

The 22Q11.2 Deletion Syndrome

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ABSTRACT

22q11. 2 deletion syndrome (velocardiofacial syndrome) is one of the most common genetic syndromes it caused by a micro deletion of chromosome 22 at the q11. 2 locus with a prevalence estimated 1 in 4, 000 live births The condition may actually be more common than is estimate.

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Key words: Velocardiofacial syndrome; 22q11.2 deletion syndrome; Radiographic finding in 22q11.2 deletion syndrome; Fluorescent in situ hybridization

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INTRODUCTION

22q11. 2 deletion syndrome (velocardiofacial syndrome) is one of the most common genetic syndromes it caused by a micro deletion of chromosome 22 at the q11. 2 locus with a prevalence estimated 1 in 4, 000 live births The condition may actually be more common than is estimate.

The clinical manifestation of the 22q11. 2 deletion are many with a wide spectrum of severity even among member of the same family, however some affected individual with a 22q11. 2 deletion have few signs and symptoms and are not diagnosed with the disorder, Characteristic signs and symptoms in 22q11. 2 deletion syndrome include congenital heart defects, palate defects, airway vascular problem and mild differences in facial features that are often present from birth. Significant feeding difficulties. Immunologic dysfunction due to abnormal T –cells, causing frequent infections. and some with autoimmune disorders rheumatoid arthritis and Graves' disease. Hemolytic anaemia Affected individuals may also have gastrointestinal or genitourinary tract abnormalities, musculoskeletal and neurological problem. Seizure as result of low level of calcium decrease in blood platelets (thrombocytopenia), and hearing loss. is seen in this children Learning disabilities, attention deficit hyperactivity disorder (ADHD) and developmental disorder such as autism and autism spectrum disorder is seen. In adult psychiatric disorders depression, anxiety, and bipolar disorder is seen.

The three distinct disorders in 22q 11. 2 deletion syndrome are DiGorge syndrome. Velocardiofacial syndrome and Conotruncal malformation.

Background

The 22q11. 2 chromosome deletion syndrome is a common genetic condition with variable features including: Airway, cardiac, vascular, gastrointestinal, genitourinary tract anomalies, musculoskeletal and neurological problems.

Objective

To describe the Radiology manifestation of the 22q11. 2 deletion Syndrome to improve recognition of these disorders.

Material and Methods

After institutional review board approval retrospective Radiographs of patient with chromosome 22q11. 2 deletion, confirmed by Fluorescence in Situ Hybridization(FISH) was reviewed.

Genetic Testing

22q11. 2 deletion syndrome is related to chromosome 22 and is Autosomal Dominant, However most cases of 22q11. 2 deletion syndrome are not inherited Majority of cases have a de novo (new to the family) The deletion occurs most often as a random event during the formation of reproductive cells or in early fetal development. Affected people typically have no history of the disorder in their family, though they can pass the condition to their children. A standard chromosome analysis will only detect 15% of the deletions associated with syndrome in approximately 10% of families, the deletion has been inherited from one of the parents. any individual who has this 22q11. 2 deletion has a 50 % chance with each pregnancy of passing it on to a child.

Fluorescent In Situ Hybridization (FISH) is highly sensitive and specific for 22q11. 2 deletion syndrome Testing for suspected of the 22q11. 2 deletion is recommended for patient with two or more relevant clinical feature of VCFS in any combination, particularly when the typical facies is associated with palatal anomalies, however there is high frequency of patient with 22q11. 2 deletion without cardiac defect so this test is recommended in children suspected 22q11. 2 deletion syndrome without cardiac defect^[1,2,3].

Prenatal Fluorescence in Situ Hybridization (FISH) analysis is available in high-risk pregnancies by amniocentesis at about 15-18 weeks of gestation. There is no genetic treatment of this disease, treatment is largely symptomatic

AIRWAY, VASCULAR MANIFESTATION

Airway

Airway problems are common and may involve either upper or lower airway or both. Upper airway obstruction is related to pharyngeal hypotonia or retrognathism, lower airway obstruction may be due to vascular ring or laryngeal web.

Velopharyngeal function is based upon, morphology of the velopharyngeal function which is composed of the soft tissues e. g.; posterior, lateral pharyngeal walls, velum, and adenoids tissue. And underlying bony structures e. g.; upper cervical spine, maxilla, basicranium. Alteration in any of these structures may play role in the pathogenesis of the velopharyngeal dysfunction. 22q11. 2 deletion syndrome is the most common genetic cause of velopharyngeal syndrome^[4,5].

Children with 22q11. 2 deletion syndrome demonstrate significant alterations in velopharyngeal anatomy, these patients have a significantly wider velopharynx, a shorter hard palate and a larger osseous pharyngeal depth (OPD); Velar length (VL) ratio (OPD; VL ratio), significantly more obtuse and voluminous airway, as there is flattened cranial base making it longer and the deeper pharynx. Alteration in cranial –base anatomy may be the single most important determinant of velopharyngeal dysfunction in 22 q11. 2 deletion syndrome (Figure 1) Magnetic Resonance Imaging provides an accurate assessment of airway without ionizing radiation, is

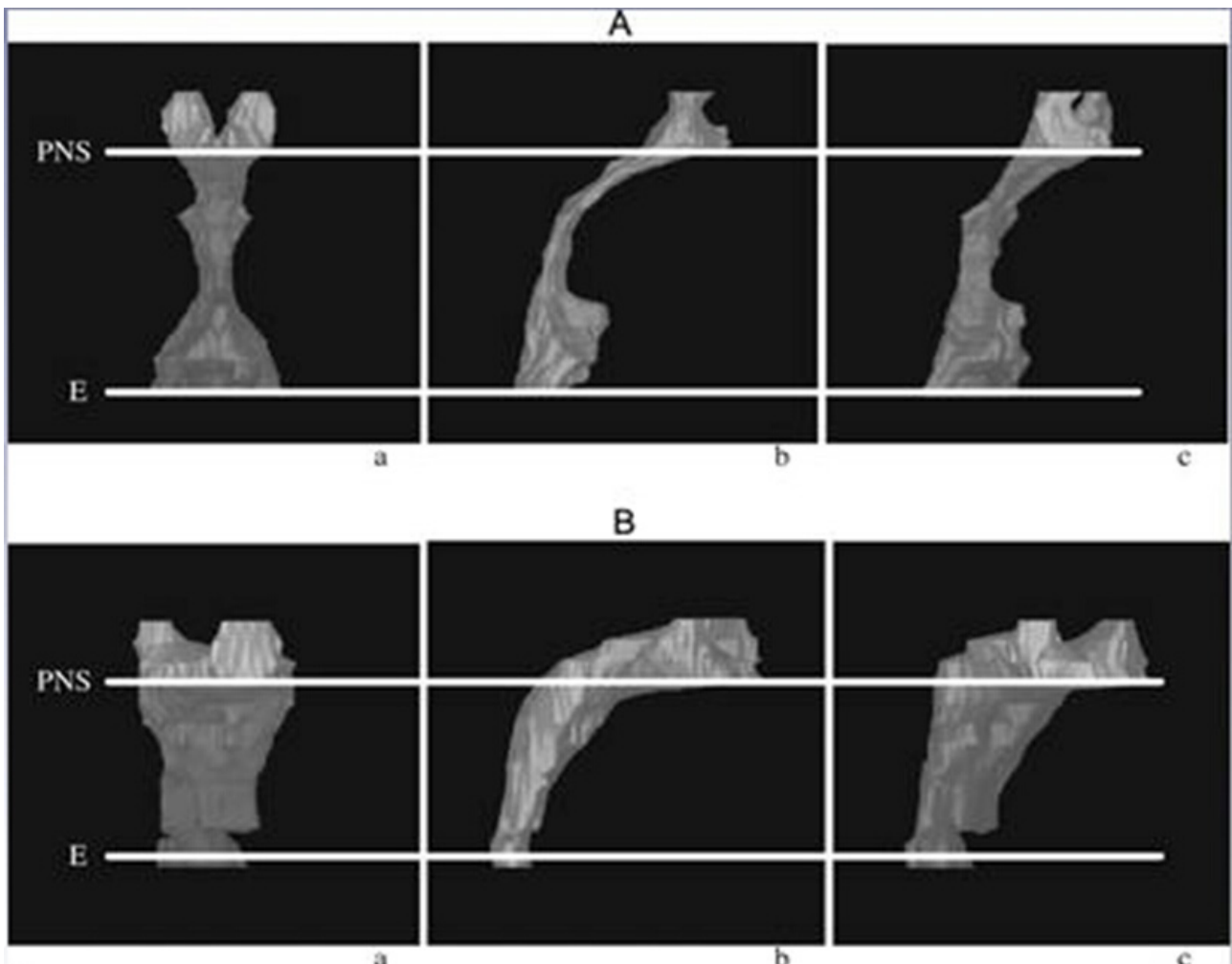


Figure 1 Courtesy Kirschner RE^[4]. A. normal airway VS; B airway in 22q11.2 deletion syndrome show significantly more Obtuse and voluminous airway wider velopharynx, Shorter hard palate, and larger OPD; VL ratio.

reproducible, rapid image acquisition and quantifiable assessment of velopharyngeal structures in 3D dimension imaging^[4-7].

Cardiovascular

There is high frequency of cardiac anomalies (70%) among children with 22q11.2 deletion syndrome. Congenital heart disease, particularly conotruncal malformations e.g. VSD tetralogy of fallot's, and truncus arteriosus (figure 3a, 4) While cardiac anomalies are fairly common and is major cause of mortality, head and neck vascular anomalies occur less frequently, interrupted aortic arch, lower carotid artery bifurcations, vascular ring (Figure 2), medial displacement of the carotid arteries, absence of the left common carotid artery with cervical origin of the right subclavian artery is seen. Thyroid abnormalities such as absence of a lobe, absence of the isthmus or retroesophageal extension of thymus is seen. Airway symptoms may related to subglottic stenosis, vocal cord paralysis, or laryngeal stenosis or squeals of vascular rings, and tortuous aortic arch^[1, 5, 6, 7].

MUSCULOSKELETAL

Skeletal abnormalities are common, including pre-post axial polydactyly in upper extremities, postaxial polydactyly of the feet, club foot and syndactyly of toes (Figure 6), Vertebral anomalies including butterfly vertebrae, hemi vertebrae coronal clefts scoliosis may be congenital or develop over time (Figure 3 bc), and coronal cleft, rib anomaly cranial synostosis (Figure 5), In spine cervical spine anomaly are significant it occur primarily in upper cervical spine including developmental variation of the occiput and cervical spine, e.g. platybasia (cranial basal angle is formed by a line drawn from tip of nasion to center of sella turcica then to anterior margin of foramen magnum. Normal angle is > 136 in patient with 22q11.2 deletion there is increase in this angle), basilar impression, C1-C2 dysmorphic shape spine Open posterior arch, occipitation are seen in atlas, upward lamina of the posterior element is seen in axis fusion of C2-C3 with increase mobility of C3-C4, increase occipitalatlantal motion are seen as well (Figures 7a, b, c)^[9, 10].

GENITOURINARY ANOMALIES

Genitourinary anomalies are usually asymptomatic, renal anomalies including large (Figure 13) or small kidney single kidney, renal agenesis, echogenic kidney, multicystic dysplastic kidney, horseshoe kidney duplicated collecting system and vesicoureteral reflux, absent uterus are seen in this children^[11, 12, 13].

GASTROINTESTINAL ANOMALIES

Feeding problems related to dysmotility in the pharyngo-esophageal area secondary to palatal defects and pharyngeal hypotonia dysphasia gagging regurgitation poor weight. Constipation delay gastric emptying may seen due to hypotonic gut muscles, multiple anatomic abnormalities are seen such as, anterior placed anus or imperforate anus, esophageal Atresia esophageal web esophageal diverticula (Figure 9), diaphragmatic hernia (Figure 10), intestinal Malrotation (Figure 11), Hirshprung, s disease (Figure 12)^[14].

NEUROLOGICAL DEFECT

Developmental delay, hypotonia are very common, Microcephaly, pachygyria, and polymicrogyria enlarge sylvian fissures tethered cord are reported. Protrusion of cerebellum tonsil through the foramen magna (Chiari 1) (Figure 8).

Reduced spinal canal and spinal cord dimensions is seen in 22q11.2 deletion relative to normal children in children with 22q 11.2 morphology of corpus callosum is different than normal children, the rostrum of the corpus callosum is larger and longer and has prominent bowing at the anterior callosum than in normal children^[15, 16].

Micro deletions in chromosomal 22q11 are associated with a roughly 30 fold increased risk of schizophrenia and are frequently detected in schizophrenic patients^[17].

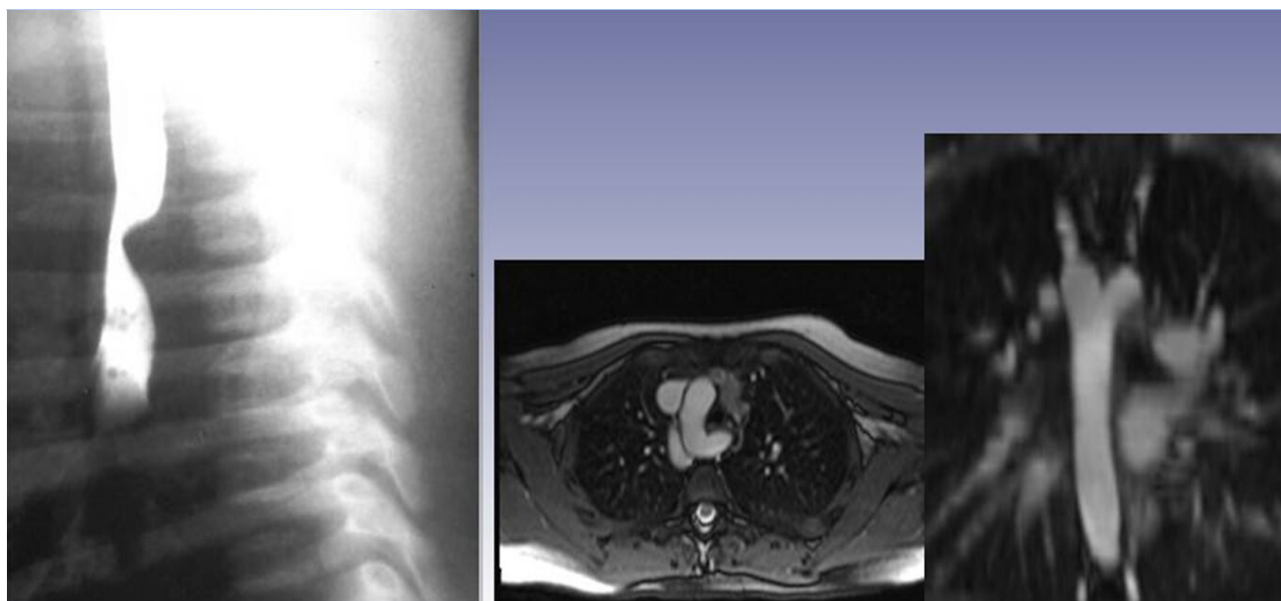


Figure 2 A: Barium swallow show posterior indentation of esophagus. B: Axial Coronal MRI shows right aortic arch with left aberrant subclavin.

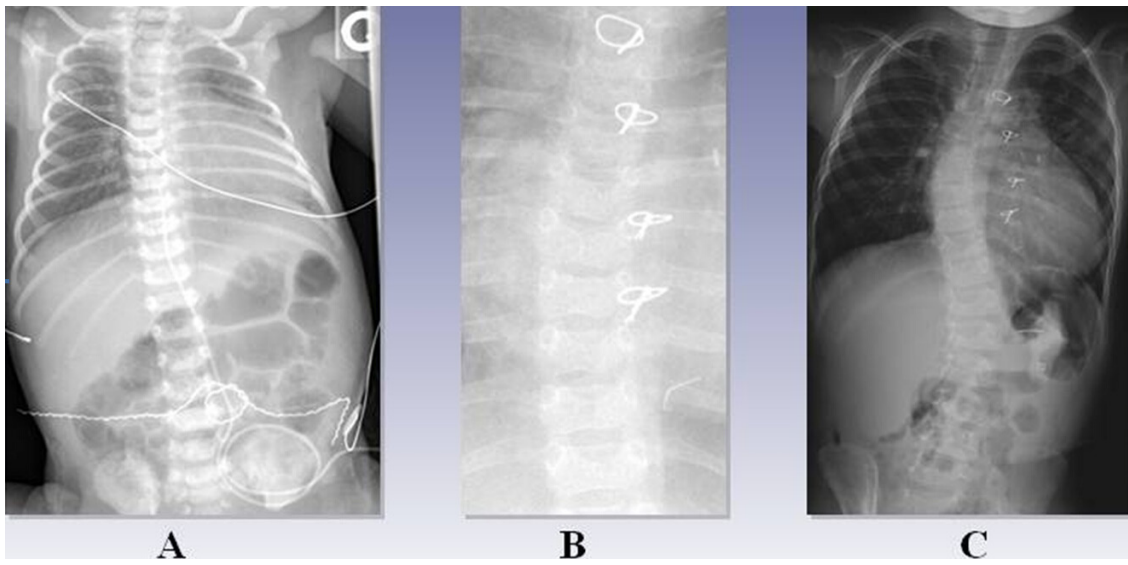


Figure 3 A: New Born with common truncus and butterfly vertebra. B: Condone view of spine post OP shows C6 butterfly vertebra. C: Scoliosis seen at age 4.

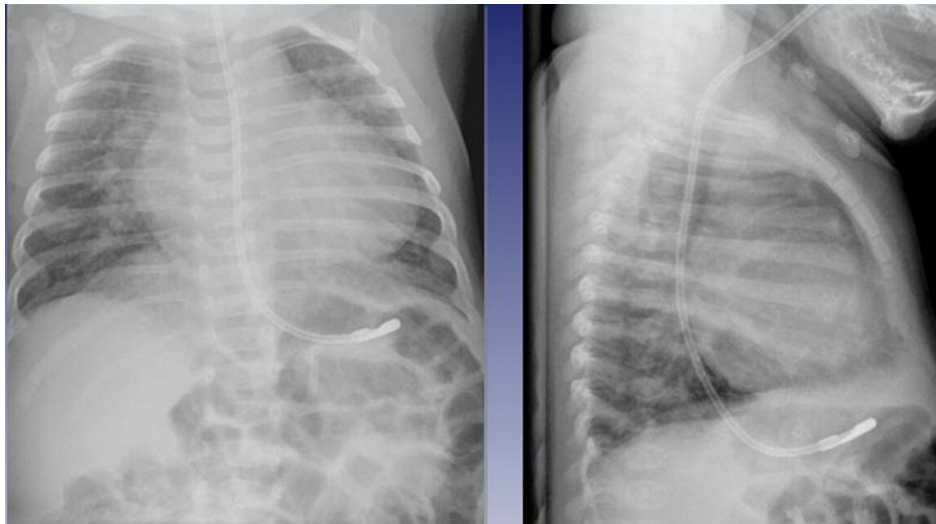


Figure 4 AP/Lateral chest shows large heart and increase blood flow (VSD) in 4 year old with 22q11.2 deletion.

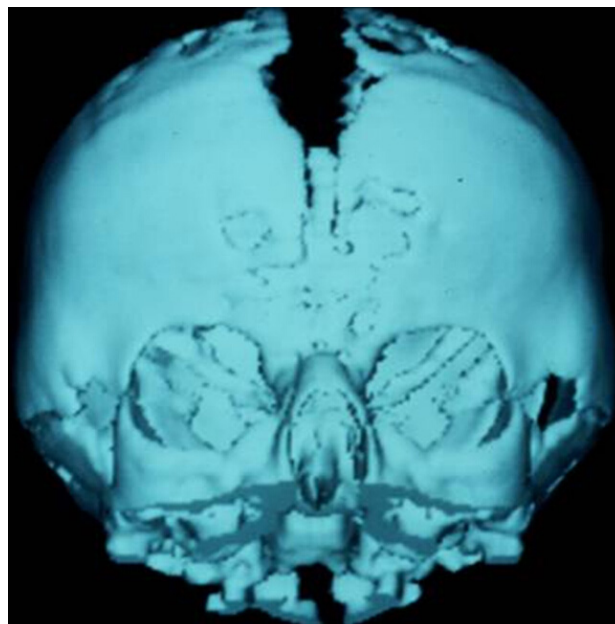


Figure 5 Cranial synostosis seen in 3D image in 22q.11.2 deletion syndrome.



Figure 6 A. B in 22q11.2 deletion. A: pre.postaxial polydactyly of both hands. B: Posaxial polydactyly of both feet.

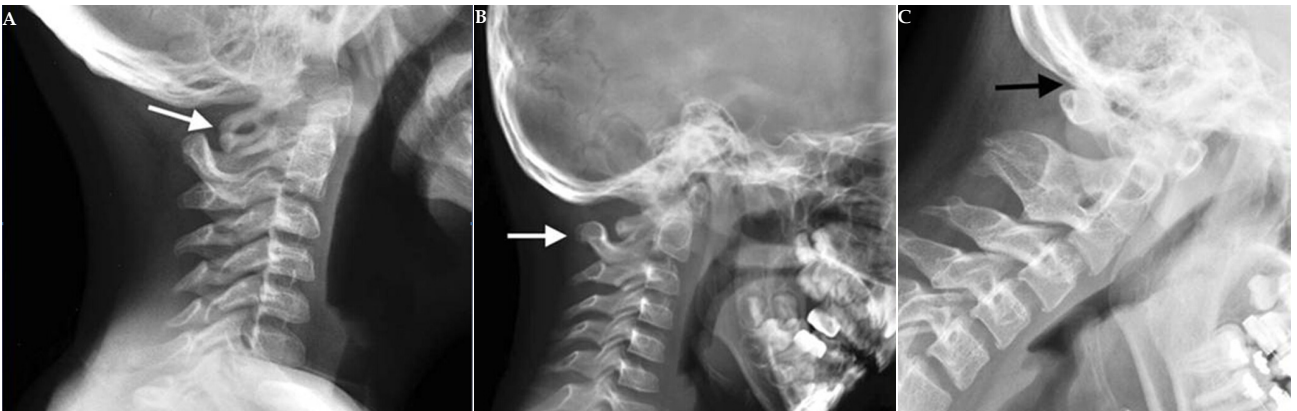


Figure 7 A: 3 year old with platybasia ,fusion of posterior element of C2/C3,and open posterior arch of C1; B: 2 year old with platybasia ,small dimorphic atlas and upward lamina of posterior axis. 7: 6 year old with occipitization C1 and fusion of C2/C3.

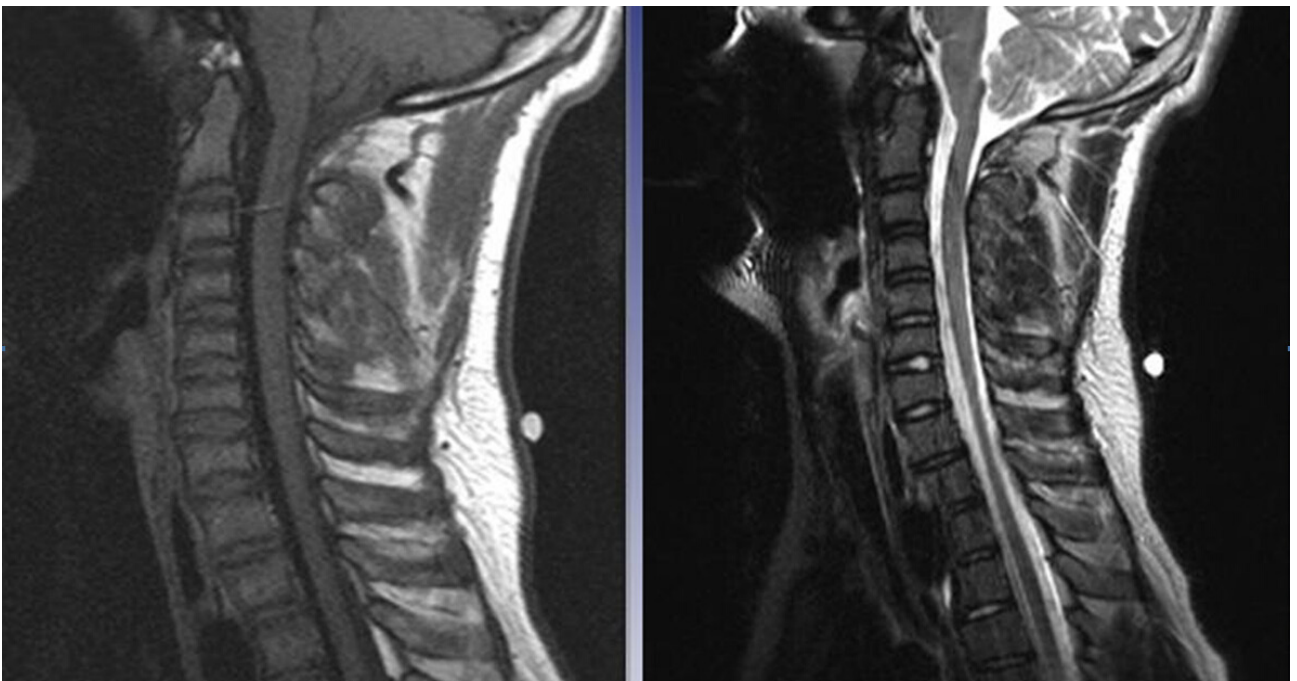


Figure 8 MR cervical spine in 13 year old. With Chiari1 Sagittal T1/T2 Weighted image shows mild protrusion of cerebella through the foramen of magna.



Figure 9 A: 6year with 22q11.2 deletion syndrome old with severe GE reflux. B: 2 year old 22q11.2 deletion syndrome with esophageal diverticulum and web.



Figure 11 3 year old with 22q11.2 deletion syndrome UGI shows malrotation.



Figure 10 3 year old with 22q11.2 deletion syndrome, plain radiograph of chest shows delayed left diaphragmatic hernia.



Figure 12 2 years old with 22q11.2 deletion syndrome Lateral Barium enema shows short segment Hirschsprung's disease.

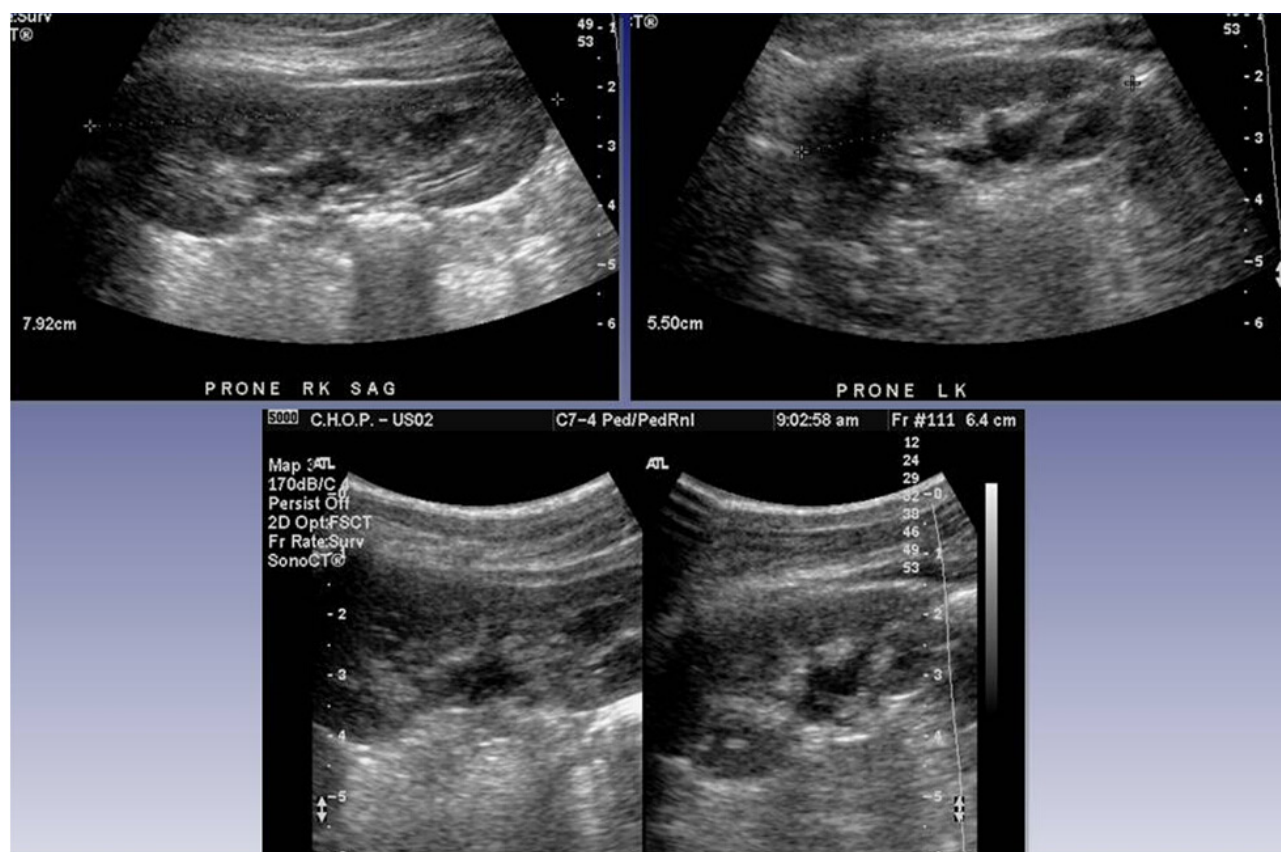


Figure 13 2 years old 22q11.2 deletion syndrome „Renal ultrasound shows bilateral enlarge kidneys.

DIFFERENTIAL DIAGNOSIS

Some of the anomalies that seen in 22q11. 2 deletion syndrome area seen as an isolated finding in children without 22q11. 2 deletion these overlapping features of 22q11. 2 deletion syndrome are seen in; Smith –Lemli-Optiz syndrome when there is polydactyly and cleft palate are present in this group molecular genetics formulation of the DHCR7 gene is available for this diagnosis, other one is Alagille syndrome when there is congenital heart disease and butterfly vertebra is present and also in Goldenhar syndrome when there is vertebral, renal anomalies and congenital heart disease are present^[11].

CONCLUSION

Radiographic finding in 22q11. 2 deletion syndrome are relatively common and should be recognize by General and Pediatric Radiologists.

CONFLICT OF INTEREST

There are no conflicts of interest with regard to the present study.

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