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CASE REPORT

A Rare Case of a Male Infant with Down-Turner Syndrome and Review of Cases

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ABSTRAK

Individu dengan dua aneuploidi sindrom Down-Turner adalah amat jarang ditemui dan penemuan terkini menunjukkan kurang dari 50 kes dilaporkan dari seluruh dunia. Kami melaporkan satu kes bayi lelaki yang mempunyai ciri-ciri klinikal yang mempunyai keabnormalan pada mata, hidung, dada serta makroglosia. Berdasarkan dari ciri-ciri tersebut, beliau telah didiagnosis mengalami sindrom down. Sampel darah periferi beliau telah diambil dan dihantar untuk analisa kromosom bagi pengesahan. Analisa kromosom dari kultur sel limfosit beliau menunjukkan mosaik dengan dua jenis aneuploidi iaitu monosomi X dalam 31 metafasa dan trisomy 21 dalam 14 metafasa: (45,X[31]/47,XY,+21[14]). Analisa selanjutnya dengan Fluorescence In Situ Hybridisation (FISH) menggunakan Vysis LSI SRY Spectrum Orange/CEP X Spectrum Green Probe dan Vysis CEP Y Spectrum Aqua Probe, serta Vysis LSI 21 Spectrum Orange Probe ke atas sel-sel (interfasa dan metafasa) mengesahkan kehadiran dua jenis sel abnormal tersebut (81% adalah monosomi X, 19% trisomy 21) pada pesakit ini. Ultrabunyi pada bahagian pelvik pesakit menunjukkan testes yang normal dan tiada uterus, ovari dan vagina dikesan. Berdasarkan pengetahuan kami setakat ini, ini merupakan kes sindrom Down-Turner yang pertama dilaporkan di Malaysia. Kesimpulannya, kes ini menunjukkan kepentingan karyotip pewarnaan-Giemsa dan analisa FISH sebagai kaedah diagnostik bagi mengenal pasti keabnormalan kromosom serta mengetahui nisbah sel-sel normal:abnormal pada pesakit. Bibliografi anotasi beserta dengan karyotip bagi kes-kes sindrom Down-Turner yang telah dilaporkan sebelum ini disertakan dalam laporan ini.

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Kata kunci: dua aneuploidi, Fluorescence In Situ Hybridization, keabnormalan kromosom, sindrom Down-Turner

ABSTRACT

Individuals with double aneuploidy of Down-Turner syndrome are very rare and to date, fewer than 50 cases have been reported, worlwide. We report a case of a male infant who presented with dysmorphic features of upslanting eyes, flat nasal bridge, wide spaced nipples and macroglossia. Based on the clinical features, he was diagnosed with Down syndrome. His peripheral blood sample was taken and sent for cytogenetic analysis for confirmation. Chromosome analysis of his lymphocyte cell culture revealed a mosaic pattern of double aneuploidy with monosomy X identified in 31 metaphases and trisomy 21 in 14 metaphases: (45,X[31]/47,XY,+21[14]). Further analysis with fluorescence *in situ* hybridization (FISH) using Vysis LSI SRY Spectrum Orange/CEP X Spectrum Green Probe and Vysis CEP Y Spectrum Aqua Probe and Vysis LSI 21 Spectrum Orange Probe performed on the cells (nuclei and metaphases) has confirmed the presence of the abnormal two cell lines (81% monosomy X and 19% trisomy 21) in the patient. Ultrasound investigations of his pelvic region showed normal testes and no evidence of uterus, ovary or vagina. To the best of our knowledge, this is the first Down-Turner syndrome reported in Malaysia. In conclusion, this case demonstrates the importance of Giemsa-banded karyotype and FISH analyses as diagnostic tools in identifying the chromosomal abnormality and determining the ratio of the normal:abnormal cells present in the patient. An annotated bibliography of earlier reported cases of Down-Turner with documented karyotyping is also included in this report.

Keywords: chromosome abnormality, Down-Turner syndrome, double aneuploidy, fluorescence *in situ* hybridization

INTRODUCTION

Aneuploidies are caused by chromosome non-disjunction which can occur during meiosis (in the formation of gametes) or during mitosis (after fertilization of gametes). Approximately 0.3% of liveborns are aneuploid with trisomy 21 (Down syndrome) being the most frequently found (Hassold et al. 1996). In Malaysia, the incidence of Down syndrome in one of the largest government hospital was 1:959 with the highest incidence reported among the Malays 1:981, followed by the Chinese 1:940 and Indians 1:860 (Hoe et al. 1989). Turner syndrome (TS) is a rare sex chromosome disorder (1 in 2500 livebirths), caused by loss of part or all of an X chromosome. Monosomy X is the most common

(~45%) karyotype in TS patients. Other types of chromosomal abnormalities associated with TS include 45, X mosaicism, isochromosome Xq, ring X chromosome, Xp or Xq deletion, Y-chromosome mosaicism.

Double aneuploidy in an individual is very rare and the underlying mechanism still remains unclear. It is hypothesized that double aneuploidy results either from two nondisjunctional events in gametogenesis or a single nondisjunctional event in a trisomic zygote (Reddy 1997). It has also been shown that the most frequently involved chromosomes in double aneuploidies are the sex chromosomes and acrocentric chromosomes. An example is Down-Turner syndrome which is very rare and was estimated to occur with a frequency of ~1 in 2 million births (Musarella & Verma 2001). Other types of aneuploidy that have been reported to simultaneously occur with Down syndrome include Down-Klinefelter, Patau/Down, Edwards/Down, 47,XXX/Down, 47,XYY/Down (Soylemez 2015).

Here, we report a case of an infant who presented with clinical features of Down syndrome. With the combination of Giemsa-banding (G-banding) karyotyping and fluorescence in situ hybridisation (FISH) analysis using locus specific probes, we were able to identify mosaic Down-Turner syndrome in the patient. To the best of our knowledge, this maybe the first case reported in Malaysia.

CASE REPORT

The proband was a one-month-old Malay male infant, born at term with a birth weight of 3.05 kg. He was the second child of healthy non-consanguineous parents. The mother was 31-years-old and the father was 33-years-old. He had an elder brother who was also well and healthy. There was no family history of dysmorphism or learning difficulties. The patient was referred to our clinic due to soft dysmorphism of Down syndrome which include upslanting eyes, flat nasal bridge, wide spaced nipples and macroglossia. His blood test showed a normal level of thyroid-stimulating hormone (TSH). However, free T4 was slightly high (19.86 pmol/L; normal range 9-19.05 pmol/L). Ultrasound investigation on his pelvis region showed no uterus, ovary or vagina. Both testes are seen within the scrotum with normal size and echo pattern. No focal lesion or abnormal calcification. However, both testes were occasionally seen ascending to the inguinal region upon scanning. Right testis measured 0.6cm x 1.0cm x 1.4cm. Left testis measures 0.9cm x 0.7cm x 1.4cm. There was no hydrocele, bilaterally. Findings of ultrasound of his urinary tract showed no evidence of urinary tract anomaly in both kidneys.

His peripheral blood sample was taken and sent for cytogenetic analysis to confirm the clinical diagnosis of Down syndrome. In brief, the sample was cultured in RPMI medium with folic acid which contain fetal calf serum (15%), phytohemagglutinin (2%), L-glutamine 200 nM (1%), for 72 hours at 37˚C. The cells were harvested by the addition of 100 µl colchicine solution, 40 minutes before the 72nd

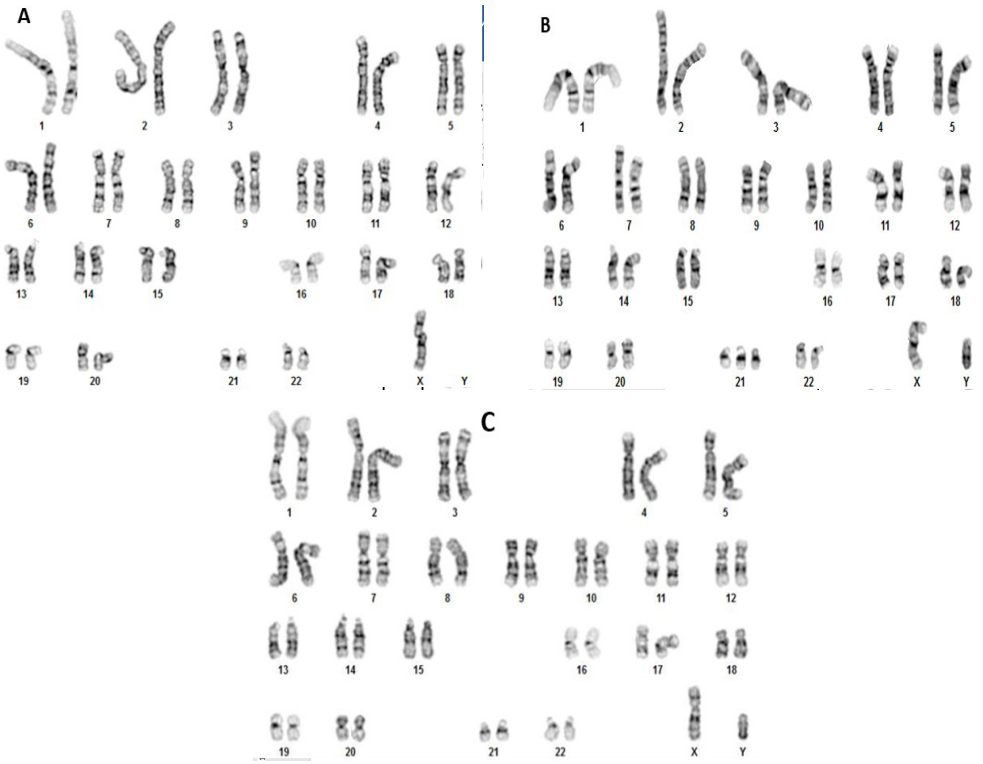

Figure 1: G-banded karyotype of the patient showing double aneuploidies in his karyotype. (A) monosomy X (45,X) and (B) trisomy 21 (47,XY,+21) (C) Karyotype of a normal male for comparison

hour. The cells were then centrifuged at 1,000 rpm for five minutes, submitted to a hypotonic solution of KCl (0.0075 M), and fixed with fixative solution (3 methanol: 1 acetic acid). The cells were then dropped on glass slides and ready for staining. Giemsa trypsin banding (GTG-banding) method was performed on the metaphases using 2% Giemsa solution for approximately 5 minutes. Band analysis was undertaken by image capturing using the system Applied System Imaging®, attached to the light microscope that identifies the number of bands by metaphase, where they were captured with a magnification of 1,000. Chromosome analysis on 45 G-banded metaphases at 450-500 bphs (bands per haploid set) revealed a mosaic pattern of double aneuploidy with monosomy X identified in 31 metaphases and trisomy 21 in 14 metaphases: (45,X[31]/47,XY,+21[14]) (Figure 1). Further analysis with fluorescence *in situ* hybridization (FISH) using Vysis LSI SRY Spectrum Orange/CEP X Spectrum Green Probe and Vysis CEP Y Spectrum Aqua Probe, and Vysis LSI 21 Spectrum Orange Probe performed on 100 cells (nuclei and metaphases) confirmed the presence of the two cell lines; about 81% of the cells were monosomy X (45,X) and the remaining were trisomy 21 (Figure 2).

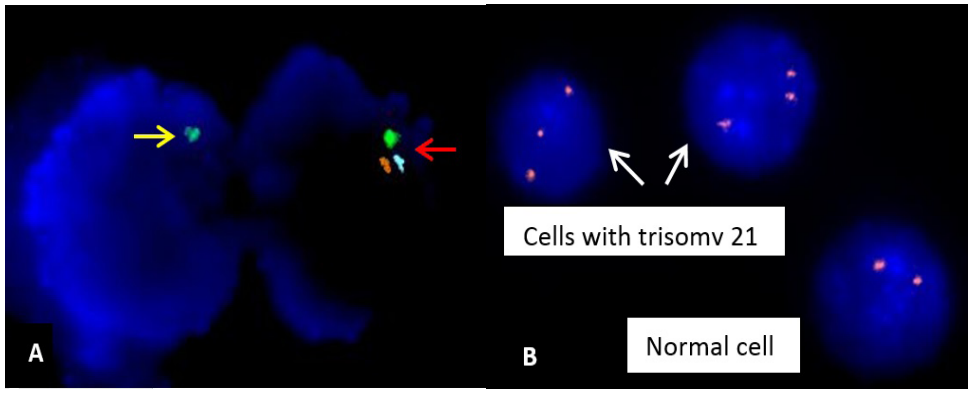

Figure 2: FISH analysis performed on the patient's sample showing the presence of two different cell lines (mosaic). (A) Results of hybridisation using probes for CEPX (Spectrum Green), CEPY (Spectrum Aqua) and SRY (Spectrum Orange) revealed two different types of cells; one with monosomy X (yellow arrow) while the other with chromosome X, Y and SRY (red arrow). (B) Hybridisation using probe LSI 21 (Spectrum Orange) identifies cells with three and two copies of chromosome 21, indicating the abnormal cell with trisomy 21 and the normal cell with two copies of chromosome 21, respectively.

DISCUSSION

In addition to intellectual disability, which is seen in all Down syndrome patients, congenital anomalies involving cardiac, eye, ear, immune system, gastrointestinal, genitourinary tract were also seen in the patients, although some of the features are more common than the others (So et al. 2007; Davidson 2008; Bull et al. 2011; Faizah et al. 2011).

Among the first few reports of Down-Turner syndrome, Cohen and Davidson (1972) hypothesized that the syndrome arose as a result of two simultaneous postzygotic non-disjunctional events within a single cell leading to two leucocyte stem lines: 47,XX,+21 and 45,X. There are two interesting features of our patient that we would like to highlight in this report. Although the population of trisomy 21 cells are lower (~19%) compared to monosomy X (~81%), our patient had typical features of Down syndrome (upslanting eyes, flat nasal bridge, wide spaced nipples and macroglossia), except wide spaced nipples, which is a common feature in Turner syndrome. Apparently, in Down-Turner syndrome, the proportion of trisomy 21 versus monosomy X cells does not always correlate with the phenotype, which can probably be explained by a different mosaic distribution in various somatic tissues, e.g. a mosaic Down-Turner syndrome patient was shown to have a mosaic karyotype 45,X/46,X,+21/47,XY,+21 from his blood lymphocytes culture but a different mosaic karyotype 45,X/47,XY,+21 was found from his skin fibroblast culture (Van Buggenhout 1994). In the present patient, we only performed chromosome analysis from the sample of his peripheral blood lymphocytes. Hence, we were not able to comment whether a different mosaic distribution could be found

from other tissues of his body.

Another interesting finding was that the present patient was phenotypically male although the main clone is monosomy X (45,X). It is well documented that individual with monosomy X (45,X) are always phenotypically female. This present case demonstrates that the presence of SRY gene on the normal Y chromosome (from the 47,XY,+21 cells), although in minority of the cells, is responsible for a normal development of male gonads (testes) and prevents the development of female reproductive structures. This was also consistent with the result of his pelvic ultrasound which showed the presence of normal testes and no evidence of female reproductive organs.

We reviewed the literature on reported cases of Down-Turner syndrome to compare with our present case (Table 1). In total, 47 cases were reported including this present report. Most of the cases are mosaics (41 out 47 cases, ~87%). Mosaics with two cell lines were seen in 29 cases, mosaics with three or four cell lines were observed in 12 cases and the remaining 6 cases were monoclonal (non-mosaic) (cases 12, 27, 33, 37, 38 and 46) . Of the total 47 cases, 36 were female, 8 were male and the remaining 3 cases were ambiguous. Twenty six patients were found to have the typical features of pure Down syndrome while the remaining 21 cases showed both features of Down and Turner syndromes. Interestingly, none of the reported cases showed features of a pure Turner syndrome as characterised by short stature, delayed sexual development, low posterior hairline, shield chest, multiple pigmented naevi, cubitus valgus, and webbing of the neck. Thus, clinical features of Down syndrome were always observed in Down-Turner syndrome patients (mosaics or monoclonal), irrespective of the proportion of trisomy 21 cells present in their karyotype.

Other than double aneuploidy, structural abnormality involving X chromosome and chromosome 21 had also been reported in Down-Turner syndrome (cases 12, 15, 27, 30, 36, 43 and 46). The abnormality include deletion of p or q arm of X chromosome (cases 12, 15, 27, 43), isochromosome X (case 30), isochromosome 21 (case 36) and ring X (case 46).

Of the 36 cases without Y chromosome, all except 1 (case 22) showed female phenotype. Eight of the 11 cases with Y chromosome were phenotypically male (cases 8, 16, 19, 29, 35, 41, 44, 47) while two showed ambiguous genitalia (cases 20 and 26) and 1 was phenotypically female (case 45). These were in accordance with the observation that patients with mosaic Turner have a wide spectrum of phenotype ranging from female with mixed gonadal dysgenesis, male pseudohermaphroditism, normal male and normal female.

CONCLUSION

This case demonstrated the importance of cytogenetic as a diagnosis tool in detecting chromosomal abnormality in patients who presented with abnormal phenotype and learning disability. With the combination of G-banding

Table 1: Published reports of Down-Turner syndrome including the present case.

Case no.	References (Year)	Karyotype	Phenotype	Genitalia
1	Medenis et al. (1962)	46,X,+G/47,XX,+G	Down	F
2	Van Wijck et al. (1964)	46,X,+G/47,XX,+G	Down	F
3	Zergollern et al. (1964)	46,X,+G/47,XX,+G/48,XXX,+G	Down	F
4	Root et al. (1964)	46,X,+G/47,XX,+G	Down	F
5	Baguena Candela et al. (1966)	46,XX/46,X,+G	Down	F
6	Baguena Candela et al. (1966)	46,X+G/47,XX,+G	Down	F
7	Feiertag-Koppen et al. (1966)	45,X/46,X,+G/46,XX/47,XX,+G	Down	F
8	Edgren et al. (1966)	45,X/46,XY/47,XY,+21	Down	M
9	van Gelderen et al. (1967)	46,X,+G/46,XX/47,XX,+G	Down-Turner	F
10	Pfeiffer et al. (1968)	46,X,+21/47,XX,+21	Down	F
11	Taylor (1970)	45,X/47,XX,+G	Down-Turner	F
12	Luthardt et al. (1971)	47,X,Xq-,+21	Down	F
13	Grosse et al. (1971)	46,XX/45,X/47,XX,+G	Down	F
14	Cohen and Davidson (1972)	45,X/47,XX,+21	Down	F
15	Mikel'saar et al. (1971)	47,XX,+21/47,XXp-q-,+21	Down-Turner	F
16	Prieur et al. (1972)	45,X/47,XY,+21	Down	M
17	Barakat et al. (1973)	45,X/47,XX,+G	Down	F
18	Hustinx et al. (1974)	45,X/47,XX,+21	Down	F
19	Hustinx et al. (1974)	45,X/47,XY,+21	Down-Turner	M
20	Mello et al. (1974)	46,X,+21/47,XY,+21	Down-Turner	A
21	Osborne et al. (1975)	45,X/46,X,+G/46,XX/47,XX,+G	Down-Turner	F
22	Villaverde et al. (1975)	45,X/46,X,+G/47,XX,+G	Down-Turner	A
23	Townes et al. (1975)	45X/46,X,+21	Down-Turner	F
24	Osborne et al. (1975)	45,X/46,X,+G/46,XX/47,XX,+G	Down	F
25	Singh et al. (1974)	46,X,+21/46,XX/47,XX,+21	Down	F
26	Yeung et al. (1976)	46,X,+21/47,XY,+21	Down-Turner	A
27	Martsolf et al. (1977)	47,X,del(X)(p11),+21	Down-Turner	F
28	Chen et al. (1978)	45,X/48,XXX,t(2;21)	Down	F
29	Sparagana et al. (1980)	45,X/46,XY/47,XY,+21	Down	M
30	MacFaul et al. (1981)	46,X,+21/47,X,i(X),+21	Down	F
31	MacFaul et al. (1981)	46,X,+21/47,XX,+21	Down-Turner	F
32	Gatrad (1981)	46,X,+21/47,XX,+21	Down-Turner	F
33	Ikonen et al. (1989)	46,X,+21	Down	F
34	Jansen et al. (1991)	45,X/47,XX,+21	Down-Turner	F
35	Van Buggenhout et al. (1994)	45,X/46,X,+21/47,XY,+21	Down-Turner	M
36	Digilio et al. (1994)	45,X/46,XX,i(21q)	Down-Turner	F
37	Ruangdaraganon et al. (1993)	46,X,+21	Down	F
38	Jarurantanasirikul et al. (1995)	46,X,+21	Down	F

Case no.	References (Year)	Karyotype	Phenotype	Genitalia
39	Harada et al. (1998)	45,X/47,XX,+21	Down-Turner	F
40	Musarella et al. (2001)	45,X/47,XX,+21/46,XX/47,XXX	Down	F
41	Zaki et al. (2005)	45,X/47,XY,+21	Down-Turner	M
42	Zaki et al. (2005)	46,X,+21/47,XX,+21	Down-Turner	F
43	Jeong et al (2005)	47,X,del(X)(p11),+21/47,XX,+21	Down-Turner	F
44	Ryu et al. (2010)	45,X/47,XY,+21	Down	M
45	Bergamaschi et al. (2012)	45,X/47,XY,+21	Down-Turner	F
46	Manassero-Morales et al. (2016)	47,X,r(X),+21	Down-Turner	F
47	Salwati et al. (present case)	45,X/47,XY,+21	Down	M

M: male; F: female; A: ambiguous; G: G-group chromosomes

karyotype and FISH, we were able to identify Down-Turner syndrome in a patient who was clinically diagnosed with Down syndrome.

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