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# Facio- Auriculo- Vertebral Sequence in association with Congenital Hypoparathyroidism

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Although, Facio-auriculo-vertebral sequence (FAVS) is a well recognized condition with cranio-facial, ocular and vertebral anomalies, extreme variability of expression is characteristic. Association of cardiac, CNS, lungs, kidneys and limb defects are described. We report a neonatal case with FAVS in association with congenital hypoparathyroidism.

**Key words:** *Branchial arch anomaly, Congenital hypoparathyroidism, Embryology, Facio-auriculo-vertebral sequence.*

Facio-auriculo- vertebral sequence (FAVS) is a spectrum of developmental disorders involving oculo- auriculo- vertebral disorder, Hemifacial microsomia, FAV syndrome and Goldenhar syndrome [1,2]. FAVS consists of facial asymmetry, maxillary and mandibular hypoplasia, cleft palate, macrostomia, microtia or anotia and pre- auricular ear tags or pits, in addition to vertebral anomalies. Goldenhar syndrome consists of above defects plus epibulbar dermoids and/ or lipodermoids. Association of anomalies of heart, kidneys, CNS, lungs, limbs have been described [3,4]. There is only one fetal autopsy case report of FAV sequence with associated DiGeorge sequence (with hypoplasia of parathyroid glands) [5].

## CASE REPORT

A 15-day-old neonate, second child of a non-consanguineous marriage, presented to us with two days history of multiple brief episodes of seizures. On clinical examination, baby had facial asymmetry with hypoplasia of the right mandible and right macrostomia, cleft palate, small deformed and very low set right pinna with a pre-auricular tag and atresia of the right external auditory canal (***Fig.* 1**). Apart from anti-mongoloid slant and hypertelorism, both the eyes were normal. The neonatal reflexes (including Moro's, sucking, rooting, etc) and other systemic examination were normal.

On evaluation, his sepsis screen (including total white cell count, band count, random blood sugar, C- reactive proteins, blood culture and CSF study) was negative. Biochemical evaluation revealed a serum calcium concentration of 6 mg /dL, the serum phosphorus concentration of 11 mg /dL and serum alkaline phosphatase concentration of 150 U/L. The serum concentration of magnesium was 1.8 mg /dL, the serum concentration of 25-hydroxyvitamin D was 7 ng /ml (normal range- 5-42) and the serum concentration of

1,25- dihydroxyvitamin D was 48 pg /mL (normal range- 8- 72). The serum concentration of the intact parathyroid hormone (PTH) was undetectable (done by intact PTH immunometric assay).

Skeletal survey (***Fig.* 2**) revealed cervical hemivertebrae and fusion of $8^{th}$- $9^{th}$ thoracic and 1st- $2^{nd}$ lumbar vertebrae and scoliosis. The thymus gland was seen. The ultrasonography of skull; kidneys, ureter and urinary bladder (KUB); and the two dimensional echocardiography and color Doppler of the heart and aorta failed to reveal any abnormality. The Brain Stem Evoked Response was suggestive of a normal hearing on the left side and a conductive deafness on the right side. Parents did not afford FISH or other chromosomal studies for DiGeorge sequence to reveal the diagnostic deletion on chromosome 22.

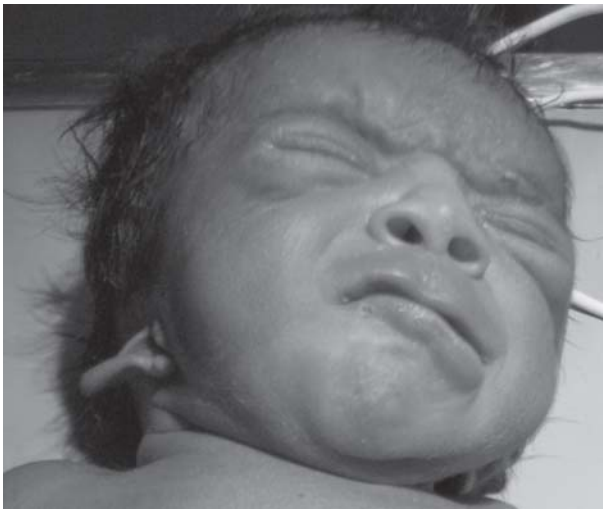

**FIG. 1** *Clinical photograph showing right microtia, mandibular hypoplasia and macrostomia and facial asymmetry suggestive of FAVS.*

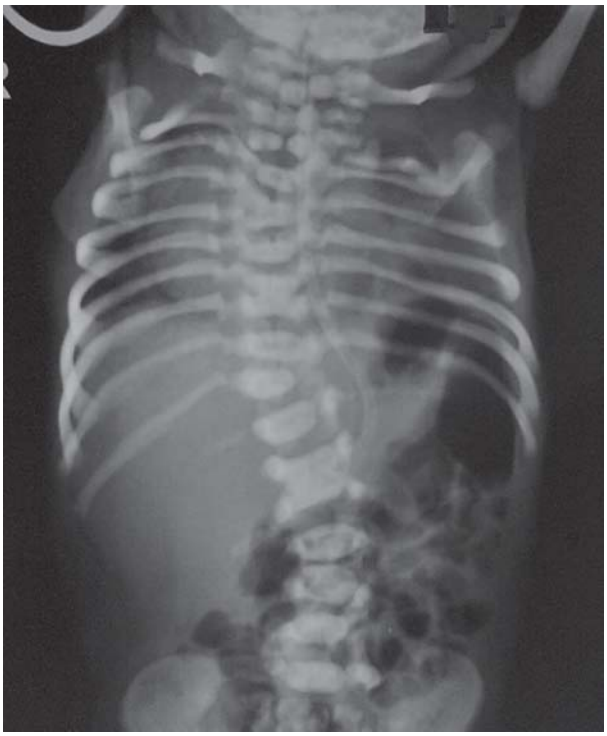

**FIG. 2** *X- Ray spine showing cervical hemivertebrae, fusion of $8^{th}$- $9^{th}$ thoracic and $1^{st}$- $2^{nd}$ lumbar vertebrae and scoliosis.*

The above clinical, biochemical and radiological findings were suggestive of Facio-auriculo-vertebral syndrome with associated congenital hypoparathyroidism. The baby was treated with intravenous 10% calcium gluconate 2 mL/kg /dose (infused at a rate of 0.5 - 1 mL/min with heart rate monitoring) eight hourly for three days and oral calcitriol 0.1 micro gm (1 mL) 12 hourly. Subsequently, the baby was discharged on oral calcitriol and supplemental calcium.

## DISCUSSION

FAVS occurs as a result of abnormality in the morphogenesis of the first and the second branchial arches [1,2]. It is a well-recognized condition characterised by cranio-facial, ocular and vertebral anomalies. In addition, a more complex phenotype with skeletal, cardiac, pulmonary, renal and CNS manifestations is also known to occur [3,4]. Congenital hypoparathyroidism with FAVS has not yet been reported in the literature with the exception of a fetal autopsy case report [5].

The parathyroid glands develop from the third and the fourth branchial arches [6]. Congenital absence of the parathyroid glands with facial anomalies is known to occur with branchial arch anomalies. Thus, embryologically it is possible that a developmental malformation sequence involving the branchial arches may result in FAVS and agenesis or hypoplasia of the parathyroid glands (either isolated or as a part of DiGeorge sequence) and hence, congenital hypoparathyroidism could be a part of the same sequence that leads to FAVS. It should also be noted that, embryologically FAVS is considered an anomaly of first and second branchial arches, but this alteration does not explain the associated anomalies in the heart, kidneys, lungs, CNS or vertebrae. Hence, extreme variability of expression is characteristic of FAVS.

Early detection and effective treatment of congenital hypoparathyroidism prevents the potentially debilitating physical and mental retardation, including refractory seizure disorder. Embryologically there is a probability of having agenesis or hypoplasia of the parathyroid glands

with defects of the branchial arches such as in FAVS. Hence, all babies of FAVS should have an estimation of serum calcium and phosphorus as a screening test, so that physical and mental retardation could be prevented.

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# Rituximab for Treatment of Autoimmune Hemolytic Anemia

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We report the successful use of rituximab as single treatment modality in a five-month-old boy with fulminant warm autoantibody autoimmune hemolytic anemia, resistant to standard treatment. On admission, laboratory tests showed a profound anemia with a hemoglobin of 2.6 g/dL. Indirect and direct antiglobulin tests were strongly positive, and nonspecific IgG autoantibodies were detected. Two days of intravenous corticosteroids (methylprednisolone 4mg/kg) and immunoglobulins (1g/kg) did not halt the hemolysis and the infant was severely transfusion-dependent. Rituximab 375mg/sq m weekly was given for 4 weeks, the hepatosplenomegaly gradually regressed, the lymphocytes normalized and he is free from hemolysis two years after treatment.

**Key words**: *Autoimmune hemolytic anemia, Rituximab*.

Autoimmune hemolytic anemia (AIHA) constitutes a group of diseases classified on the basis of the temperatures at which the autoantibodies exhibit their maximal reactivity to erythrocytes; warm AIHA has maximal reactivity at 37°C, and cold AIHA at 28-31°C [1]. Glucocorticoids and/or intravenous immunoglobulins are the mainstay of treatment in the majority of patients with warm AIHA [2,3]; however, when these treatments fail patients often require cytotoxic drugs or splenectomy.

We describe a 5-month old boy with a fulminant type warm AIHA resistant to the standard treatment who was successfully treated with rituximab.

**CASE REPORT**

A 5-month-old boy with an uneventful prior medical history was admitted to a regional hospital for investigation following two days of sudden onset pallor, malaise and anorexia. At presentation, his laboratory tests revealed a profound anemia with a hemoglobin (Hb) of 2.6 g/dL, RBC $0.9\times10^9$/L, MCV 98.2 fl, RTC 5.7%, WBC $15.4\times10^9$/L and platelets $638\times10^9$/L; total bilirubin levels were 127 micromol/L, with a direct fraction of 19.2 micromol/L. Indirect and direct antiglobulin tests were strongly positive, and nonspecific IgG autoantibodies were detected. Serum immunoglobulin levels were within the normal range for his age. Chest radiography was normal, and abdominal ultrasound revealed a mild splenomegaly and hepatomegaly. He received intravenous immnunoglobulins and corticosteroids; however the hemolysis continued and a transfusion of packed red cells was followed by severe hemoglobinuria. He then