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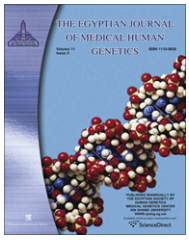

CASE REPORT

Baraitser–Winter syndrome: An additional Arab patient

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KEYWORDS

Baraitser–Winter syndrome;
Eye coloboma;
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Abstract An Arab child is presented herein with a phenotype that fits the rare Baraitser–Winter syndrome. Her clinical features included a unilateral iris coloboma, ptosis, hypertelorism, epicanthic folds, broad nasal bridge, full cheeks, pointed chin, low set abnormal ears and short neck. In addition, she had cardiac defect, previously undescribed brain anomaly, seizures, hypotonia and developmental delay. Chromosomal analysis of the peripheral lymphocytes and FISH study revealed a normal 46, XX karyotype. To date, Baraitser–Winter syndrome has only been reported in 19 patients of different ethnic families. The present case adds a new finding to the spectrum of malformations published before.

1. Introduction

Baraitser–Winter syndrome (OMIM 243310); was first described in sibs of unrelated parents as a combination of iris coloboma, bilateral ptosis, hypertelorism, broad nasal bridge, prominent epicanthic folds, growth and mental retardation [1]. Since then, 19 more cases had been reported showing characteristic clinical features resembling that of Baraitser–Winter syndrome [2–13]. Consequently, the phenotypic spectrum had been broadened including; microcornea, microphthalmia, microcephaly, trigonocephaly, gyral malformation, seizures, hypotonia, cardiac, urogenital, and skeletal defects. The precise genetic mechanism behind this syndrome is not identified so far. It has been postulated that mutation in the PAX-8 gene, which maps to 2q12–q14, may be responsible for the malformations in this syndrome [8]. This was because of the two cases that had been reported with pericentric inversions of chromosome 2; involving 2p12–q14, which were inherited from phenotypically normal mothers [2,3]. Moreover, the presence of affected siblings in two of the previously reported families [1,10], supported by the familial consanguinity in other reports [4,10], suggested an autosomal recessive inheritance.

2. Case report

The proband was the first child of a healthy unrelated young couple. She was the product of a mixed marriage between an Egyptian mother and a Kuwaiti father. She had one normal younger sister and the family history was unremarkable. She was born after a normal pregnancy and a non-complicated

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delivery at 38 weeks of gestation. Birth weight was 2750 g (10th centile), length 51 cm (75th centile), and head circumference 35.5 cm (90th centile). Apgar score was 9 and 10 at 5 and 10 min, respectively. At birth the following anomalies were noted: hypertelorism, epicanthic folds, bilateral ptosis, deep set downward slanted eyes, long eye lashes, right sided iris coloboma, frontal bossing, bitemporal constriction, low set posterior rotated ears with large lobule, short nose with broad nasal bridge, long hypoplastic philtrum, small carp shaped mouth, high arched narrow palate, thin lips, full cheeks, pointed chin, micrognathia, short neck with folded skin and low posterior hair line (Figs. 1 and 2). Chromosomal analysis of the peripheral lymphocytes using G–T–G high resolution banding technique, and applying the FISH techniques on metaphase spread and interphase nuclei with N-myc specific probe for 2p23–p24, cyclineD1 (11q13)/CEP11 and telomeric regions for chromosomes 2 and 11 revealed normal 46, XX karyotype. Thyroid functions test, serum ammonia, lactic acid levels and metabolic screening were all normal. Pelvi-abdominal ultrasound, skeletal survey and audiometry showed no abnormality. Echocardiography detected a small patent ductus arteriosus. Ophthalmic examination revealed right sided iris coloboma with a thin retina. MRI of the brain at ages 11 days and at 1 year demonstrated dilated lateral ventricles, prominent basal cistern and sylvian fissures and about a 5 mm choroid plexus cyst in the posterior aspect of cavum septum pellucidum (Fig. 3). At 11 months of age, she developed repeated attacks of a febrile generalized fits controlled by Phenobarbital. EEG showed abnormal record on account of diffuse background activity slowing with regional accentuation of slow waves. She was re-evaluated at 18 months of age, with a weight of 11.5 kg, length of 82 cm and HC of 47.5 cm, all were on the 50th centile. She was hypotonic with global developmental delay. Informed consent was obtained from parents of the child and this work was done after approval of the ethics committee.

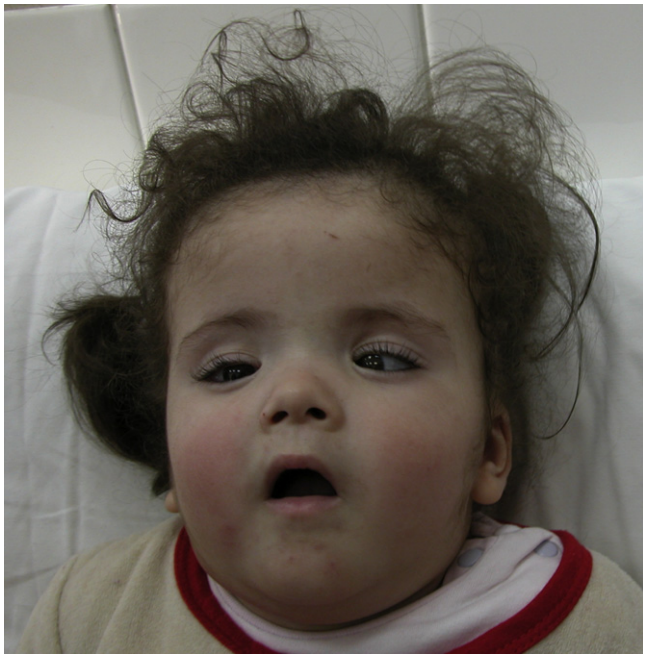

Figure 1 The proband at age of 17 months reveals short nose with a broad base, ptosis, strabismus, long eye lashes, hypertelorism, full cheeks, long hypoplastic philtrum, thin lips with downturned angles of the mouth and short neck.

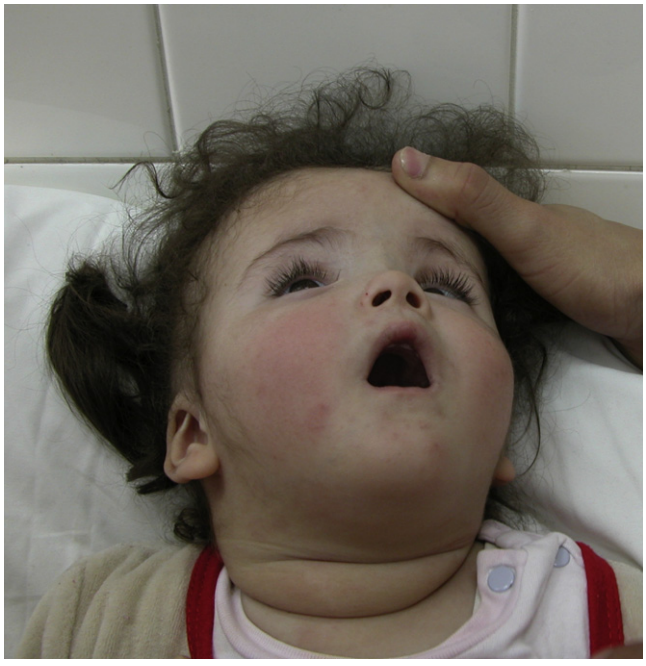

Figure 2 Note low set posterior rotated ears with large lobule and short neck with folded skin.

3. Discussion

The combinations of the iris coloboma, ptosis, hypertelorism, broad nasal bridge, epicanthic folds, growth and mental retardation were considered as a distinct syndrome, first

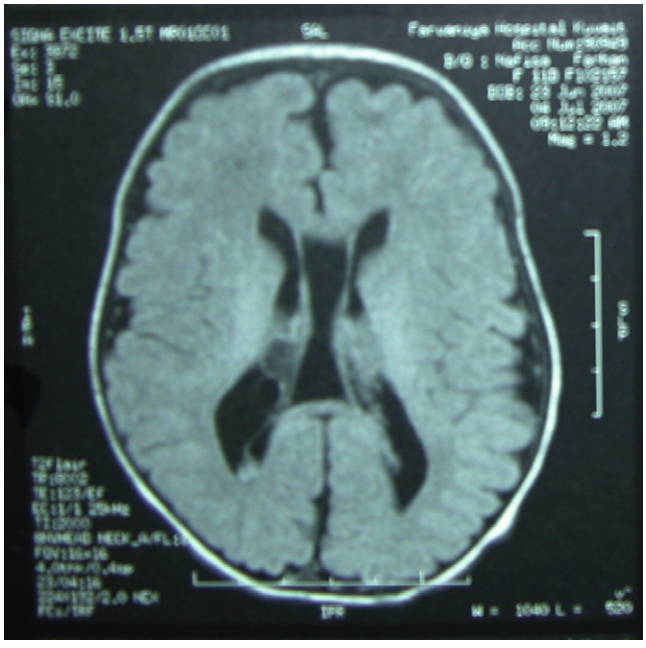

Figure 3 Coronal brain MRI images of the proband at age of 11 months. Note choroid plexus cyst in the posterior aspect of cavum septum pellucidum.

described by Baraitser and Winter in 1988 [1]. To the best of our knowledge, this is the fifth Arab patient to be reported in the literature, bringing the total number of cases to 20. Subsequent to the previous reports, the phenotypic spectrum of the syndrome has been extended (Table 1). Iris coloboma, which is a major feature of the syndrome, was described in 17 individuals in addition to our patient (case 20); either unilateral (cases 3 and 20), or bilateral. However, this malformation was not observed in some other cases [1,10]. Further ocular abnormalities were also reported; such as microphthalmia, microcornea, iris heterochromia, bilateral aniridia, optic nerve and choroidal coloboma, refractive errors, esotropia, nystagmus and strabismus [4,7,8,12]. Variable structural brain abnormalities have been observed in 13 cases previously (Table 1) and in our case too; this makes it another major manifestation of this syndrome. These malformations included; Lissencephaly, pachygyria, polymicrogyria, subcortical band heterotopia, periventricular heterotopia, hypoplasia of the anterior pituitary, absence of olfactory lobes, agenesis of the corpus collosum, ventricular dilatation, cerebral atrophy, lobar holoprosencephaly, porencephaly and hippocampal inversion [4,5,8,11–13]. It was suggested to consider this disorder as another example of syndromic neuronal migration defect due to association of the dysmorphism with of the previously mentioned structural brain anomalies [11]. However, the cystic lesion of the choroid plexus in the cavum septum pellucidum, which was observed in our patient, has not been reported before in conjunction with this syndrome. Isolated choroid plexus cyst occurs in around 1% of pregnancies. Choroid plexus cysts resolve by 26–28 weeks of gestation and in karyotypically normal fetuses [14]. It has no clinical significance in normal neonates and in the absence of other associated anomalies, such as trisomy 18, trisomy 21 and Klinefelter syndrome [15,16]. Choroid plexus cyst of cavum septum pellucidum in our case could represent a new associated clinical finding not described before or probably a coincidence not correlated to this syndrome.

Table 1 Clinical features of our patient compared with those of 19 cases reported before.

Patient findings	Present case	Total cases
Consanguinity	–	5/20
Sex	F	12 M/8 F
Birth weight $\leqslant 5^{th}$	–	0/20
Stature $\leqslant 5^{th}$	–	15/20
Coloboma	+	15/20
Other eye malformation	+	15/20
Ptosis	+	18/20
Hypertelorism	+	18/20
Epicanthic folds	+	15/20
Broad/broad nasal bridge	+	16/20
Long philtrum	+	9/20
Short/hypoplastic philtrum	–	9/20
Large mouth	–	3/20
Thin tips	+	12/20
Full cheek	+	13/20
Pointed chin	+	12/20
Short/webbed neck	+	11/20
Ear anomalies	+	11/20
Hearing loss	–	6/20
Microcephaly	–	12/20
Metopic ridge/trigonocephaly/ bitemporal constriction	+	10/20
Developmental/mental delay	–	20/20
Hypotonia	+	12/20
Seizures	+	7/20
Cardiac anomaly	+	6/20
Urogenital anomalies	–	8/20
Brain anomalies	+	13/20
Mental retardation	+	18/20
Skeletal anomalies	–	11/20
Other anomalies	–	3/20
Abnormal karyotype	N	2/20

M: male; F: female; N: normal.
Cases 1–19 reported by authors in Refs. [1–13].

Other anomalies have been also reported (Table 1); such as ear anomalies and/or deafness [5,7–9,11], which was found in our case as well. Renal anomalies included horse shoe kidney, hydroureter and hydronephrosis [7,13]. Genital anomalies have been also documented in few patients [3,11]. Severe eczema and un-explainable marked eosinophilia were detected in only one case [13].

Additionally, few cases have manifested unique internal organ anomalies; like lung hypoplasia, accessory spleen [4], omphalocele and inguinal hernia [8]. Variable cardiac anomalies were described by many authors, such as patent ductus arteriosus, ventricular septal defect, mitral valve prolapsed, mitral regurgitation, tricuspid valve prolapsed, tricuspid regurgitation, or other severe complex structural defects [5,7–9,13]. A small patent ductus arteriosus was detected in our patient.

Furthermore, many cases showed variable skeletal anomalies; including pectus excavatum, a broad chest, sternal or rib defects, hemivertebrae and scoliosis. Varieties of limb anomalies have been reported too; such as rocker bottom feet, mild coxa valga, cutaneous syndactyly, phalangeal hypoplasia/or shortness and others [3–5,7–11]. Our patient did not carry any of the aforementioned malformations although she had a short neck with folded skin. Also, she showed an abnormal EEG similar to some other cases 7 [10,11,13]. Growth retardation/short stature was found in most of the reported cases, however, our case and that of Ganesh et al. [12] had normal growth pattern. This patient manifested hypotonia and developmental delay, which is found to be severe in cases with lissencephaly [8,13], however, she did not show apparent structural anomaly involving the cerebral cortex or any of the associated defects like subcortical band heterotopias [7]. Long term follow up examination of our patient would clarify all these matters.

Our patient and the majority of the studied cases revealed normal chromosomal constitution; however, a submicroscopic aberration cannot be ignored. The precise genetic mechanism behind this syndrome is currently unknown. It has been postulated that mutation in the PAX-8 gene, which maps to chromosome 2q12–14 and involved in embryonic organogenesis, may interfere with normal neural migration causing the cerebral malformations found in Baraitser–Winter syndrome [8], as two cases had revealed pericentric inversions involving 2p12q14, inherited from their phenotypically normal mothers [2,3].

To date, many genes are known to be involved in genesis of human lissencephaly; including, LIS1, 14-3-3e, DCX, RELN and ARX. The severity of structural brain and/or cortical malformations varies according to the implicated gene(s), the specific mutations identified and sex of the patients [17,18]. As an example; LIS1 gene is located on human chromosome 17p13.3. Mutations of LIS1 cause isolated lissencephaly sequence or rarely isolated subcortical-band heterotopias, while corpus cal-

losum and cerebellum appear normal or mildly hypoplastic on brain MRI [17]. About 75% of patients with isolated lissencephaly showed mutation in LIS1 genes, whereas 85% of patients with subcortical band heterotopias carried mutation in DCX gene [18].

However, another form of distinct syndromic lissencephaly which is comprised of perisylvian predominant pachygyria to diffuse posteriorly predominant pachygyria combined with internal capsule dysgenesis, cerebellar dysplasia and callosal hypotrophy found to be associated with mutations in TUBA1A gene. Patients with this kind of brain malformation are clinically presented with severe congenital microcephaly (−3 to −4 SD), mental retardation, spastic diplegia and epilepsy [19].

We have considered many disorders that have similar clinical features to that of Baraitser–Winter syndrome. Miller–Dieker lissencephaly syndrome (OMIM 247200), a contiguous gene deletion syndrome of chromosome 17p13.3 shares some dysmorphic features with Baraitser–Winter syndrome. The cranio-facial features include microcephaly, prominent forehead, bitemporal narrowing, depressed nasal bridge, anteverted nares, midface hypoplasia, protuberant upper lip, thin vermilion border, and small jaw. Severe lissencephaly and midline focus of calcification in the callosal remnant, severe developmental delay, feeding problem and epilepsy were also reported. In the neonatal period there is vertical furrowing of forehead and prolonged jaundice. Congenital heart and postaxial polydactyly are also associated features. Deletion of chromosome 17p13.3 has been identified in 50–70% of patients, while submicroscopic deletion of LSI1 gene is implicated in other reported cases [20].

Ocular coloboma is one of the phenotypic manifestations of many disorders, such as CHARGE association (OMIM 214800); which involves other features like coloboma of the eye; heart anomaly; choanal atresia; structural brain anomaly, retardation of mental and somatic development; microphallus; ear abnormalities and/or deafness. The CHD7 gene on chromosome 8q12.1 was found to be mutated in the majority of the cases (69 of 107) with CHARGE syndrome [21].

A new unclassified autosomal recessive multiple congenital anomaly syndrome was presumed by two independent authors. To date, only four children from two different families have been reported with the combination of these abnormal features. Their clinical phenotype included; prenatal growth retardation, microcephaly, coloboma of iris/eye anomalies, variable congenital heart defects and urogenital anomalies [22,23]. It was considered sublethal in one report as the three infants died [22]. The fourth patient had severe life-threatening arrhythmias following his cardiac operation at age of 4 months. However, he was reported to be alive at the time of publication [23].

Some of the cranio-facial features of Baraitser–Winter syndrome also overlap with that of Noonan syndrome (OMIM 163950), which is an autosomal dominant dysmorphic syndrome, characterized by hypertelorism, a downward eye slant and low-set posteriorly rotated ears. In addition, phenotype includes short stature, a short neck with webbing or redundancy of skin, cardiac anomalies, epicanthic folds, deafness, motor delay, and a bleeding diathesis. Iris coloboma, which is a major feature of Baraitser–Winter syndrome, was manifested in few patients with Noonan syndrome/Noonan-like syndrome [24,25]. Mutations in PTPN11, KRAS and SOS1 genes are responsible for majority of cases of Noonan syndrome [26].

Recently, a new autosomal recessive syndrome (OMIM 612379) was reported in four children from an inbred Emirati family of Baluchi origin, with ocular colobomas, ichthyosis, congenital heart defects, and endocrine abnormalities associated with midline brain malformations and developmental delay/mental retardation. The cranial dysmorphism involved a broad spectrum of midline structural defects; including a small vermis with frontal polymicrogyri, hypoplastic corpus callosum, absent septum pellucidum, dilated lateral ventricles, hypoplasia of the pituitary gland and atrophic optic chiasma/or visual pathway [27]. The cranio-facial phenotypes of our patient are different from that presented in the previous report; moreover ichthyosis was not observed in our patient.

In conclusion, Baraitser–Winter syndrome is a rare genetic disorder, which can demonstrate a wide collection of phenotypes that are shared by many syndromes. Therefore, choroid plexus cyst found in our case could represent an additional disease spectrum. Autosomal recessive mode of inheritance has been suggested first knowing that the majority of reported cases (18/20) showed no chromosomal abnormality, including our patient; hence the genetic etiology remains to be resolved.

The authors confirm that no conflict of interest and consent of the parents was taken.

References

[1] Baraitser M, Winter RM. Iris coloboma, ptosis, hypertelorism, and mental retardation: a new syndrome. J Med Genet 1988;25:41–3.
[2] Ayme S, Mattei MG, Mattei JH, Giraud F. Abnormal childhood phenotypes associated with the same balanced chromosome rearrangements as in the parents. Hum Genet 1979;48:7–12.
[3] Pallotta R. Iris coloboma, ptosis, hypertelorism, and mental retardation: a new syndrome possibly localised on chromosome 2. J Med Genet 1991;28:342–4.
[4] Le Marec B, Odent S, Urovy M. A new syndrome with ptosis, coloboma and mental retardation. Genet Couns 1992;3:119–20.
[5] Ramer JC, Mascari MJ, Manders E, Ladda RL. Syndrome identification #149: trigonocephaly, pachygyria, retinal coloboma, and cardiac defect: a distinct syndrome. Dysmorph Clic Genet 1992;6:15–20.
[6] Schaap C, Schrander-Stumpel CT, Fryns JP. Optiz C-syndrome: on the nosology of mental retardation and trigonocephaly. Genet Couns 1992;3:209–15.
[7] Verloes A. Iris coloboma, ptosis, hypertelorism, and mental retardation: Baraitser–Winter syndrome or Noonn syndrome? J Med Genet 1993;30:425–6.
[8] Ramer JC, Lin AE, Dobyns WB, Winter RM, Ayme S, Pallotta R, et al. Previously apparently undescribed syndrome: shallow orbits, ptosis, coloboma, trigonocephaly, gyral malformations, and mental and growth retardation. Am J Med Genet 1995;57:403–9.
[9] Fryns JP. Previously apparently undescribed syndrome: shallow orbits, ptosis, coloboma, trigonocephaly, gyral malformations, and mental and growth retardation. Am J Med Genet 1996;64:521–2.
[10] Megarbane A, Le Merrer M, El Kallab K. Ptosis, down-slanting palpebral fissures, hypertelorism, seizures and mental retardation: a possible new MCA/MR syndrome. Clin Dysmorphol 1997;6:239–44.
[11] Rossi M, Guerrini R, Dobyns WB, Andria G, Winter RM. Characterization of brain malformations in the Baraitser–Winter syndrome and review of the literature. Neuropediatrics 2003;34:287–92.
[12] Ganesh A, Al-Kindi A, Jain R, Raeburn S. The phenotypic spectrum of Baraitser–Winter syndrome: a new case and review of literature. JAAPOS 2005;9:604–6.

[13] Shiihara T, Maruyama KI, Yamada Y, Nishimura A, Matsumoto N, Kato M, et al. A case of Baraitser–Winter syndrome with unusual brain MRI findings: pachygyria, subcortical-band heterotopia, and periventricular heterotopias. Brain Dev 2009;PMID:19477093.
[14] Epelman M, Daneman A, Blaser SI, Ortiz-Neira C, Konen O, Jarrín J, et al. Differential diagnosis of intracranial cystic lesions at head US: correlation with CT and MR imaging. Radiographics 2006;26:173–96.
[15] Porto M, Murata Y, Warneke LA, Keegan Jr KA. Fetal choroid plexus cysts: an independent risk factor for chromosomal anomalies. J Clin Ultrasound 1993;21:103–8.
[16] Hurt K, Sottner O, Záhumenský J, Halaska M, Krcmár M, Driák D, et al. Choroid plexus cysts and risk of trisomy 18. Modifications regarding maternal age and markers. Ceska Gynekol 2007;72:49–52.
[17] Kato M, Dobyns WB. Lissencephaly and the molecular basis of neuronal migration. Hum Mol Genet 2003;12(Review issue):R89–96.
[18] Haverfield EV, Whited AJ, Petras KS, Dobyns WB, Das S. Intragenic deletions and duplications of the LIS1 and DCX genes: a major disease-causing mechanism in lissencephaly and subcortical band heterotopia. Eur J Hum Genet 2009;17:911–8.
[19] Bahi-Buisson N, Poirier K, Boddaert N, Saillour Y, Castelnau L, Philip N, et al. Refinement of cortical dysgeneses spectrum associated with TUBA1A mutations. J Med Genet 2008;45:647–53.
[20] Dobyns WB, Curry CJ, Hoyme HE, Turlington L, Ledbetter DH. Clinical and molecular diagnosis of Miller–Dieker syndrome. Am J Hum Genet 1991;48:584–94.
[21] Jongmans MC, Admiraal RJ, van der Donk KP, Vissers LE, Baas AF, Kapusta L, et al. CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. J Med Genet 2006;43:306–14.
[22] Fryns JP, Verresen H, Van Den Berghe H. Prenatal growth retardation, microphthalmos/iris coloboma, cloudy cornea, urogenital anomalies and microcephaly. A possible new sublethal syndrome. Clin Genet 1997;51:164–6.
[23] Cuturilo G, Jovanovic I, Vukomanovic G, Djukic M, Stefanovic I, Atanskovic-Markovic M. Prenatal growth retardation, microcephaly, and eye coloboma in infant with multiple congenital anomalies: further delineation of presumed new dysmorphic syndrome. Birth Defects Res A Clin Mol Teratol 2008;82:166–8.
[24] Hall BD. Iris coloboma, ptosis, hypertelorism, and mental retardation. J Med Genet 1989;26:69.
[25] Gravholt CH, Warburg M, Friedrich U. Mild Noonan phenotype associated with coloboma of the iris and choroid. Clin Dysmorphol 2002;11:75–7.
[26] Tartaglia M, Pennacchio LA, Zhao C, Yadav KK, Fodale V, Sarkozy A, et al. Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. Nat Genet 2007;39:75–9.
[27] Al-Gazali L, Hertecant J, Algawi K, El Teraifi H, Dattani M. A new autosomal recessive syndrome of ocular colobomas, ichthyosis, brain malformations and endocrine abnormalities in an inbred Emirati family. Am J Med Genet 2008;146A:813–9.