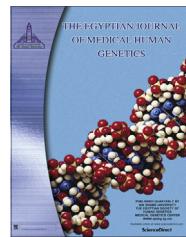




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CASE REPORT

Baraitser–Winter syndrome: An additional Egyptian patient with skeletal anomalies, bilateral iris and choroid colobomas, retinal hypoplasia and hypoplastic scrotum



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KEYWORDS

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Abstract We report a 3.5 year old male child, second in order of birth of non consanguineous Egyptian parents with Baraitser–Winter syndrome (BRWS). The patient had bilateral colobomas of the iris and choroid. Our patient had also retinal hypoplasia, which was not reported previously in this syndrome, bilateral congenital ptosis, hypertelorism, moderate mental retardation, short stature, short neck, hyperextensibility of the joints of the hands, talipes equinovarus, kyphoscoliosis and unilateral hypoplastic scrotum and testis.

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1. Introduction

Baraitser–Winter syndrome (BRWS) is a rare but well-defined developmental disorder recognized by the combination of congenital ptosis, high-arched eyebrows, hypertelorism, ocular coloboma and a brain malformation consisting of anterior predominant lissencephaly. Other typical features include postnatal short stature and microcephaly, intellectual disability, seizures and hearing loss [1–4]. BRWS may be considered another example of syndromic neuronal migration defect [5].

We report a case with the typical features of BRWS which has in addition some unreported features after taking consent of the parents.

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2. Case report

A 3.5 year old male child, second in order of birth of healthy non consanguineous Egyptian parents. The patient was delivered at full term by cesarean section. His birth weight was 3 kg. No problems were noted by the mother during pregnancy. The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of developmental delay and abnormal features.

At the age of 3 days, the mother noticed that her son had poor sucking and difficulty in breathing which necessitated admission to neonatal intensive care unit (NICU) for 3 days. At the age of 1 week he developed convulsions. He was admitted to NICU again and started epanutin and sominaletta for 40 days. The convulsions stopped after 1 month and the patient stopped anticonvulsant drugs. The mother also noticed

abnormal features in the form of squinted eyes and foot deformity. He had developmental delay as he can only stand with support and can say 3 words only.

Family history was unremarkable. He had two healthy sibs. Both parents were normal.

On examination, the patient had moderate mental retardation, his weight was 12 kg (5th percentile), his length was 86 cm (below 3rd percentile), and his skull circumference was 49.5 cm (50th percentile).

The patient had high forehead, high arched eyebrows, prominent glabella, depressed nasal bridge, downward slanting palpebral fissures with epicanthus inversus, slight hypertelorism, bilateral iris colobomas, wide palpebral fissures, bilateral convergent squint and bilateral congenital partial ptosis, broad bulbous nose, with broad nasal tip, hypoplasia of malar regions, full cheeks, long philtrum, thin upper lip, macrostomia, high arched palate and pointed chin (Fig. 1). The ears were small and low set. The neck was short with mild webbing. The patient had also low posterior hair line and hyperextensibility of the joints of the hands (Fig. 2).

He also had dystrophic nails, broad end of big toes, wide space between big toes and second toes, deviation of other toes medially, overriding of 4th and 2nd toes over 3rd toe and talus equinovarus more marked on the left side (Figs. 3 and 4).

Also there were narrow shoulders, pectus excavatum and kyphoscoliosis of the back (Figs. 1 and 2).

Abdominal examination revealed small umbilical hernia. Cardiac examination was normal. Genital examination revealed hypoplastic right scrotum and testis (Fig. 5). Neurologic examination demonstrated mild hypotonia in lower limbs.

Abdomino-pelvic ultrasonography and ECHO cardiography were normal. Extended metabolic screen, serum lactate and serum ammonium were normal. Karyotype was also normal. Fundus examination revealed bilateral choroidal colobomas with retinal hypoplasia over the colobomas defects of the



Figure 2 Short neck, small low set ears and kyphoscoliosis.

choroid. X-ray spine demonstrated kyphoscoliosis, however vertebrae were normal. MRI brain (axial T1WI) revealed cortical thickening in the right occipitotemporal region (arrows) keeping with pachygryria (Fig. 6). Audiometry was normal. X-ray of the feet revealed adduction and varus deformity of the left fore foot (Fig. 4).

3. Discussion

We report a 3.5 year old male child with BRWS with bilateral colobomas of the iris and choroid, bilateral congenital ptosis, hypertelorism, moderate mental retardation, short stature, broad nasal bridge, prominent cheeks which slope down to a pointed chin, long philtrum, large mouth, thin upper lip, short

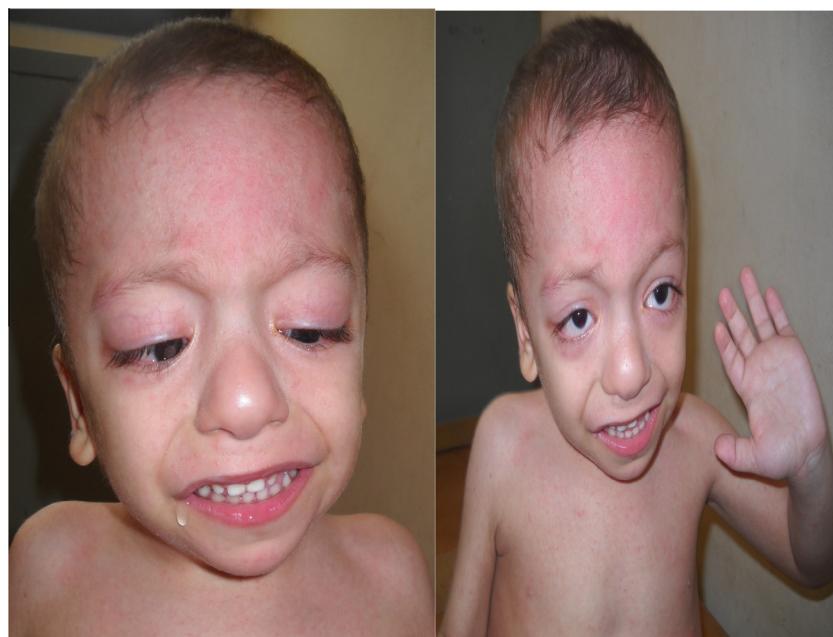


Figure 1 Facial features with short neck and narrow shoulders.



Figure 3 Broad ends of big toes, wide space between big toes and second toes and talipes equinovarus more marked on left side.

neck with low posterior hair line, hyperextensibility of the joints of the hands, talipes equinovarus, kyphoscoliosis and unilateral hypoplastic scrotum and testis.

Iris coloboma which was detected in our patient is a major feature of the syndrome [6]. It may be unilateral or bilateral [7]. However it was not observed in some cases [8,9]. Our patient had also bilateral choroidal colobomas and bilateral strabismus as reported in other cases [6]. Bilateral ptosis which was also detected in our patient is almost universal in BRWS (93%) [10]. Our patient also had downslanting palpebral fissures with epicanthus inversus which were also reported in some cases [10].

Other ocular abnormalities reported in BRWS included microphthalmia, microcornea, iris heterochromia, bilateral aniridia, optic nerve coloboma, refractive errors, esotropia and nystagmus [1,3,11,12].

Also our patient had retinal hypoplasia over the colobomas defects of the choroid which was not reported previously.

Other facial anomalies reported in our patient as well as in other reported cases [10] included hypertelorism, broad nasal



Figure 5 Hypoplastic right scrotum and testis.

bridge with large flat tip of the nose, hypoplasia of malar region, thin upper lip and pointed chin.

The phenotypic spectrum of BRWS had been broadened to include postnatal microcephaly and trigonocephaly [6].

Other anomalies reported in patients with BRWS included ear anomalies and/or deafness [3,13]. Our patient had small low set posteriorly rotated ears, however his hearing was normal.

Our patient had short neck with mild webbing which was described before [6].

In addition our patient had pectus excavatum, kyphoscoliosis, broad end of big toes, wide space between big toe and second toe, deviation of other toes medially, overriding 4th and 2nd toes over 3rd toe and talipes equinovarus.

Many cases with BRWS 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 [7,11,13].

Variable cardiac anomalies were described in BRWS and were not detected in our patient including patent ductus arteriosus, ventricular septal defect, atrial septal defect, bicuspid aortic valve, mitral valve prolapse, mitral regurgitation, tricuspid valve prolapse, tricuspid regurgitation, or other severe complex structural defects [1,3].

Renal anomalies in patients with BRWS include horse shoe kidney, hydronephrosis [3,14] which were not detected in our patient.

Additionally, few cases have manifested unique internal organ anomalies; like lung hypoplasia, accessory spleen, omphalocele and inguinal hernia [1]. Our patient had an umbilical hernia.

Genital anomalies have been also documented in few patients [3,13,14]. Our patient had hypoplastic right scrotum and testis.

Severe eczema and un-explainable marked eosinophilia were detected in only one case [14] which were not present in our case.



Figure 4 X-ray of the feet shows adduction and varus deformity of left fore foot.



Figure 6 Brain MRI (axial T1WI) shows cortical thickening in the right occipitotemporal region (arrows) keeping with pachygryia.

BRWS may show variable muscular involvement. This may contribute to narrow sloping shoulders [10], as detected in our patient. Many patients have also dorsal kyphosis [10] as detected in our patient. Bilateral talipes equinovarus was also detected in our patient.

Our patient had also moderate mental retardation which was reported in some patients [6].

Seizures are common in these patients and age of onset ranged from 2 month to 14 years and it may be intractable in some patients [10]. Our patient suffered from seizures at the age of 1 week which stopped at the age of 2 month. There are reports that individuals with normal MRI scan did not have seizure disorder [10]. Also EEG abnormalities were reported in some cases [10].

Intrauterine growth is usually normal in BRWS as detected in our patient at birth, however moderate short stature was observed in most of the reported cases as well as in our patient [6].

MRI brain scan of our patient demonstrated right cortical temporal pachygryia. Other brain anomalies reported in BRWS and not detected in our patient included cortical atrophy [12], lissencephaly, polymicrogyria, subcortical band heterotopia, periventricular heterotopia and others [11,13]. So it was suggested to consider this syndrome as a syndromic neuronal migration defect [6]. Also a cystic lesion of the choroid plexus in the cavum pellucidum was observed in an Arab patient [6].

Karyotype was normal in our patient. In other studied cases a pericentric inversion of chromosome 2: inv (2) (p12q14) was reported [1,7] which was inherited from his phenotypically normal mother. This may be due to the possibility that an odd number of crossovers in the 'inversion loops' of chromosome 2 caused a very small duplication or deletion of chromosomal material in the affected offspring [7]. Pax 8 gene was reported to be mapped to this site [1].

BRWS is caused by a heterozygous gain of function mutations in two different actin encoding genes (ACTB and ACTG1). OMIM identifies two types of BRWS. BRWS1 is

caused by heterozygous mutation in the ACTB gene on chromosome 7p22-p12. BRWS2 is caused by heterozygous mutation in the ACTG1 gene on chromosome 17q25.3, although the phenotypes linked to both genotypes are largely indistinguishable [15].

Actins are a family of essential cytoskeletal proteins implicated in nearly all cellular processes [16,17]. Among the six human genes encoding actins, only ACTB and ACTG1 are ubiquitously expressed; the remaining four are expressed primarily in muscle.

Nearly all patients with ACTG1 mutations and around 60% of those with ACTB mutations have some degree of pachygryia with anteroposterior severity gradient, rarely lissencephaly or neuronal heterotopia [10].

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 [1] because of the two cases that had been reported with pericentric inversions of chromosome 2; involving 2p12-q14 [7,18].

The parents of our patient were non consanguineous, although consanguinity is high in Egypt [19]. Our patient had no family history of similarly affected persons which probably represents a sporadic occurrence in the family [4]. All reported patients with Baraitser-Winter syndrome have been sporadic except in one report of 2 affected sibs; however, Shawky et al. [20] reported a case of BRWS with consanguineous parents.

To conclude: Baraitser-Winter syndrome is a developmental disorder with craniofacial, visceral and muscular involvement due to gain-of-function mutations in ACTB and ACTG1. Our patient has the typical features of BRWS syndrome in addition to some unreported features illustrating the wide-ranging phenotypic spectrum of Baraitser-Winter Syndrome.

References

- [1] Ramer JC et al. Previously apparently undescribed syndrome: shallow orbits, ptosis, coloboma, trigonocephaly, gyral malformations, and mental and growth retardation. *Am J Med Genet* 1995;57(3):403-9.
- [2] Fryns JP, Aftimos S. New MR/MCA syndrome with distinct facial appearance and general habitus, broad and webbed neck, hypoplastic inverted nipples, epilepsy, and pachygryia of the frontal lobes. *J Med Genet* 2000;37(6):460-2.
- [3] Verloes A. Iris coloboma, ptosis, hypertelorism, and mental retardation: Baraitser-Winter syndrome or Noonan syndrome? *J Med Genet* 1993;30(5):425-6.
- [4] Riviere JB, Van Bon BWM, Hoischen A, Kholmansikh SS, O'Roak BJ, Gilissen C, et al. De novo mutations in the actin genes ACTB and ACTG1 cause Baraitser-Winter syndrome. *Nature Genet* 2012;44:440-4.
- [5] 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(6):287-92.
- [6] Abou Henedy MM, Marafie MJ, Abulhasan SJ. Baraitser-Winter syndrome: an additional Arab patient. *Egypt J Med Hum Genet* 2010;11(2):187-91.
- [7] Pallotta R. Iris coloboma, ptosis, hypertelorism, and mental retardation: a new syndrome possibly localised on chromosome 2. *J Med Genet* 1991;28(5):342-4.

- [8] Baraitser M, Winter RM. Iris coloboma, ptosis, hypertelorism, and mental retardation: a new syndrome. *J Med Genet* 1988;25(1):41–3.
- [9] 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(3):239–44.
- [10] Verloes A, Di Donato N, Masliah-Planchon J, Jongmans M, Abdul-Raman OA, Albrecht B, et al. Baraitser–Winter cerebrofrontofacial syndrome: delineation of the spectrum in 42 cases. *Eur J Hum Genet* 2015;23(3):292–301.
- [11] Le Marec B, Odent S, Urovy M. A new syndrome with ptosis, coloboma and mental retardation. *Genet Couns* 1992;3:119–20.
- [12] Ganesh A, Al-Kindi A, Jain R, Raeburn S. The phenotypic spectrum of Baraitser–Winter syndrome: a new case and review of literature. *JAPOS* 2005;9(6):604–6.
- [13] Ramer JC, Mascari MJ, Manders E, Ladda RL. Syndrome identification #149: trigonocephaly, pachygyria, retinal coloboma, and cardiac defect: a distinct syndrome. *Dysmorphol Clic Genet* 1992;6:15–20.
- [14] 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* 2010;32(6):502–5.
- [15] Di Donato N, Rump A, Koenig R, et al. Sever forms of Baraitser–Winter syndrome are caused by ACTB mutations rather than ACTG1 mutations. *Eur J Hum Genet* 2014;22:179–83.
- [16] Gupton SL, Gertler FB. Filopodia: the fingers that do the walking. *Sci STKE* 2007;2007(400).
- [17] Shawlot W, Deng JM, Fohn LE, Behringer RR. Restricted beta-galactosidase expression of a hygromycin-lacZ gene targeted to the beta-actin locus and embryonic lethality of beta-actin mutant mice. *Transgenic Res* 1998;7:95–103.
- [18] 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.
- [19] Shawky RM, El-Awady YM, Elsayed SM, Hamadan GE. Consanguineous matings among Egyptian population. *Egypt J Med Hum Genet* 2011;12(2):157–63.
- [20] Shawky RM, Elabd HSA, Gamal R. Bilateral iris, choroid, optic nerve colobomas and retinal detachment in an Egyptian patient with mild Baraitser–Winter syndrome. *Egypt J Med Hum Genet* 2014;15(1):95–7.