Abstract. – The Pierre-Robin Syndrome (PRS) is a rare congenital abnormality, with an approximately 1/30,000 estimated rate, characterized by the presence of the combination of mandibular hypoplasia (micrognathia or small jaw), glossoptosis (retrusion of the tongue into the pharyngeal airway) and, often, a posterior cleft of the secondary palate. It may be an isolated occurrence or part of a more complex syndrome and it is associated with long-term respiratory, nutritional, and developmental difficulties. Stickler syndrome (SS) is a rare autosomal dominant connective tissue disorder estimated to affect approximately 1/7500 newborns. It is diagnosed clinically and, at present, there is no consensus on a minimal clinical diagnostic criterion. The most frequent diagnosis in patients with syndromic Pierre Robin sequence is Stickler syndrome, which may be complicated by congenital high myopia and substantial risk of retinal detachment. However, cases of Stickler syndrome with probable visual complications are rarely identified among this group of patients by members of the cleft team.

Micrognathia is a facial abnormality characterized by a small mandibular size resulting in the impression of a receding chin that is detected by midsagittal imaging of the fetal facial profile; frequently in PRS there is an associated posterior cleft palate or a high arched palate.

We report two extremely rare cases of prenatal diagnosis of PRS and SS, prematurely identified by oculists ophthalmologists and successively managed by oculists ophthalmologists.

Key Words:

Pierre-Robin Syndrome, Stickler syndrome, Ultrasonography, Prenatal diagnosis neonatal disease, Ocular disease, Micrognathia, Glossoptosis, Respiratory distress, Ipertelorism, Strabismus, Myopia.

Introduction

The Pierre-Robin Syndrome (PRS) is a rare malforming pathology and its estimated frequency is approximately 1/30,000\(^1\). PRS is characterized by micrognathia, glossoptosis and respiratory distress at birth due to a glossoptosis-apnea syndrome, which determines an obstructive respiratory symptoms\(^2\).

Stickler syndrome (SS) is a rare autosomal dominant connective tissue disorder estimated to affect approximately 1/7500 newborns. It is diagnosed clinically and, at present, there is no consensus on a minimal clinical diagnostic criterion\(^3\). The most frequent diagnosis in patients with syndromic Pierre Robin sequence is Stickler syndrome, which may be complicated by congenital high myopia and substantial risk of retinal detachment. However, cases of Stickler syndrome with probable visual complications are rarely identified among this group of patients by members of the cleft team\(^4\).

Micrognathia is a facial abnormality characterized by a small mandibular size resulting in the impression of a receding chin that is detected by midsagittal imaging of the fetal facial profile; frequently in PRS there is an associated posterior cleft palate or a high arched palate\(^5\).

In about 30% of cases PRS may be an isolated occurrence, while, in the following 30%, it is related to other anomalies and in the last third of cases it is part of a more complex syndrome (most frequently Stickler Syndrome). This multiplicity of expressions is the result of a mixed genetic origin: in 40% of cases PRS is genetically isolated, otherwise it is a recessive or dominant autosomal condition\(^6\).
Diagnosis of PRS may be made immediately when a neonate presents in respiratory distress with micrognathia. Further clinical examinations may show the posterior placement of the tongue and possibly a cleft palate, but neonatal diagnosis may be delayed if mandibular malformations and cleft palate are minimal and difficulties only occur with feeding and supine positioning.

Prompt detection leads to effective airway management and prevention of hypoxic sequelae. PRS is not generally diagnosed before birth, because of prenatal diagnosis is extremely hard, since there are no specific pathologic signs. Thus, to the best of our knowledge, a rare cases of prenatal diagnosis had been described.

Case Report 1

A 32 year’s old female, IInd pregnant woman, was referred to our Department of Obstetric and Gynaecology, for a routine ultrasonic check at 28 gestation’ weeks. In this occasion the biometric fetus parameters were appropriate with assigned gestational age, but a moderate polyhydramnios and a slight high inter ventricular sub-aortic imperfection were detected by ultrasonography (US). Besides, a mid-saggital US scan showed a typical image of “receding chin” (called micrognathia) (Figure 1).

After these US findings, a careful anamnesis was conducted and no anomalies appeared during this gestational age, while a particular maternal phenotype characters (height above norm, hypoplasic chin) with a paternal ones (serious myopia, with more than 15 dioptres) were founded.

The complexity of the situation suggested the hypotesis of a more complex syndrome, most likely on the cromosome basis. Through a funicular scan, a rapid fetal karyotype was obtained and it was normal. The sum of all these findings lead to belive that a PRS or SS existed, without altered karyotype. Submitted to further sonographic examinations, the fetus didn’t shown any significant US alterations, if compared with previous findings and the woman delivered in eutocia, during the 36th week, preceded by the breaking membrane.

The male newborn weight was of 3150 g, with an Apgar index of 8, at first minute and 5, at fifth minute, because of respiratory distress with cyanosis during the inspiratory phase (glossoptosis-apnea syndrome). Neonatal immediate examination confirmed the troubles caused by micrognathia of medium degree and by glossoptosis. PRS also pointed out by the presence of a posterior cleft palate, which gave value to the antenatal diagnostic suspect of the PRS.

Heart US scan confirmed the prenatal diagnosis of an interventricular subaortic defect, with a slight mitral insufficiency, but a pulmonary hypertension was absent. After a temporary endotracheal intubation, the infant had no respiratory difficulties; the feeding was necessary primarily through a nose gastric tube and, successively, by a palatine plaque.

Six months later, the palatoschisis was perfectly surgically corrected, than the infant was submitted to surgery for retina detachment. At the present time, the inter ventricular defect is compensated and he doesn’t need any surgical intervention. Moderate ipertelorism, strabismus and high myopia were showed by ophtalmic test, but the infant is in good health and he has a normal psychomotor and intellective development.

**Figure 1.** In this second-trimester (28 weeks’ gestation), a midsaggital US scan of the fetus profile [A] shows a typical image of “receding chin” (micrognathia). The prenatal findings fetal facial profile, with micrognatia were confirmed at birth [B].
Six months later, the palatoschisis was perfectly surgically corrected. The infant showed, at multidisciplinary consulting, a Stikler syndrome associated to a Pierre Robin sequence (micrognathia, glossoptosis and respiratory distress at birth, due to a glossoptosis-apnea syndrome), so he was referred to the emergency Department of Ophthalmology, Sapienza University, Rome, Italy.

The patient had an acute unilateral hydrops, with a monolateral keratoconus (Figure 3). The ocular abnormalities included: severe myopia, abnormalities of the vitreous, and high risk of retinal detachment (with subsequent blindness). Initial management consisted in eye patching, hypertonic saline and cycloplegia. However, the long-term prognosis for visual rehabilitation remained poor in this young patient, because of the presence of a central corneal opacity and inability to comply with contact lenses. She was not an appropriate candidate for keratoplasty, due to her mental retardation. This report highlights an association of keratoconus and myopia in patients with SS associated at Pierre Robin sequence.

Discussion

The examination of normal facial profile and the distance between the ocular orbits is one of the most important phases in US scan and, actually, it should be routine in all medical centres,
but the presence of US fetal anomalies, at this level, often could reveal some problems of chromosomal and genetic origin.

In our case, the PRS has been supposed on the basis of described US findings, the presence of a slight high interventricular defect and of a particular family phenotype. Anyway, the negative karyotype didn’t invalidated our doubts about the possibility that PRS may occur both isolated or associated with other syndromes independently from any chromosomal pathology8. Otherwise, any heredity related to a chromosome defect of genetic origin, could not be pointed out by a simple karyotype examination.

A recent study was undertaken, by fetal US was prospectively performed in 8000 consecutive pregnancies at 14 to 24 weeks’ gestation and retrospectively revaluated ultrasound recordings of 4 fetuses from other hospitals at 22 weeks’ gestation diagnosis, in order to describe the US features of fetal glossoptosis in the PRS. Glossoptosis, defined as a posteriorly displaced tongue that never reached the anterior mandibular alveolar ridge while watching the fetal profile, with micrognathia was excluded in mostly of pregnancy and there were no false-negative diagnoses in 7,998 fetuses. The study conclusion was that a US identification of glossoptosis with fetal micrognathia strongly suggests the possibility of fetal PRS1,2.

The presence of craniofacial anomalies, associated to a particular and suggestive family phenotype for the PRS associated a Stikler syndrome of myopia and other ocular diseases9, with high risk of retinal detachment have to induce obstetrics to search other connected clinical anomalies and, first of all, to study the karyotype and to put a particular attention in the US analysis for labiopalatoschisis and heart fetus diseases10.

In conclusion, Authors consider prenatal diagnosis of PRS as very important, since it permits to face glaucofungnosis-apnea syndrome at birth, to get ready for further closure of palate anomalies and to get back the cleft palate to normal within the first six years11. Stikler syndrome can be sub-classified into type 1, 2 and 3, but there is a considerable clinical overlap in symptoms. Patients with mild symptoms may be undiagnosed. Once the diagnosis is established, a coordinated multidisciplinary follow-up approach is recommended12.

Early identification of Stikler syndrome in children with Robin sequence by cleft surgeons is necessary to insure early referral to an ophthalmologist for detection of myopia, monitoring for retinal detachment, and prevention of visual complications4,13,16.

References