Proceedings of the First Study Day on 4q Deletion Syndrome in Coventry, United Kingdom

P.M. Middlemiss[1,*], E.M. Strehle[2], D. Gurudutt[2], S.L. Wynn[1] and B.A. Searle[1]

[1]*Unique, Rare Chromosome Disorder Support Group, PO Box 2189, Caterham, Surrey CR3 5GN, England*

[2]*North Tyneside General Hospital, Tyne and Wear NE29 8NH, England and Institute of Human Genetics, International Centre for Life, Newcastle University, Newcastle upon Tyne NE1 3BZ, England*

Abstract: 4q deletions are rare chromosome disorders (RCD), with an estimated incidence of 1:50,000-100,000 that is rising as a result of routine introduction of chromosomal microarray testing. The diagnosis of a 4q deletion, as of any RCD, confers a sense of exclusion, isolation and guilt on families with an affected child. Reliable information available to a lay audience is scant. To address these issues, Unique, the Rare Chromosome Disorder Support Group, hosted the first international meeting on 4q deletions. Families valued the opportunity to meet genetics and medical professionals with an interest in 4q deletions and to exchange information with each other. In this paper, we intend to summarize all the information presented in this study meeting.

Keywords: Rare chromosome disorder, 4q deletion syndrome, 4q- syndrome, 4q deletion, Unique.

INTRODUCTION

The term 4q- syndrome has been used to describe people who have a deletion of the long arm of chromosome 4, detectable by standard karyotyping. Clinical features seen include facial and digital dysmorphism; cardiac, skeletal, gastrointestinal and renal abnormalities; developmental delay; learning difficulties and growth failure.

Unique, the worldwide rare chromosome disorder support group (www.rarechromo.org), hosted the first-ever international meeting for families with a child having 4q- syndrome, in Coventry, United Kingdom in April 2010.

This was a three-day meeting that brought families from Great Britain, the Netherlands and the US together with researchers, interested doctors and therapists.

Unique has 184 members with 4q- syndrome. Of these, 131 members have a 'pure', interstitial or terminal deletion or microdeletion. 53 members have a deletion from chromosome 4 as part of a wider chromosome imbalance, typically an unbalanced translocation.

Sixteen families and their children met eight professionals, including paediatricians, clinical geneticists, a psychiatrist, a computational biologist, a sleep counsellor and an occupational therapist. Families heard presentations on 4q- syndrome and had individual 1:1 clinics with a clinical geneticist and/ or pediatrician.

*Address correspondence to this author at the [1]Unique, Rare Chromosome Disorder Support Group, PO Box 2189, Caterham, Surrey CR3 5GN, England; Tel: +44 (0)20 8992 9933; Fax: +44 (0)20 8992 4178; E-mail: prisca@rarechromo.org

Unique's 4q- syndrome weekend was the first topic in a series of five, disorder-specific weekends. Kleefstra syndrome (9q34.3 deletions); 8p23 deletions and inverted duplication and deletion of 8p; 2q37 deletions and Pallister-Killian syndrome completed the series.

PROCEEDINGS

Part 1: Review of 4q- Syndrome and Case Presentation

Dr. Eugen-Matthias Strehle, consultant pediatrician at North Tyneside General Hospital and honorary consultant in neuromuscular genetics at the Institute of Human Genetics, Newcastle, United Kingdom, presented '4q-syndrome.'

The first patient was reported by Dr. Charles Ockey in 1967 [1]. Twelve years later, Dr. Phillip Townes first used the term 4q- syndrome, applying it to a terminal deletion syndrome with a breakpoint in band 4q31 [2]. The presence of a critical region was not established. In 2001, Dr. Strehle suggested using the term for all microscopically visible deletions of the long arm of chromosome 4.

Reviewing 100 patients with 4q- syndrome, Dr. Strehle reported an incidence of ~1:100,000 [3] with recent data suggesting ~1: 50,000 (Huang, personal communication). Male to female ratio was approximately equal at 48:53. The ratio of interstitial to terminal deletions was 52:49; some deletions occurred more frequently, for instance 4q12q21 interstitial deletions and 4q31 and 4q33 terminal deletions. Parental chromosomes were normal in ~ 86% of cases (Table **1**).

1875-693X/11

Table 1. Clinical Characteristics and Affected Organ Systems in Patients with 4q- Syndrome [4]

Characteristic	Percentage	M/F
Male/Female ratio	0.91	(48/53)
Abnormal parental chromosomes	14	(13/90)
Prematurity	14	(12/85)
Developmental delay	94	(77/82)
Growth failure	60	(56/94)
Mortality	28	(28/101)
Craniofacial dysmorphism	99	(100/101)
Pierre-Robin sequence/cleft lip & palate	37	(37/101)
Central nervous system	34	(34/101)
Ocular apparatus	44	(44/101)
Hearing	37	(16/43)
Digital dysmorphism	88	(89/101)
Skeleton & extremities	54	(54/101)
Muscular system	45	(45/101)
Cardiovascular system	50	(50/101)
Respiratory tract	32	(32/101)
Dentition	18	(18/101)
Gastro-intestinal tract	40	(40/101)
Hepatobiliary system and pancreas	17	(17/101)
Lymphatic system and spleen	8	(8/101)
Endocrine system	6	(6/101)
Renal and urinary tract	19	(19/101)
Genitalia	28	(28/101)
Skin/hair	43	(43/101)

Dr. Strehle suggested the following program of investigations

1 Cranial imaging because brain anomalies occur fairly frequently

2 X-rays as indicated if the child has any significant abnormality of the arms or legs

3 An abdominal ultrasound scan

4 pH studies to test for gastro-esophageal reflux

5 Electrocardiogram or echocardiogram because of the common heart anomalies

6 Electroencephalogram for seizures, a relatively frequent feature

7 Hearing and vision tests.

Children with 4q- syndrome should be cared for by a multidisciplinary team consisting of a pediatrician, geneticist, surgeon where relevant, dietician to support growth, speech and language therapist for any swallowing difficulties, physical therapist, occupational therapist, psychologist for behavior difficulties, and special education teacher.

Dr. Strehle presented the first child with an occipital encephalocele with a terminal deletion at 4q33. The index patient was born by Cesarean section, with a birth weight of 2.9 kilograms and Apgar scores of 8 and 9 [5]. The occipital encephalocele was successfully removed at two days. A brain scan and MRI at three months showed a neuronal migration defect and Arnold-Chiari malformation.

The index patient had severe complex congenital heart disease successfully corrected with surgery. She also had a large fontanel, hypertelorism, overfolded ears, a small mouth and chin, overlapping fingers, unusually placed toes and a sacral hemangioma.

Routine karyotyping showed a de novo terminal deletion with a breakpoint at 4q33. Array-CGH revealed a 25.7Mb deletion with a breakpoint at 4q32.3. On follow-up, the patient had growth deficiency and feeding difficulties. Her developmental milestones were delayed, walking by 2.5 years, and saying single words and following a simple instruction at 5 years. At 5 years the facial dysmorphism was still visible and the short stature was striking.

In summary, 4q- syndrome is a valid disease entity characterized by overlapping features. With regard to the encephalocele, a gene or genes responsible for the development of the basement membrane may reside on chromosome 4 (see talk below by Prof. Huang).

Part 2: Unique Survey

Dr. Strehle described a survey conducted through Unique [6]. The survey focused on questions pertaining to physical characteristics and skills, general health, behavior of the child, relationship and communication between carers/ parents and health care professionals and finally accessibility of healthcare to carers.

Fifty-five questionnaires were sent out, with an abbreviated form sent to five parents of affected children identified after their child was diagnosed.

Four of the Patients were well into Adulthood. These Adults Included:

1 Female (28 yr) woman with an interstitial 4q25q27 deletion studying for a psychology degree.

2 Male (47 yr) male with a 4q34 terminal deletion who self-reported aggressive behavior and special education but was otherwise well.

3 Female with a 4q34 terminal deletion with a cleft palate and hypermobile joints working as an accounting technician.

4 Male with a 4q35 terminal deletion who completed public secondary school education and self-reported aggressive behavior and dyspraxia.

Of 32 returned questionnaires (58% response rate), there were 16 interstitial and 20 terminal deletions. The mean age of children was 11 years, ranging from 10 months to 47 years. The mean age of diagnosis was two years, ranging from one week to 14 years; 38% were diagnosed in the first month of life. The chromosome abnormality was inherited in 16%.

All children had a learning difficulty but in almost half, it was mild; in one third it was moderate and it was rated severe in rest of them. 38% had growth deficiency; 65% had small hands and feet. Two thirds of children with a terminal deletion showed an anomaly of the fifth finger and finger nail in which the finger is small and the nail is not well developed. More than two thirds had feeding difficulties, in some cases needing nasogastric tube feeding, a gastrostomy and sometimes a fundoplication.

What were parents' feelings at diagnosis? They said that it was the worst experience ever but didn't change the way they loved their child. One parent said: 'The baby I brought home 'died' that day'.

The survey revealed some criticism of doctors. Two thirds of parents complained they were not given enough information or said no-one was interested in the whole child.

Many health professionals involved in the care of the child were perceived to either not have the time or to focus on one part of the child, leading to fragmented care. There was criticism from parents who felt that the clinician imparting the diagnosis had insufficient knowledge or time to research the disorder thoroughly. Some professionals were felt to be insensitive, giving an unnecessarily poor prognosis and referring to older literature and outdated mortality rates. Parents felt the diagnosis should be given by someone knowledgeable, in a personal, sincere and sympathetic manner.

As children grew older, parents became more positive and confident and searched for more information themselves. They became more accepting and learnt to look at the immediate rather than long term future. Parents' own knowledge of their child's chromosome disorder was good. The medical advice given to parents was deemed to be cautious.

Some families felt abandoned by the geneticist without follow up appointments. Practice varies but it may be more appropriate for a pediatrician to follow families up.

What were families' positive experiences? They said that bringing up a child with 4q- syndrome had enriched their lives and provided new perspectives. Parents referred to their child as 'our gift', 'the best thing that ever happened' and 'a constant reminder of what is important'. Many children surpassed geneticists' and other doctors' predictions. Some parents were impressed with the level of care they received and acquired detailed medical knowledge themselves.

A GENOTYPE-PHENOTYPE CORRELATION FOR 4q- SYNDROME

Dr. Taosheng Huang, associate professor with tenure in pediatrics, developmental biology and pathology at University of California, Irvine, CA, USA and director for the Cardiovascular Genetics Clinic and co-director for the MitoMed Molecular Diagnostic laboratory, presented a genotype: phenotype correlation for 4q- syndrome.

He presented the cases for 4q- and 4q- syndrome, and suggested that the term 4q- syndrome may be appropriate for the terminal deletions. Third generation array-CGH has revealed microdeletions on 4q and shown that 4q-/ 4q- syndrome is more common than thought. His work has tentatively identified a hotspot for break points at 4q33, suggesting that the structure of the chromosome in that region is vulnerable to breaks.

Reviewing 20 patients with detailed clinical histories, he has found a similar phenotypic pattern to that identified by Strehle and Bantock in 2003 [4]: craniofacial dysmorphism in 100%; developmental delay in 95%; digital anomalies in 70%; muscular anomalies in 55%; and skeletal and cardiac anomalies in 50%.

The work has revealed clusters at 4q25-q28.2 and 4q32.2-q35.2. Recent research has shown that in some cases the clinical phenotype is similar, whether there is a deletion or duplication [7]. The *HAND2* gene in 4q34.1 is expressed in the right side of the heart and could be associated with congenital heart defects; a hypothetical cleft palate gene has been identified at 4q33q35.1. *BMP3* in 4q21.21 is associated with bone development and may be important for growth, since many children have short stature.

Dr. Huang suggested that it may be possible to intervene in the *BMP3* pathway, 'borrowing' drugs from related fields such as osteoporosis. Similarly it might be possible to intervene in the *FGF2* (in 4q27) pathway. This gene encodes a protein of the fibroblast growth factor family which has mitogenetic and angiogenetic properties. Dr. Huang emphasized that treatment at the moment is speculative because sample sizes are small, but it is feasible.

SLEEP

Moira Draper, a sleep counselor for the specialist service Cerebra, Carmarthen, UK, a charity for people with brain-related disorders, talked about sleep difficulties which are commonly observed in children with 4q- syndrome. She pointed out that management of sleep problems can often be the same for a child with a chromosome or other disorder as for a typically-developing child. She explained the circadian rhythms that underlie the sleep: wake cycle and emphasized that early training is important to align the sleep: wake rhythm. Cues such as daylight influence the sleep: wake cycle, with natural melatonin release during darkness and suppression during daylight hours. Some children with 4q deletions have a visual impairment and this will impact their melatonin response.

Ms. Draper explained the three basic states: wakefulness, rapid-eye-movement (REM) or 'dream' and non-rapid-eye-movement (NREM) or 'deep' sleep. In the first third of the night NREM periods are both deeper and longer than later in the night and an unbroken spell of 3 to 4 hours sleep will give all the 'deep' sleep needed. During each cycle there are times when a child wakes briefly before dropping back into sleep. A child who has incorrect associations with these brief wakings can learn to start screaming or shouting or crying for their parents. In a child with a physical disability

who may wake because they are stiff or in pain, there are increased opportunities for incorrect associations.

During the early part of sleep more growth hormone is released and frequent, regular disturbance could cause a difficulty with growth. Consolidation of memory and learning occurs during sleep and is essential for emotional wellbeing.

There are two categories of sleep disturbance: first, problems such as inappropriate parental expectations, lack of a sleep routine or lifestyles that are not conducive to regular sleep patterns. Embedding a lifestyle where a child sleeps at different homes or divides time between home and respite takes longer for a child with a learning difficulty/ developmental delay.

Sleep disorders are the second category. An underlying medical condition such as epilepsy, obstructive sleep apnea, or the medications used to treat epilepsy can alter sleep patterns. In Sleep Onset Association Disorder, children associate certain conditions, such as having a parent with them, with falling asleep. This can occur in children whose health is precarious in their early life. Sleep apnea is seen in children with Down syndrome and others with low muscle tone. Everyone relaxes during sleep, but those with low muscle tone relax further and in sleep apnea can be heard first snoring, then stopping for a few seconds, then gasping for breath. A child with these symptoms should be considered for an overnight sleep study. Children diagnosed with sleep apnea may have their tonsils and adenoids removed or given a CPAP (continuous positive airway pressure) machine for correct oxygen flow.

Some children experience nocturnal seizures and anticipation can cause anxiety at bedtime, especially in a child who cannot express their fears. Other children have a shifted sleep phase that may be early, late or irregular. An irregular sleep phase is the hardest to manage.

Reflux can disturb sleep; signs of silent reflux include arching the back, sore throats and toothache. Positioning the child in a more upright position can help and medication is available. Avoiding a large meal or bottle of milk before bedtime, where possible, plays a role.

In the context of a child with a disability, Ms. Draper said that parents should consider a number of points for sleep management. Children with a physical disability may not take much exercise, but their activity should follow a similar pattern to a typically-developing child. For example, a child with a physical disability can stand in their walking frame, have a massage session or do their physiotherapy exercises before their evening meal rather than afterwards.

Ms. Draper recommended a fixed bedtime routine including 30 minutes of wind-down time without television, possibly with music, followed by a light supper and a relaxing bath before going straight to bed. The set of associations has to be especially clear and consistent for a child with a learning difference.

The session ended with questions on melatonin, sleep needs in children with autism and children who need very little sleep and suggestions included trial of melatonin from the age of 1 month at physician's discretion.

CREATING A 3D MODEL OF TYPICAL FACES IN 4q- SYNDROME

Professor Peter Hammond, Professor of Computational Biology at the Molecular Medicine Unit at the UCL Institute of Child Health UK, presented 'Creating a 3D model of typical faces in 4q-'. Following the presentation, he captured 3D photographs of the faces of the attending children and adults with 4q deletions.

Professor Hammond explained his interest in facial and latterly brain development. This meeting was his first exposure to 4q- and he told families how he might build a 3D model of a typical face in 4q-, showing models of other genetic conditions and how they are used.

Professor Hammond showed how face shapes vary with different conditions and differ from an average face with no known genetic condition. For example, differences in the face of a child with 22q11 deletion syndrome can be very subtle around the nostrils, mouth and the eyes. In Williams syndrome the facial differences are much stronger, such as the short nose with a bulbous tip and very full lips as well as a fullness around the eyes and a narrow forehead.

The 3D models are used to visualize the differences in genetic conditions which can help in training people to recognize them. This speeds up diagnosis and reduces uncertainty for the family. In situations where the child has no diagnosis the models can help select an appropriate genetic test.

Professor Hammond said that a challenging task is to look for subgroups within a syndrome with common features. The literature on 4q- suggests there is a wide range of differences, with some subgroups associated with the amount of genetic material lost that show some similarities. Is that echoed in the face? The suggestion is that it is, he ventured.

Generally speaking, depending on the number of faces studied, the analysis shows that greatest variation in face shape (over 80%) is to do with growth; by comparison, only five per cent might reflect the length/ovalness of the face (like a football or rugby ball), 2.5% with the flatness of the face, 2% with ear and eye position etc. The analysis allows Professor Hammond to identify normal variation and the differences in children with certain genetic syndromes.

Using his analysis, Professor Hammond can identify whether an undiagnosed face is more like the average of a control group face or, for example, the average of a group of children with Williams syndrome.

For 4q-, an important question is concerned with phenotype: genotype correlations. Given the subgroups identified in terms of the genetic material missing, what are the face shape differences?

In summary, Professor Hammond said that the models of face shape in genetic conditions would be used in three ways:

A. Training of the recognition of characteristic facial features

B. Screening undiagnosed children or assisting in diagnosis

C. Identification of face shape difference within a syndrome that is associated with different genetic causality.

REALISTIC EXPECTATIONS OF DEVELOPMENT

Dr. Pru Allington-Smith, Consultant Psychiatrist in child and adolescent learning disability and Ann Clarke, specialist occupational therapist, Coventry Children's Community Learning Disability Team, presented 'Realistic expectations of development'.

Ann Clarke described the service that the Coventry Children's Community Learning Disability Team offers. This service consists of a multidisciplinary team. The team members are child learning disability psychiatrist, specialist nurses, occupational therapists and speech and language therapists with access to clinical psychological services. Hence the team offers a holistic approach for children aged 0-19 years with particular and sometimes complex needs. Team members work directly with children and run family support groups for example the EarlyBird autism program, Cygnet for children diagnosed with autism over 5 years.

Mrs. Clarke took families through the natural cycle of reactions to diagnosis: denial, followed by blame, uncertainty, mourning and bargaining. Anger is followed by guilt, isolation, flight and finally acceptance.

Talking about developmental progress, Mrs. Clarke stressed that all children can make excellent progress even if at a different rate to typically developing children. She pointed out that progress can be uneven and stressed the importance of looking positively at the things that the child can do.

Dr. Pru Allington-Smith emphasized the uniqueness of each child. Observing the children in the crèche, she noticed different levels of ability, some with and some without autism, most looking quite different from each other. She pointed out that children had different health and physical problems and had different family backgrounds.

The aim of her work is to enable any child to grow up to fulfill their potential and to have a happy and fulfilled life. Her team's philosophy is to intervene early because tackling a problem like temper tantrums in a young child is more successful and it is better for that child growing up than trying to tackle the problem at 18. By taking children on early, the team focuses not only on problems but also on promoting skills and abilities. The team also works with families to adjust to realistic expectations for their child and to provide the right environment to achieve those expectations. A lot of their work is around how families interact with their children. For some children with more severe disabilities getting an interaction going is really hard work. She stressed that it is important to make young people feel better about themselves. Young people with a learning disability will compare themselves with their brothers and sisters and be aware of opportunities that are not open to them, such as going to university or learning to drive a car. They then need help with their feelings about this.

The team can make sure that families are receiving the right benefits, adaptations and so on by signposting and supporting them. She described as an example a Safespace – a room within a room that can be filled with soft furnishings and sensory equipment to make a safe environment for a child who perhaps self injures, tries to escape or has sleep problems.

Dr. Allington-Smith said children should know who to come/go to with their problems. They should be offered as many opportunities as possible. They should be supported to realize their strengths and appreciate that they can have a good, if different, life for themselves. The team will work on their social skills guiding them to become independent, reinforcing appropriate behaviors and also on communication and problem-solving skills.

Dr. Allington-Smith said that for half the children she sees, the cause of their cognitive impairment is unknown. Having a precise diagnosis can make a difference to the service provided. Some genetic syndromes are associated with severe behavioral problems. In velocardiofacial [22q11 deletion] syndrome, for example, children and adults are at increased risk of psychiatric disorders. In Prader-Willi syndrome there are very difficult behaviors associated with overeating. In Smith-Magenis syndrome, children often have very difficult behaviors and appalling sleep but specific treatments have been developed. For 4q- syndrome, it's early days, but very useful research may come out later.

COMMUNICATION

Dr. Allington-Smith presented a talk on communication on behalf of Jill Hoddell, a retired speech and language therapist unable to be present due to ill health. Ann Clarke made contributions and clarifications.

Communication is the exchange of information and ideas. People start communicating because they want their needs to be met, later they learn to listen and respond to what others say. The process then gets more complex until people talk about ideas and theoretical issues. Communication is not only with words but gestures and appearance too. People communicate in many ways as well as speech, including signing.

Paying attention matters for good communication. To improve one's communication, aim for few distractions and try to establish eye contact, although some children with autism are not good at looking at other people. Encourage this by sitting at the same level as the child, touching their face to bring their eyes round so they are looking at you. Using their name is a good idea. Many children find it difficult to register information and do not remember it well, so check their understanding. They may not be motivated if not in the right mood. Giving too much information at once impedes understanding. Keeping sentences short and clear and not using long words helps. Using words in context helps – talking about dinner when a child is feeling hungry and can smell food helps the words to make sense. Understanding is helped if information is presented in short, clear sentences, using short, clear words in chronological sequence: not We're going to the park so get your coat but Get your coat, we're going to the park. Children with a learning difficulty may need time processing and a repetition needs to be word for word the same.

Alternatives to speech include symbols and signing, including Makaton, a simplified version of British Sign Language. Research has shown that using an alternative communication system such as signing in a child who is not speaking makes it more likely that they will eventually communicate with speech, not less likely. What matters is communication, however. Speech is one way but there are lots of others. Children usually pick up some signs very quickly (eg biscuit, cake); toilet is useful to learn. For some children with a severe learning disability, signing and symbols may be too complex and they might need something easier, such as an object of reference (toilet roll), part of the object (inner cardboard tube), a miniature or toy object, a photograph or a picture. These can be used to show the child what is going to happen, for the child to show what they want and to indicate choices. Many children with a learning difficulty have little opportunity for choice.

A child who can read or write may use printed or written words as well. Some children need a mixture of simultaneous approaches. When tired or stressed, a child may regress and be unable to understand or process words and need reinforcement with symbols or images to be sure they have understood.

Social stories are a way of communicating to manage a particular problem, often in children with autism. Books of social stories are available but they work best when individualized and can be used in many settings – how to get on with somebody, how to speak to somebody, what to do when you go to the dentist or doctor, what you should be doing when it's bedtime, how you're expected to behave when you go to a funeral.

Dr. Allington-Smith spoke briefly about communication passports, a way of telling others about a child who cannot communicate about himself. These can be used, for example, when a child has to go to hospital. By including favorite conversation topics as prompts in the passport, they can be used to help the person with a learning disability to talk. The prompts can be in pictures, organized in the easiest way for the individual to handle.

Dr. Allington-Smith Summed up Do's and Don'ts:

1 Don't ask more than one question at a time

2 Don't rush me

3 If you want me to stop an activity and move on to another, you must warn me

CONCLUSION

Families and professionals valued the opportunity to meet and exchange information on a rare chromosome disorder. Families especially valued the opportunity to hear disorder-specific presentations and to contribute to research into aspects of 4q syndrome. Professionals valued the opportunity to enlarge their knowledge of 4q- syndrome. More international disorder-specific meetings should be organized to heighten the profile of RCDs, stimulate research, enhance information quality and relieve the isolation associated with the diagnosis of a specific disorder.

ACKNOWLEDGMENTS

Financial support from Jeans for Genes and the Grocers' Charity was provided for the Unique series of syndrome-specific meetings.

REFERENCES

[1] Ockey CH, Feldman GV, Macaulay ME, Delaney MJ. A large deletion of the long arm of chromosome No. 4 in a child with limb abnormalities. Arch Dis Child 1967; 42: 428-34.

[2] Townes PL, White M, Di Marzo SV. 4q- syndrome. Am J Dis Child 1979; 133: 383-5.

[3] Strehle EM, Ahmed OA, Hameed M, Russell A. The 4q- syndrome. Genet Couns 2001; 12: 327-39.

[4] Strehle EM, Bantock HM. The phenotype of patients with 4q- syndrome. Genet Couns 2003; 14: 195-205.

[5] Quadrelli R, Strehle EM, Vaglio A, *et al.* A girl with del(4)(q33) and occipital encephalocele: clinical description and molecular genetic characterization of a rare patient. Genet Test 2007; 11: 4-10.

[6] Strehle EM, Middlemiss PM. Children with 4q- syndrome: the parents' perspective. Genet Couns 2007; 18: 189-99.

[7] Rossi MR, DiMaio MS, Xiang B, *et al*. Clinical and genomic characterization of distal duplications and deletions of chromosome 4q: study of two cases and review of the literature. Am J Med Genet A 2009; 149A(12): 2788-94.

Received: January 31, 2011 Revised: April 01, 2011 Accepted: April 04, 2011