., LAMONICA A., BOYLE W., FULLER B., BURKHOLDER G.J.:* Self-assessment of communication skills preparedness: adult versus pediatric skills. *Ambul. Pediatr.,* 2003, *3(3),* 137-141.
6. *EICHENLAUB-RITTER U.:* Mouse genetic models for aneuploidy induction in germ cells. *Cytogenet. Genome Res.,* 2005, *111(3-4),* 392-400.
7. *FRANCKE U.:* Digitized and differentially shaded human chromosome ideograms for genomic applications. *Cytogenet. Cell Genet.,* 1994, *65(3),* 206-218.
8. *HOWLIN P., UDWIN O.:* Outcome in adult life for people with Williams syndrome – results from a survey of 239 families. *J. Intellect. Disabil. Res.,* 2006, *50(2),* 151-160.
9. *KAYE P.L., FISKE J., BOWER E.J., NEWTON J.T., FENLON M.:* Views and experiences of parents and siblings of adults with Down syndrome regarding oral healthcare: a qualitative and quantitative study. *Br. Dent. J.,* 2005, *198(9),* 571-578.
10. *PICKARD B.S., HOLLOX E.J, MALLOY M.P., PORTEOUS D.J., BLACKWOOD D.H., ARMOUR J.A., MUIR W.J.:* A 4q35.2 subtelomeric deletion identified in a screen of patients with co-morbid psychiatric illness and mental retardation. BMC Med. Genet., 2004, *5,* 21.
11. *PRICE J., MCNEILLY P., SURGENOR M.:* Breaking bad news to parents: the children's nurse's role. *Int. J. Palliat. Nurs.,* 2006, *12(3),* 115-120.
12. *RAMANATHAN S., WOODROFFE A., FLODMAN P.L., MAYS L.Z., HANOUNI M., MODAHL C.B., STEINBERG-EPSTEIN R., BOCIAN M.E., SPENCE M.A., SMITH M.* A case of autism with an interstitial deletion on 4q leading to hemizygosity for genes encoding for glutamine and glycine neurotransmitter receptor sub-units (*AMPA 2, GLRA3, GLRB*) and neuropeptide receptors *NPY1R, NPY5R. BMC Med. Genet.,* 2004, *5,* 10.
13. *SANDLER L., HECHT F.:* Annotation: genetic effects of aneuploidy. *Am. J. Hum. Genet.,* 1973, *25(3),* 332-339.
14. *SARI H.Y., BASER G., TURAN J.M.:* Experiences of mothers of children with Down syndrome. *Paediatr. Nurs.,* 2006, *18(4),* 29-32.
15. *SCHULMAN G.S., REDFORD-BADWAL D., POOLE A., MATHIEU G., BURLESON J., DAUSER D.:* Taurodontism and learning disabilities in patients with Klinefelter syndrome. *Pediatr. Dent.,* 2005, *27(5),* 389-394.
16. *SEARLE B.A., HULTEN M.: The Little Yellow Book. A Guide to Rare Chromosome Disorders, Volume 1.* Caterham, UK, Unique, 2000.
17. *STEINHAUSEN H.C., EIHOLZER U., HAUFFA B.P., MALIN Z.:* Behavioural and emotional disturbances in people with Prader-Willi Syndrome. *J. Intellect. Disabil. Res.,* 2004, *48(1),* 47-52.
18. *STREHLE E.M., AHMED O.A., HAMEED M., RUSSELL A.:* The 4q-syndrome. *Genetic. Couns.,* 2001, *12(4),* 327-339.
19. *STREHLE E.M., BANTOCK H.M.:* The phenotype of patients with 4q-syndrome. *Genet. Couns.,* 2003, *14(2),* 195-205.
20. *WILTON L.:* Preimplantation genetic diagnosis for aneuploidy screening in early human embryos: a review. *Prenat. Diagn.,* 2002, *22(6),* 512-518.

ADDRESS FOR CORRESPONDENCE:

Dr. Eugen-Matthias Strehle
Department of Paediatrics
North Tyneside General Hospital
North Shields NE29 8NH, UK
Tel. 0044 191 2596660
E-mail: strehle@doctors.org.uk