Baller-Gerold syndrome (BGS) is characterized by craniosynostosis and pre-axial upper-limb malformations, and this disorder has an autosomal recessive inheritance pattern. As a rare genetic disorder, it overlaps with other malformations, including cardiac, central nervous system (CNS), and urogenital anomalies. Herein, we report a female newborn who was exposed to the use of Depakin (sodium valproate), Topamax (topiramate) and Lamictal (lamotrigine) during the intrauterine period. On postnatal examination, right radius aplasia, hypoplastic right thumb, craniosynostosis, trigonocephaly, ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), and left renal hypoplasia were determined. In addition to characteristic findings of BGS phenotype, the case had serious renal and cardiac anomalies. We present this very rare case in order to draw attention to the grave fetal congenital malformations caused by the maternal use of anti-epileptic drugs, especially sodium valproate and lamotrigine.

**Case Report**

It was learned that the 34-year-old female partner of a consanguineous couple (3rd generation cousins) had been using anti-epileptic drugs since she was 10 years old due to the diagnosis of epilepsy. Before and throughout her second pregnancy, she had taken sodium valproate regularly (1000 mg/day), and topiramate (25 mg/day) and lamotrigine (200 mg/day) at irregular intervals. Her female infant, our patient, who was delivered by cesarean section, was dispatched to our hospital due to extremity and cranial anomalies. The patient was accepted in the neonatal intensive care unit. Her weight was measured as 2780 g (10-25th percentile), her height as 48.5 cm
(10th percentile) and her head circumference as 34 cm (3rd percentile). On physical examination, prominent nasal bridge, downslanting palpebral fissures, long philtrum, bifrontal narrowing (trigonocephaly), prominent cranial sutures (especially metopic sutures), high-arched palate, short right upper limb, radial deviation with her right wrist, and small right hand (especially right thumb) (Figs. 1 a, b, c, d) and 2-3/6 pansystolic murmur in the mesocardiac region were determined. The other systemic findings and hematological and biochemical laboratory findings of the patient were normal in the neonatal period and at 14 months of life.

Echocardiographic examination was performed to evaluate cardiac murmur. VSD, ASD and PDA were determined. On radiological examination, right radius aplasia, hypoplastic right thumb and craniosynostosis were demonstrated (Figs. 1 e, f, g). In addition to

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**Fig. 1.** Presentation of the current patient:
A and B) Right upper-limb abnormalities (short right upper limb, radial deviation with her right wrist and small right hand) and prominent nasal bridge; view of the patient in the neonatal period and at 14 months of life.
C) Bifrontal narrowing (trigonocephaly) and long philtrum.
D) Hypoplasia of the right thumb.
E) X-ray shows aplasia of right radius and hypoplastic right thumb.
F) Lateral X-ray of the head.
G) Craniosynostosis as demonstrated on CT.
these abnormalities, left renal hypoplasia was detected by the urinary system ultrasonography (US) and by the renal perfusion scintigraphy scanned through Tc-99m MAG-3. Digoxin, diuretic and enalapril were administered to the patient for cardiac problems, and amoxicillin prophylaxis was begun for her renal problems. Normal peripheral blood chromosome analysis was performed, and 46, XX was found. Molecular analysis was performed on DNA extracted from peripheral leukocytes of the patient and her family for mutation analysis of the RECQL4 gene. Sequence analysis showed no mutation. Based on clinical and laboratory findings, the patient was diagnosed with BGS. The patient, who was consulted with pediatric cardiology, nephrology, orthopedics, neurosurgery, and genetics departments, was taken under multidisciplinary follow-up and treatment.

Our patient had a 10-year-old brother. On his physical examination, trigonocephaly, polymastia and hypospadias were determined. He had no extremity anomalies. His urinary system US and echocardiographic and radiological examinations were normal (Figs. 2 a, b). His intelligence quotients were between 77 and 87. After an investigation, it was learned that his mother had also used anti-epileptic drugs of unknown dose and label combined with Depakin during her first pregnancy. Therefore, we concluded that the findings of the brother were consistent with fetal valproate syndrome.

Fig. 2. Presentation of the patient’s brother: A) trigonocephaly and B) polymastia.
Discussion

This syndrome was originally reported by Baller4 and Gerold5 in the medical literature, and later in 1979, it was named as Baller-Gerold syndrome by Cohen6. The major features of BGS are craniosynostosis and pre-axial upper-limb malformations2. Craniosynostosis (100%) in BGS may affect one of the cranial sutures or some of them3. However, coronal involvement, alone or combined, is the most common (64%). Other sutures involved, alone or combined, are the metopic suture (36%), lambdoid suture (27%) or sagittal suture (9%)2,7,8. Craniosynostosis was detected in all cranial sutures of our patient. The second major characteristic of BGS is some form of pre-axial limb malformations affecting the radius (aplasia/hypoplasia 77%) and/or the thumbs (absent/hypoplasia 100%) unilaterally or bilaterally3,7. On radiological examination, the absence of the right radius bone and hypoplastic right thumb were noted in our patient. Consequently, the patient was diagnosed with BGS phenotype.

Patients with BGS may also have urogenital, cardiac, CNS, and vertebral defects2. Left renal hypoplasia, VSD, ASD and PDA were also determined in the presented patient.

Before diagnosis of BGS, other conditions with overlapping clinical features, including Fanconi pancytopenia syndrome, Roberts syndrome, and Rothmund-Thomson syndrome (RTS), should be excluded. Fanconi pancytopenia syndrome is characterized by radial hypoplasia, hyperpigmentation and pancytopenia1,3,9. The diepoxybutane (DEB) test is highly effective in discriminating Fanconi anemia (FA) from other conditions. However, it was reported that the DEB test was found positive in only 12 of 34 patients with FA having findings including aplastic anemia, short stature, hyperpigmentation, and typical abnormalities10. Quarrell and Harrison9,11 reported that a newborn patient initially diagnosed with BGS was later re-diagnosed with FA because of abnormal cytogenetic analysis at 16 months of life. Investigators have reported that a patient with BGS requires longer-term follow-up and that results of extensive cytogenetic and hematological studies should be normal. Hematological and clinical findings of the presented patient were normal in her neonatal period and at 14 months of life. In addition, we followed the patient for any hematological abnormalities. Roberts syndrome is a rare genetic disorder characterized by pre- and postnatal growth retardation, limb defects and craniofacial anomalies12. RTS is a rare disorder characterized by early poikilodermatous skin lesions, small stature, skeletal abnormalities, cataracts, and predisposition to specific cancers13. However, craniosynostosis and pre-axial limb malformation (especially absent or hypoplastic thumbs) are associated most constantly in BGS1,3. Therefore, our patient with BGS phenotype was distinguished from the other syndromes by these two distinctive clinical features.

Baller-Gerold syndrome has an autosomal recessive inheritance pattern3. Some mutations in the TWIST gene and the RECQL4 gene have been identified in patients with BGS1,14. Interestingly, three different disorders including RTS, RAPADILINO syndrome and BGS have been associated with mutations in the RECQL41,14-16. On the other hand, Oliveira et al.2 reported for the first time in the literature that sodium valproate (1500 mg/day) exposed in utero could cause BGS. Chromosome analysis of the presented patient was normal and mutation analysis of the RECQL4 gene showed no mutation. Therefore, we believe that fetal sodium valproate exposure may have caused the BGS phenotype, and this presented study supports the previously published report by Oliveira et al.2.

Approximately 0.4% long bone and upper-limb deficiencies in infants exposed to valproic acid in utero have been reported18-20. Trigonocephaly is the characteristic finding of valproate syndrome, and this syndrome can be encountered with upper extremity defects20. However, upper extremity defects are not required for the diagnosis of this syndrome. Although trigonocephaly can be observed at the rate of 36% in BGS, upper extremity defects and craniosynostosis are absolute requirements for the diagnosis of BGS2,3,21. Trigonocephaly was detected in the presented patient and her brother. The teratogenic effect of sodium valproate has been associated with the dose taken. The risk of major congenital malformation in the babies of the mothers who took sodium valproate at doses exceeding 1000 mg/day throughout pregnancy noticeably increased in comparison to the infants of
the mothers who took 600 mg/day\textsuperscript{22}. We learned that the presented patient had a history of fetal exposure to sodium valproate (=1000 mg/day). Furthermore, she was diagnosed with BGS phenotype. However, we could not learn the dose and duration of this drug use for her brother during the first pregnancy of the mother. We concluded that the findings in the proband’s brother were consistent with fetal valproate syndrome. We have reported for the first time that fetal sodium valproate exposure can cause both phenotypes (BGS and fetal valproate syndrome) in the same family. The heterogeneity in the phenotype may be explained by a lower exposure dose to valproate in utero.

Infants with malformations such as VSD, congenital respiratory stridor, cleft palate, hypospadias, and undescended testis following intrauterine exposure to lamotrigine have been reported. Particularly, the use of sodium valproate together with lamotrigine appears to be associated with the highest risk of major congenital defects\textsuperscript{23}. Infants with malformations such as hypospadias, delayed psychomotor development, hirsutism, short nose with anteverted nostrils, deficiency of distal phalanx and nails, and hypoplasia in the fifth nail after intrauterine exposure to topiramate alone or combined with the other antiepileptics of at least 100 mg/day or more were also reported\textsuperscript{24}. During the intrauterine period, the presented patient was exposed to irregular use of lamotrigine (200 mg/day) and topiramate (25 mg/day); only VSD was detected among the findings stated above.

In conclusion, the presented patient was diagnosed with BGS phenotype based on craniosynostosis, right radius aplasia and hypoplastic right thumb. Furthermore, trigonocephaly, VSD, ASD, PDA and left renal hypoplasia were determined in the patient. Her brother was also detected to have trigonocephaly, polymastia and hypospadias and was diagnosed with fetal valproate syndrome. It can be said that all these serious congenital malformations occurred particularly due to the exposure to high-dose sodium valproate (≥1000 mg/day), and the combination of lamotrigine contributed to the cases. In view of these presented patients, we aimed with this report to add further evidence to the literature indicating that the use of sodium valproate combined with lamotrigine as antiepileptic drugs throughout pregnancy can increase the risk of serious fetal congenital malformations based on the doses.

REFERENCES


