GENETIC COUNSELING, Vol. 19, No 1, 2008, pp 47-58

DISTAL 11q MONOSOMY SYNDROME: A REPORT OF TWO EGYPTIAN SIBS WITH NORMAL PARENTAL KARYOTYPES CONFIRMED BY MOLECULAR CYTOGENETICS

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Summary: *Distal 11q monosomy syndrome: a report of two Egyptian sibs with normal parental karyotypes confirmed by molecular cytogenetics:* Jacobsen syndrome is a rare disorder, caused by segmental monosomy for the distal end of the long arm of chromosome 11 with variable phenotypic expressivity. We report on the first male (6 years old) and female (3 years old) sibs with clinical and cytogenetics characterization of Jacobsen syndrome. Their karyotypes showed deletion 11q23.3-qter. Patients presented with growth and psychomotor retardation, facial dysmorphism, eye anomalies, and congenital heart disease (variable degrees of septal defect). Family history revealed a clinically similar brother, who died at 2 months old from cardiac anomalies in the form of single ventricle without being subjected to further investigations. Chromosomal analysis of the parents was normal. Karyotyping for the 2 patients and their parents was confirmed by fluorescence in situ hybridization analysis (FISH) using whole chromosome painting probes for 11 (WCP 11). Relevant investigations for both sibs showed mild thrombocytopenia with normal platelets morphology and striking periventricular demyelination on neuroimaging. Inguinal small testicles as well as focal epileptiform dysfunction were recorded in the male patient only. Abdominal ultrasound, hearing test, and DEXA scan were normal in both patients. Due to of the presence of apparently 3 affected offspring and normal parental karyotypes, an inherited predisposition was highly suspected. The large size of the distal deleted 11q segment in our patients support the recent hypothesis, that Jacobsen syndrome is a chromosomal deletion syndrome with genetic predisposition, due to expansion of p(CCG)n trinucleotide in the folate-sensitive fragile site FRA11B, at breakpoint 11q23.3. In conclusion, identification and further delineation of more similar patients will contribute to understanding the genetic basis of the 11q- phenotype.

Key-words: Jacobsen syndrome – Distal 11q deletion – Molecular cytogenetics

INTRODUCTION

The 11q terminal deletion disorder, also called Jacobsen syndrome (JBS: MIM 147791), is a contiguous gene disorder. It was first described by Jacobsen and his co-workers in 1973 (8). Since then, over 120 cases have been reported in the literature presenting a wide range of phenotypes of varying severity (1, 4, 5, 22). Different organ systems can be affected in JBS. The main cause of early infant death is severe cardiac anomaly (5). Common clinical findings are growth retardation starting intrauterine, psychomotor delay, facial dysmorphism, congenital heart defects, digital anomalies (camptodactyly, syndactyly, clinodactyly), thrombocytopenia, genitourinary anomalies, gastrointestinal and ophthalmological problems (12, 13, 19). Facial dysmorphism includes prominent forehead, hypertelorism, downslanting palpebral

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fissures, broad nasal bridge with short nose, thin upper lip and low-set malformed ears. Eye abnormalities consist of strabismus, ptosis, atrophy of optic nerve, and coloboma of the eyelid or iris (11). The incidence of distal 11q deletions is estimated to be 1 in 100000, while the male to female ratio is 1: 3 (1, 23).

Based on karyotype analysis, the breakpoints arise typically in subband 11q23.3 with deletions extending to the telomere. Most cases arise from de novo deletion or rarely as an unbalanced segregation from a balanced carrier (15). Voullaire *et al.* (21) suggested that the origin of Jacobsen syndrome was a familial folate-sensitive 11q23.3 fragility carried by one of the parents. They hypothesized, that the fragile chromosome 11 was transmitted to the embryo and subsequently broke at the site of fragility, producing a predominant cell line with deleted chromosome 11q23.3-qter. Molecular studies of the deletion breakpoints led to the identification of one subset of 11q terminal deletions (9). In this subset, the deletion was caused by expansion of a CCG – trinucleotide repeat at the site of the deletion breakpoint and consequent expression of the folate-sensitive fragility site (FRA11B) in 11q23.3 (10).

Here, we describe two affected sibs with clinical and cytogenetic features of Jacobsen syndrome (JBS) derived from normal parents by molecular cytogenetics. To our knowledge, this is the first report from Egypt on terminal deletion 11q syndrome.

CLINICAL REPORT

The present family was referred to our Clinical Genetics Clinic, National Research Centre, for genetic counseling because of 3 children with congenital heart disease and delayed physical and mental milestones (Pedigree Fig. 1).

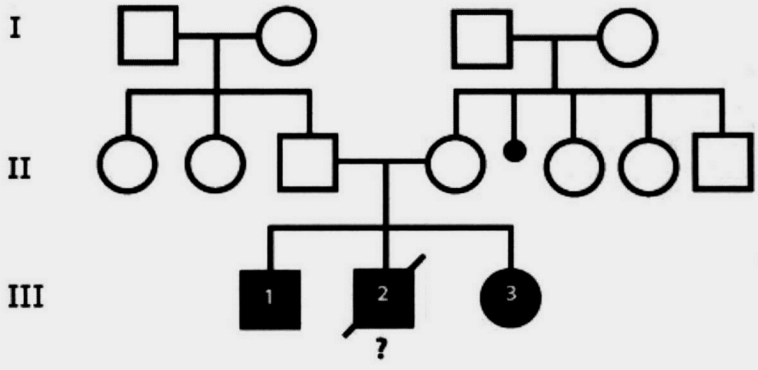

Figure 1: Family Pedigree

PATIENT 1 (III-1) (Fig. 2)

This 6-year-old male, was the first child of a healthy Egyptian non-consanguineous 27 years old mother and 40 years old father. He had 2 affected younger sibs: a sister (III-3, see patient 2) and a brother (III-2). This second boy was born with a low birth weight (1.850 kg, - 3 SD) (Pedigree Fig. 1), and had nearly same facial features as his sister and congenital heart defect in the form of single ventricle. He died at the age of two months, because of the overwhelming cardiac problem without being further investigated.

Patient 1 was born at term after uneventful pregnancy. At birth, weight, length and head circumference were 1.7 kg (- 3.4 SD), 42 cm (- 4.1 SD) and 30 (- 3 SD), respectively. He had cyanosis, and mild respiratory distress that required incubation for a month without artificial ventilation. Echocardiogram revealed restrictive peri-membraneous outlet VSD. Global development delay was noticed by the parents; he sat supported at 3 years, could sit alone at 4 years and walked with support at age 6 years. He recognized his parents, fairly reacted with surrounding, was unable to control urine and stool, and only vocalized two words sentences. History of constipation since early infancy was present which improved over the past year. Frequent upper and lower respiratory tract infections was recorded.

On examination, his weight, height and head circumference were 13.5 kg (-2.8 SD), 97 cm (- 3.4 SD), and 48 cm (- 2.9 SD), respectively. Facial dysmorphism showed hypertelorism, downward slanting pal-

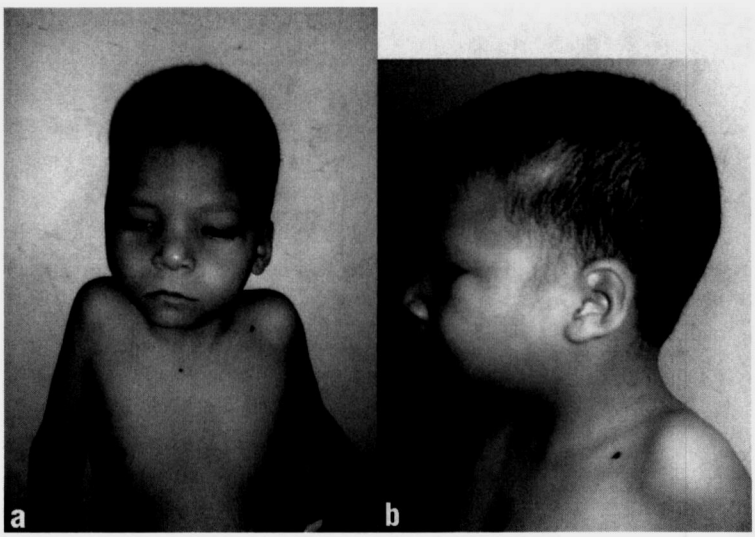

Figure 2: Patient 1: (a) face; (b) profile. Note facial dysmorphism (hypertelorism, downward slanting palpebral fissures, ptosis, sparse eyebrows, broad nasal bridge, thin upper lip and low-set malformed ears) and nevi on the neck and chest

pebral fissures, ptosis, sparse eyebrows, broad nasal bridge, thin upper lip and low-set malformed ears. Few nevi were present on his neck and chest. He had bilateral simian creases, malaligned toes, and bilateral soft tissue syndactyly between the 2nd and 3rd toes. Chest and heart examinations revealed pansystolic murmur over the pericardium. Abdominal examination was normal, while genital examination showed hypoplastic scrotum and bilateral undescended testicles. Hypotonia, normal deep tendon reflexes and intact sensation were present on neurological evaluation.

Investigations revealed patent VSD by echocardiography, normal hearing test, normal bone density using DEXA scan and bilateral inguinal testicles on pelvi-abdominal ultrasound. Complete ophthalmologic assessment showed bilateral ptosis and normal fundi. Blood investigation showed mild thrombocytopenia (98000/mm^3) with normal morphology of the platelets. EEG recorded bilateral focal epileptogenic dysfunction with left side preponderance, although the patient did never experienced seizures. Brain CT showed remarkable white matter hypointensity indicating deep white matter demyelination (Fig. 4). Psychomotor assessment using both Vineland test and Portage program revealed moderate to severe delay in different developmental fields.

PATIENT 2 (III-3)(FIG. 3)

This 3-year-old sister was born at 40 weeks of gestation by Caesarian section, because of breech presentation. Her birth weight, length, and head circumference were 2.15 kg (-2.2 SD), 43 cm (- 3.1 SD) and 30

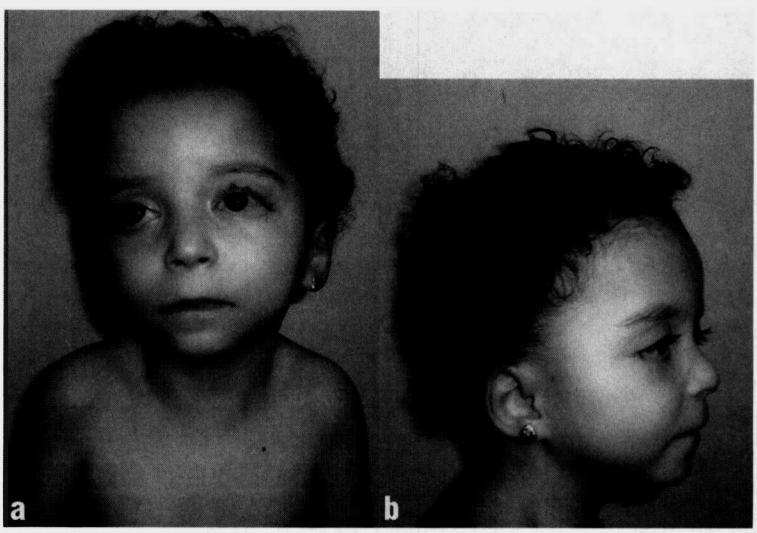

Figure 3: Patient 2: (a) face; (b) profile. Note facial dysmorphism (hypertelorism, downward slanting palpebral fissures, squint, coloboma of right upper eyelid, sparse eyebrows, broad nasal bridge with short nose, thin upper lip and low-set malformed ears)

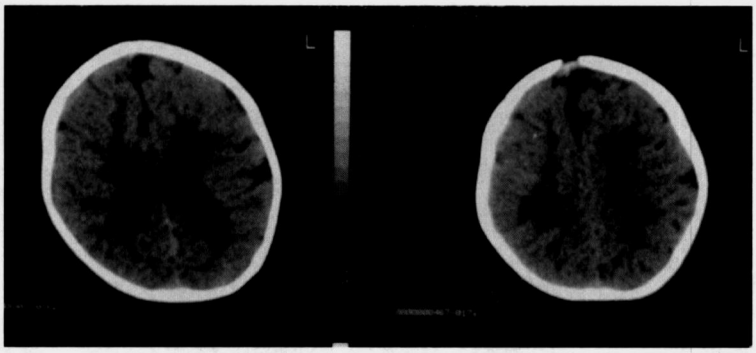

Figure 4: CT scan brain of patient 1 showing hypodensity of white matter in periventricular area indicating white matter demylination

cm (- 2.5 SD), respectively. Congenital heart defect was diagnosed at the age of 14 months. All developmental milestones were delayed; she sat supported at 2 years and at the time of examination she could sit alone for a few minutes. She recognized her parents, was unable to control urine and stool, and vocalized with single syllable words. As her brother, she had chronic constipation since early infancy and suffered from recurrent respiratory tract infections.

On examination, weight, height, and head circumference were 9.5 kg (- 3.1 SD), 78 cm (- 3.9 SD), and 46 cm (- 2.7 SD), respectively. She had dysmorphic features with hypertelorism, downward slanting palpebral fissures, squint, coloboma of right upper eyelid, sparse eyebrows, broad nasal bridge with short nose, thin upper lip, low-set malformed ears and short neck. There were bilateral complete simian creases, and bilateral soft tissue syndactyly between the 2nd and 3rd toes. Abdominal and genital examinations revealed no abnormality. Chest and heart examinations showed pansystolic murmur over the pericardium and accentuated second sound over the pulmonary area. Neurologically, hypotonia, detectable deep tendon reflexes and normal sensation were present.

Recent echocardiogram showed high ostium secundum ASD and perimemberanous VSD. Complete ophthalmologic examination detected normal fundi, exotropia and small coloboma of the right upper eyelid. She also had mild thrombocytopenia (100000/mm^3) with normal platelets morphology. Hearing test, abdominal ultrasound, EEG records and DEXA scan revealed no abnormality. MRI of brain showed hyperintense signal of the white matter on T2W in the periventricular region especially around frontal and occipital horns, with irregular patterns, indicating white matter demyelination (Fig. 5). Psychomotor evaluation was done using Vineland test and Portage program and revealed moderate to severe delay in different developmental fields.

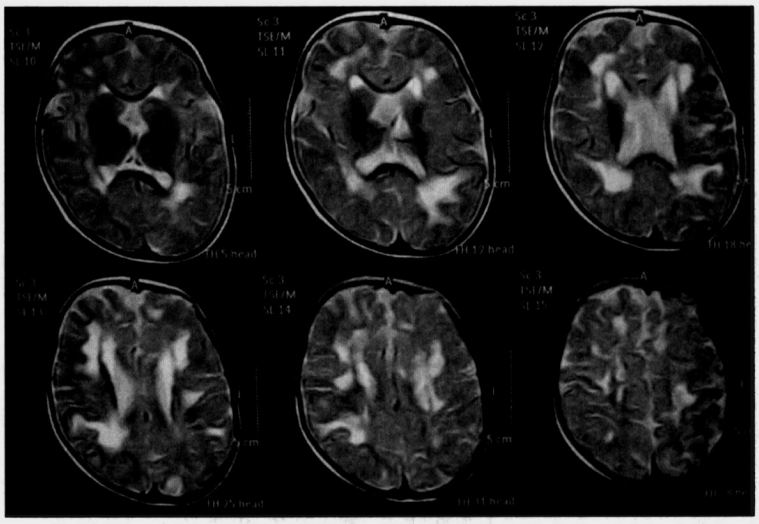

Figure 5: MRI of patient 2: T2W axial cuts showing hyperintense signal of the white matter in the periventricular region especially around frontal and occipital horns indicating white matter demyelination. Note the patchy, irregular shape of demyelination

CYTOGENETICS ANALYSIS

Standard cytogenetic analysis following GTG banding technique was carried out for the two sibs on metaphases derived from phytohemagglutinin (PHA) stimulated peripheral blood lymphocytes by standard methods (20). A total of 50 metaphases were karyotyped and analyzed according to ISCN (7) and revealed deletion 11q23.3-qter of both patients in all metaphases with karyotypes, 46, XY,del 11q23.3-qter and 46, XX,del 11q23.3-qter for the male and female patients, respectively (Fig. 6). Cytogenetic analysis of the parents was done in order to discover the origin of the detectable deletion. Both parents showed normal karyotypes (Fig. 7).

Fluorescence in situ hybridization (FISH) according to the method described by Pinkel *et al.* (17) was performed on metaphases from the two affected children and their parents using whole chromosome painting probes (WCP) for chromosomes 11 (spectrum green). The deletion was confirmed in both sibs (Fig. 8) and the normal karyotype was confirmed in both parents (Fig. 9). FISH using telomeric probes of chromosome 11 were done to exclude an interstitial deletion. Both patients showed a terminal deletion (Fig. 10) and their parents were normal (Fig. 11).

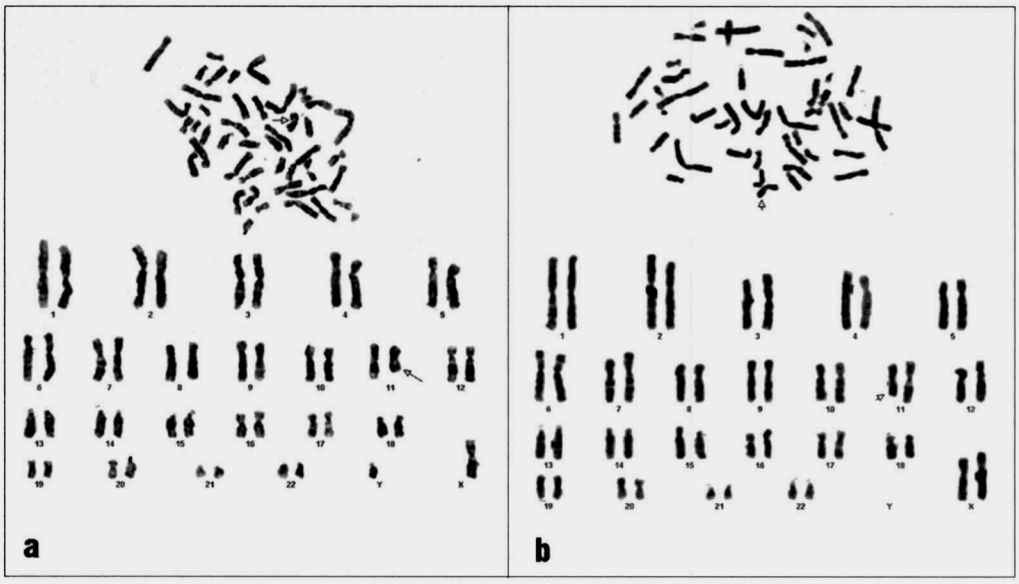

Figure 6: Karyotype of the probands: (a) karyotype of patient 1 showing 46,XY,del(11)(q23-ter); (b) karyotype of patient 2 showing 46,XX,del(11)(q23-ter)

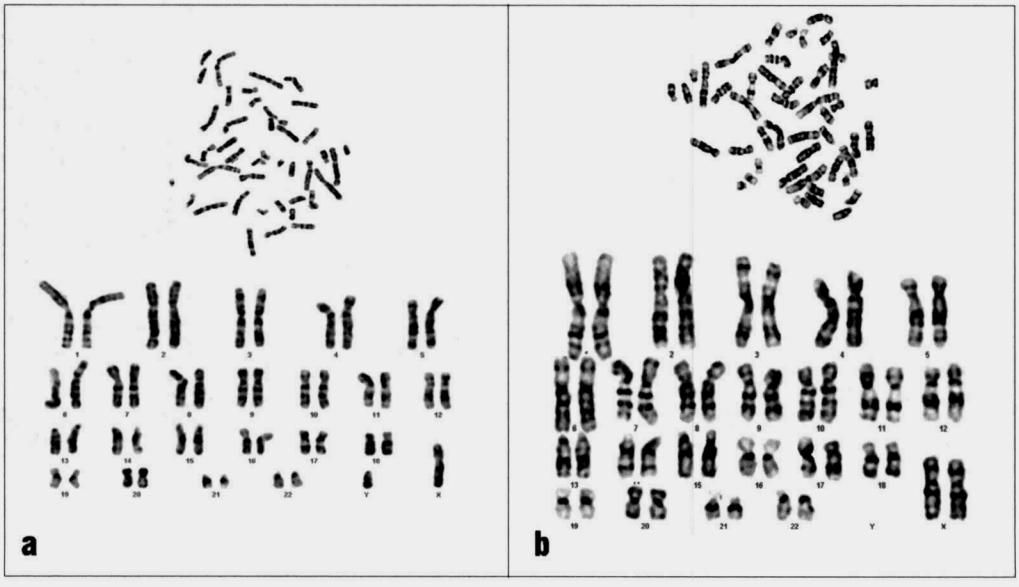

Figure 7: Karyotype of the parents showing (a) karyotype of father 46,XY; (b) karyotype of mother 46,XX.

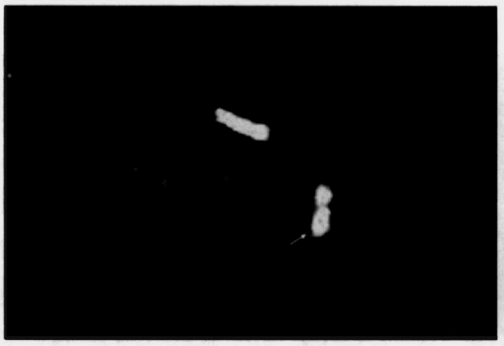

Figure 8: Fluorescent In Situ Hybridization (FISH) on metaphase using WCP of chromosome 11 (arrow) showing terminal deletion in chromosome 11q of patient 1.

Figure 9: Fluorescent In situ hybridization (FISH) on metaphase using WCP of chromosome 11 (arrow) showing normal chromosome 11 of mother.

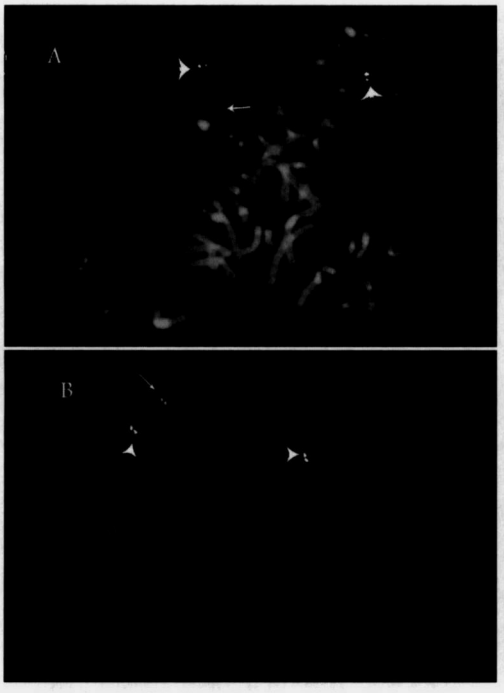

Figure 10: Fluorescent In Situ Hybridization (FISH) using telomeric probe of chromosome 11p (arrowhead) and 11q (arrow) showing deletion of the telomeric (terminal) region of 11q in patient 1 (A); and patient 2 (B).

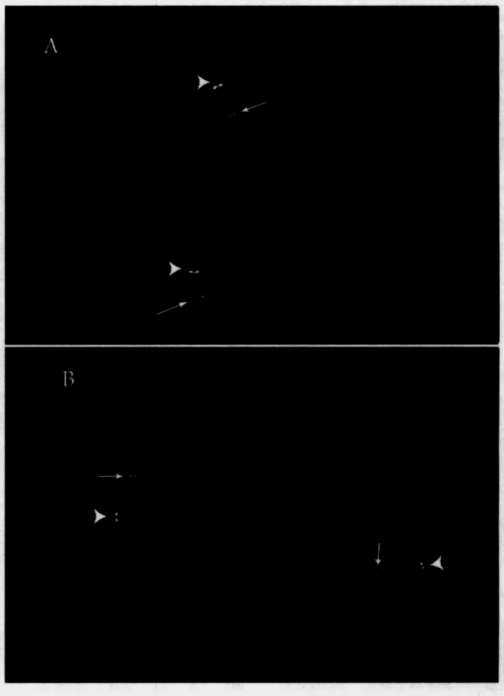

Figure 11: Fluorescent In Situ Hybridization (FISH) using telomeric probe of chromosome 11p (arrowhead) and 11q (arrow) showing normal chromosome 11 in father (A); and mother (B).

DISCUSSION

Jacobsen syndrome is a rare, but known syndrome caused by a partial terminal deletion of the distal long arm of chromosome 11. Grossfeld *et al.* (5) have reviewed the clinical features of 110 patients with 11q terminal deletion disorder, demonstrating the phenotypic variability associated with this condition.

We describe the first Egyptian patients with Jacobsen syndrome. Two sibs (male and female) had identical distal 11q monosomy (del11q23.3-qter). Both patients had facial dysmorphism with hypertelorism, sparse eyebrows, broad nasal bridge with short nose, thin upper lip, and low-set malformed ears. Their facial features are quite similar to the published features (12, 13, 19). Moreover, patient 1 had nevi on the neck and chest comparable with the report of Giampietro *et al.*(4).

Bilateral normal fundi were detected on ophthalmological examination of both patients. Also, bilateral ptosis was noted in patient 1, and squint with right upper eyelid coloboma in patient 2. Various eye anomalies have been reported in patients with JBS (11).

Echocardiac examination demonstrated an isolated VSD in patient 1, while patient 2 had ASD and VSD. The late male sib (patient III-2) had single ventricle. Previous studies have demonstrated that, over half the $11q^-$ patients had congenital heart defects (CHD) (16, 22). One third of these patients had so called "flow defects", which included left sided obstructive lesions and isolated ventricular septal defects. The other two thirds of patients had wide spectrum of heart defects. CHD is considered the major cause of lethality in this syndrome as in patient (III-2) who died at 2 months of age.

Genital anomalies were reported in 58% of JBS patients. Patient 1 had a hypoplastic scrotum and bilateral undescended testes (5).

Psychomotor delay and short stature are common features of JBS (6). Both patients had muscular hypotonia, low birth weight and short stature. Their physical and mental development was moderately to severely delayed. Previous publications (5, 22) have demonstrated a strong correlation between the deletion size and the severity of developmental delay. However for other phenotypes e.g. congenital heart defects, the genotype/phenotype relationship is less clear.

Previous neuroimaging studies of patients with JBS reported multiple pathological white matter changes in the frontotemporal and periventricular regions, and mild global brain atrophy (1, 14, 23). However, proton magnetic resonance spectroscopy detected slight reduction of all metabolites in gray matter (1). Brain neuroimaging of our patients revealed white matter demyelination in both of them.

Thrombocytopenia is a common feature in JBS (2). Laboratory inves-

tigations revealed mild thrombocytopenia with normal platelets morphology in both sibs. However, recently several adolescent age patients with distal 11q monosomy had normal platelets counts (5).
Some authors reported hearing loss in their patients (3, 18), moreover, Giampietro *et al.* (4) detected hearing loss and osteopenia in their 13-year old patient. The hearing test and DEXA scan of our two patients revealed no abnormality. A possible explanation may be, that hearing loss and osteopenia developed in older patients.
Chronic constipation and frequent respiratory tract infections are common associations with JBS, as they were reported in 42% and 58% of patients, respectively (2, 5). Both our patients complained of chronic constipation and repeated respiratory infections.
The idea of comparing the clinical and cytogentic data of patient 1 with that of patient 2 seemed interesting. Since approximately three quarters of the reported Jacobsen patients were females, a comparison between our two cases with identical distal 11q monosomy and were of opposite sexes, accompanied by review of published cases (1, 4, 5, 12, 13, 19, 22), was expected to show some interesting findings. However, no apparent gender-linked difference could be detected.
Interestingly, the cytogenetic analysis of the probands' parents using G-banding-technique and FISH revealed normal karyotype. However, they had three children, two of which proved to have JBS. The third child had low birth weight, dysmorphic similar facial features, single ventricle and died at the age of 2 months. Therefore, it seems that he also had JBS. Jones *et al.* (9, 10) reported the colocalization of JBS breakpoints with the inherited folate-sensitive site FRA11B, at 11q23.3. Hence, inheritance of an expanded p(CCG)n trinucleotide repeat at this folate-sensitive fragile has been implicated in the generation of chromosome breakpoint at 11q23.3 in several JBS patients, especially in patients with large deletions. It is tempting to speculate that there is an expanded CCG repeat in the parents of our patients.

In summary, we described the first Egyptian cases with Jacobsen syndrome. The occurrence of distal 11q monosomy in two children of parents with normal karyotype may support the suggestion that a familial folate-sensitive 11q23.3 fragility carried by the parents, is the cause of the breakpoint. We recommend professionals managing individuals with 11q deletion considering hearing evaluation and DEXA scan every 6-12 months to check for possible development of hearing loss and osteopenia. Furthermore, a karyoptype / phenotype correlation may emerge after exact analyses of the growing number of patients using recent molecular cytogenetic tools.

RERERENCES

1. *BOHM D., HOFFMANN K., LACCONE F., WILKEN B., DECHENT P., FRAHM J., BARTELS I., BOHLANDER S.K.*: Association of Jacobsen syndrome and bipolar affective disorder in a patient with a de novo 11q terminal deletion. *Am. J. Med. Genet.*, 2006, *140A*, 378-382.

2. *FAVIER R., DOUAY L., ESTEVA B., PORTUOI M.F., GAULARD P., LECOMPTE P., PEROT C., ADAM M., LECRUBIER C., VAN DER AKKER J.*: A novel genetic thrombocytopenia (Paris-Trousseau) associated with platelet inclusions, dysmegakaryopoiesis and chromosome deletion at llq23. *Acad. Sci.*, 1993, *316*, 698-701.

3. *FRYNS J.P., KLECZKOWSKA A., SMEETS B., VAN DEN BERGHE H.*: Distal llq deletion: A specific clinical entity. *Helv. Paediatr. Acta.*, 1987, *42*, 191-194.

4. *GIAMPIETRI P.F., BABU D., ZABEL C., SILBERMAN T., ZADOR I., DEBAUCHE D., RAVNAN J.B., DAVE B.J.*: Novel clinical features in a child with partial deletion of chromosome 11 [del (11)(q24.2)]: Further evidence for phenotypic heterogeneity. *Am. J. Med. Genet.*, 2006, *140A*, 385-287.

5. *GROSSFELD P.D., MATTINA T., LAI Z., FAVIER R., JONES K.L., COTTER F., JONES C., THE 11 q CONSORTIUM:* The 11q terminal deletion disorder: A prospective study of 110 cases. *Am. J. Med.. Genet.*, 2004, *129A*, 51-61.

6. *HAGHI M., DEWAN A., JONES K.I., REITZ R., JONES C., GROSSFELD P.*: Endocrine abnormalities in patients with Jacobsen (11q-) syndrome. *Am. J. Med. Genet.*, 2004, *129A*, 62-63.

7. *ISCN.*: *An International System of Human Cytogenetic Nomenclature*. Mitelman F. (Ed.). Basel, Karger, 2005.

8. *JACOBSEN P., HAUGE M.,HENNIGSEN K.,HOBOLTH N., MIKKELSEN M., PHILIP J.*: An (11;21) translocation in four generations with chromosome 11 abnormalities in the offspring. A clinical, cytogenetic and gene marker study. *Hum. Hered.*, 1973, *23*, 568-585.

9. *JONES C., PENNY L., MATTINA T., YU S., BAKER E., VOULLAIRE L., LANGDON W.Y., SUTHERLAND G.R., RICHARDS R.I., TUNNACLIFFE A.*: Association of a chromosome deletion syndrome with a fragile site within the proto-oncogene CBL2. *Nature*, 1995, *376*, 1451-149.

10. *JONES C., MULLENBACH I.I., GROSSFELD P., AUER R., FAVIER R., CHIEN K., JAMES M., TUNNACLIFFE A., COTTER F.*: Co-localisation of CCG-repeats and chromosome deletion breakpoints in Jacobsen syndrome: Evidence for a common mechanism of chromosome breakage. *Hum. Mol. Genet.*, 2000, *9*, 1201-1208.

11. *LEE W.E., O'HALLORAN H.S., GROSSFELD P.D., SCHER C., JOCKIN Y.M., JONES C.*: Ocular findings in Jacobsen syndrome. *J. A.A.P.O.S.*, 2004, *8*, 141-145.

12. *LONDON DYSMORPHOLOGY AND NEUROGENETICS DATABASES:* version 1.0.10., 2007. Oxford University Press. http://www.lmdatabases.com

10. Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD). World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/

14. *ONO J., HARADA K., HASEGAWA T., SAKURAI K., KODAKA R., TANABE Y., TANAKA J., IGARASHI T., NAGAI T., OKADA S.*: Central nervous system abnormalities in chromosome deletion at 11q23. *Clin. Genet.*, 1994, *45*, 325-329.

15. *PENNY L.A., DEL AQUILA M., JONES M.C., BERGOFFEN J.A., CUNNIFF C., FRYNS J.P., GRACE E., GRAHAM J.M., KOUSSEF B., MATTINA T.*: Clinical and molecular characterization of patients with distal 11q deletions. *Am. J. Hum. Genet.*, 1995, *56*, 676-683.

16. *PHILLIPS H.M., RENFORTH G.L., SPALLATO C., HEARN T., CURTIS A.R., CRAVEN I., HAVARANI B., CLEMENT-JONES M., ENGLISH C., STUMPER O., SALMON T., HUTCHINSON S., JACKSON M.S., WILSON D.I.*: Narrowing the critical region within 11q24-qter for hypoplastic left heart and identification of a candidate gene, JAM3, expressed during cardiogenesis. *Genomics*, 2002, *79*, 475-478.

17. *PINKEL D., LANDEGENT J., COLLINS C.*: Fluorescence in situ hybridization with human chromosome specific libraries: Detection of trisomy 21 and translocations of chromosome 4. *Proc. Natl. Acad. Sci. U.S.A.*, 1988, *85*, 9138-9142.

18. *PIVNICK E.K., VELAGALETI G.V., WILROY R.S., SMITH M.E., ROSE S.E., TIPTON R.E., THARAPEL A.T.*: Jacobsen syndrome: Report of a patient with severe eye anomalies, growth hormone deficiency, and hypothyroidism associated with deletion 11 (q23q25) and review of 52 cases. *J. Med. Genet.*, 1996, *33*, 772-778.

19. *POSSUM PROGRAM:* version 5.7.3 for windows, Murdoch Children's Research Institute, Australia, 2006. http://www.possum.net.au

20. *VERMA R.S., BABU A.: Human Chromosomes: Principal and Techniques.* 2nd ed. New York, San Francisco, Mc Graw-Hill Inc., 1995.

21. *VOULLAIRE L.E., WEBB G.C., LEVERSHA M.A.:* Chromosome deletion at 11q23 in an abnormal child from a family with inherited fragility at 11q23. *Hum. Genet.*, 1987, *76*, 202-204.

22. *WENGER S.L., GROSSFELD P.D., SIU B.L., COAD J.E., KELLER F.G., HUMMEL M.*: Molecular characterization of an 11q interstitial deletion in a patient with the clinical features of Jacobsen syndrome. *Am. J. Med. Genet.*, 2006, *140A*, 704-708.

23. *ZAHN S., EHRBRECHT A., BOSSE K., KALSCHEUER V., PROPPING P., SCHWANITZ G., ALBRECHT B., ENGELS H.:*. Further delineation of the phenotype maps for partial trisomy 16q24 and Jacobsen syndrome by a subtle familial translocation t(11;16)(q24.2;q24.1). *Am. J. Med. Genet.*, 2005, *139A*, 19-24.

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