# A case of severe type of cerebro-costo-mandibular syndrome

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**SUMMARY**

**Introduction** Cerebro-costo-mandibular syndrome (CCMS) is a rare disorder, with only 75 cases described in the literature to date. CCMS is characterized by association of micrognathia and specific multiple rib defects. It is accompanied by mental deficiency in considerable number of cases. Sometimes, there are associated anomalies and problems, such as spine deformities, brain, heart, kidney or ear anomalies, feeding difficulties, delayed psychomotor development, and growth impairment. Depending on severity of deformities and consecutive respiratory insufficiency, in about 35–50% of CCMS cases, death occurs during the first year of life. These cases are referred to as severe types of CCMS.

**Case Outline** In this paper we present a female infant with severe type of CCMS. Diagnosis was established in the first day of life, based on micrognathia and findings of posterior rib-gap defects on the chest X-ray, accompanied by dyspnea. Progressive severe respiratory insufficiency caused by chest and air-way deformities and exacerbated by episodes of pneumonia, led to respiratory failure and death at the age of 7.5 months.

**Conclusion** CCMS should be considered in every infant with micrognathia and rib-gap defects on chest X-ray.

**Keywords**: cerebrocostomandibular syndrome; rib-gap defects with micrognathia; micrognathism; respiratory insufficiency; ribs; congenital abnormalities

## INTRODUCTION

Cerebro-costo-mandibular syndrome (CCMS) is a rare disorder, originally described by Smith et al. [1] in 1966. Seventy-five cases have been published in the literature since then [2]. Most published cases are from Western European countries, Asian countries, and the USA. To the best of our knowledge, this is the only one published from Western Balkans countries.

The main characteristics of this syndrome are specific rib defects and micrognathia [2, 3]. It is accompanied by mental deficiency in a considerable number of cases. Sometimes, there are associated anomalies and problems, such as spine deformities, brain, heart, kidney or ear anomalies, feeding difficulties, delayed psychomotor development, and growth impairment.

The etiopathogenesis of CCMS is still not fully explained. A significant number of cases occur sporadically [2, 3]. Cases associated with consanguinity have also been described, as well as those with CCMS in siblings, suggesting autosomal recessive inheritance [4, 5, 6]. Finally, cases of CCMS in parents and their offspring have also been published, indicating autosomal dominant type of inheritance with variable gene expression [7, 8]. Recently, significant progress in genetic basis of CCMS has been achieved. In 2014, Lynch et al. [9] published a paper on genetic testing performed in a cohort of ten families with CCMS members – seven families with sporadic CCMS cases, two with parent-child transmission, and one with CCMS in siblings of unaffected parents. Heterozygous mutations in the small nuclear polypeptids B and B1 (SNRPB) gene were found in probands [9]. SNRPB belongs to non-coding conserved elements of the human genome. These elements have an important regulatory role through their impact on mechanism of alternative splicing, process of great importance for creation of additional protein diversity. Mutations in SNRPB gene, with consecutive defect in the splicing machinery, cause developmental disorders characteristic of CCMS. Mutation analysis suggested that CCMS is an autosomal dominant disorder with possibility of non-penetrance, as well as a high rate of de novo mutations [9]. Deregulation of SNRPB expression as the main mechanism for CCMS was confirmed by Bacrot et al. [10], through results of genetic testing of five CCMS patients.

We present a case of an infant with CCMS diagnosed on the first day of life. The authors showed the clinical course of the severe type of CCMS, and pointed to evolution of findings observed at birth and their clinical implications.

## CASE REPORT

A female infant was born as the second child of a 22-year old healthy mother, from a non-consanguineous marriage. The course of this pregnancy was uneventful, with appropriate prenatal care. The family history was unremarkable. The older sibling is a healthy girl.

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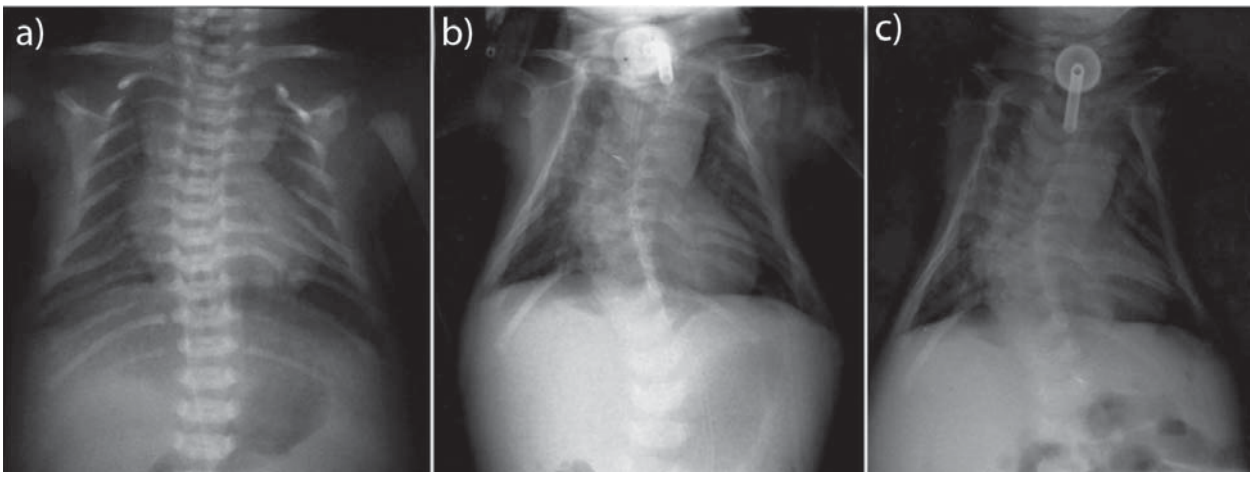


**Figure 1.** Chest X-rays of the infant showing 11 pairs of ribs, posterior rib-gap defects on the 2nd–9th rib bilaterally, narrow ribcage and spine deformity. Photographs were taken at the age of (a) one day, (b) four months, and (c) 6.5 months.

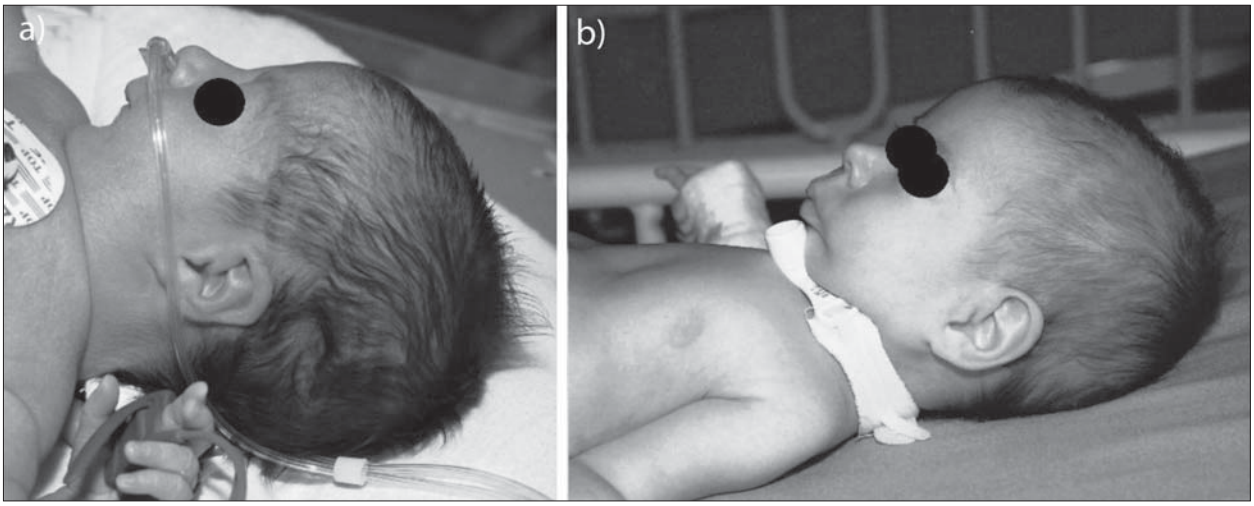


**Figure 2.** Infant's face profile with micrognathia and retrognathia. Photographs were taken when the infant was at the age of (a) two days and (b) 5.5 months; on photograph (b) tracheal stoma is present.

The pregnancy was terminated at 38 weeks of gestation, with spontaneous vaginal delivery at a local maternity hospital. Apgar score was 4, 6, and 7 at 1, 5, and 10 minutes after birth, respectively. The birth weight was 2,800 g (25 p), birth length was 49 cm (50 p), head circumference was 36 cm (>90 p), and chest circumference was 32 cm (25 p). The baby was resuscitated at birth, since she did not show spontaneous respiratory effort. Respiratory support via nasal continuous positive airway pressure was applied afterwards. During the first day of life she was transferred to our neonatal intensive care unit for further evaluation and treatment.

On admission, several malformations were observed: retromicrognathia, high-arched palate, hypertelorism, low-set malformed ears, narrow chest, wide-set nipples, redundant skin and muscle hypotonia.

Chest X-ray on the first day of life showed a narrow, bell-shaped thorax with eleven pairs of ribs, with posterior rib-gap defects of the second to ninth rib on both sides (Figure 1a). This finding, accompanied with retromicrognathism (Figure 2a), pointed to cerebro-costo-mandibular syndrome.

Cranial ultrasound showed signs of brain hypoxia. Karyotype and laboratory tests including initial laboratory screening for immunodeficiency (complete blood count with differential, measurement of serum immunoglobulin and complement levels), echocardiography, ultrasound of abdominal organs and hips, electroencephalography and ophthalmologic tests were unremarkable.

From the second day of life, the infant breathed spontaneously, with oxygen therapy (30% oxygen), but was occasionally tachypneic and dyspneic. At the age of five weeks, respiratory insufficiency appeared. The underlying cause was pneumonia. The infant was endotrachealy intubated, and mechanically ventilated, with appropriate antibiotic therapy and supportive measures. In further course, clinical, ultrasonographic and radiologic sings of pneumonia resolved, but attempt to wean the infant from respiratory support repeatedly failed. Since there was a prolonged need for mechanical ventilation, tracheotomy was performed at the age of two months. During the intervention, it was noticed that tracheal rings were rather thick, with narrower tracheal air-path than expected according to the body size. Two more occasions of pneumonia accompa-

doi: 10.2298/SARH1608431M

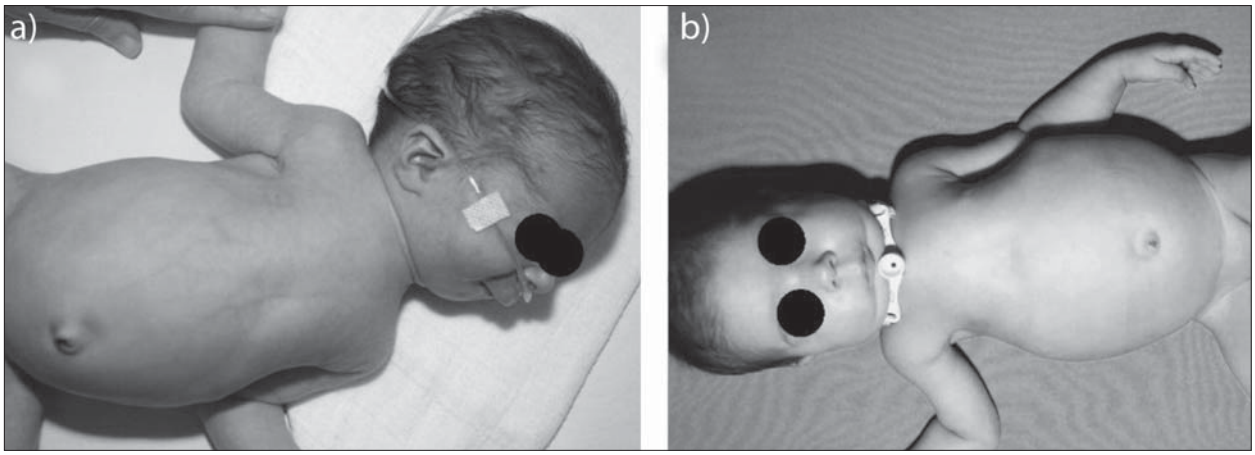


**Figure 3.** Infant's body with narrow chest. Photographs were taken when the infant was at the age of (a) two days, and (b) 5.5 months; on photograph (b) tracheal stoma is present.

nied with pleural effusions were diagnosed until the age of five months. After resolving of infections, the respiratory function improved, despite even more gracile appearance of the narrow thorax. Respiratory physiotherapy was initiated on a regular basis.

At the age of 5.5 months, mechanical ventilation was discontinued, with oxygen applied via tracheal stoma. At this age, the infant's body weight was 4,180g (< 3 p), body length was 56 cm (< 3 p), head circumference was 38 cm (< 3 p), and chest circumference 33 cm (< 3 p). Monitoring of anthropometric parameters confirmed further discrepancy between chest and head circumference, which rose from 4 cm at birth to 5 cm at the age of almost six months (Figure 3). Micrognathia also seemed more pronounced over time (Figure 2). Subsequent chest X-rays showed a more pronounced deformity of the chest, which took on a triangular shape, with reduced lung surface (Figure 1b, c). Also, scoliosis of the spine was observed. Its exacerbation over time was noticed as well (Figure 1b, c). Examination of psychomotor development showed a significant delay with pronounced muscle hypotonia at the age of six months. Nourishment was implemented through a gastric tube. Hypercaloric diet was given because of malnutrition, but weight gain was still poor. Neuromotor stimulation treatment was implemented, in order to improve infant's development as well as respiratory muscles' strength.

At the age of seven months, another episode of pneumonia appeared, caused by multiresistant strain of *Pseudomonas aeruginosa*. Over the next few days, global respiratory insufficiency developed gradually. Respiratory support was reinitiated, accompanied with already started antimicrobial and supportive therapy. Despite all the measures taken, clinical condition was further deteriorating and the infant passed away at the age of 7.5 months.

Autopsy was not performed, on parents' request.

## DISCUSSION

Clinical manifestation of CCMS may vary, but rib-gaps and micrognathia are mandatory findings. Typical posterior rib-gap defects are pathognomonic finding in CCMS [11, 12]. These basic clinical and X-ray findings are sufficient for the diagnosis. Micrognathia can be accompanied by cleft palate, but is always of significant degree. Rib abnormalities originate from replacement of the bone tissue between costovertebral junction and the lateral arch with undifferentiated fibrous and muscle tissue, or cartilage [7, 13].

In differential diagnosis one should take into consideration other entities accompanied by micrognathia and thoracic and rib abnormalities [14, 15, 16]. Thoracic X-ray may mimic multiple costal fractures at birth, especially when resuscitation is applied, as in our patient. Spontaneous rib fractures were also described in some cases of vaginal delivery [17]. Concomitant presence of micrognathia and posterior rib-gap defects which are present on subsequent X-rays without callus formation are clues for correct diagnosis. In trisomy 18, 11 pairs of thin and hypoplastic ribs and micrognathia are often present [15]. Other typical features and organ abnormalities, as well as karyotype reveal the true diagnosis. Robin sequence is characterized by micrognathia, but without accompanied rib abnormalities. More than 50% of infants born with Robin sequence have associated syndrome or anomalies, including skeletal dysplasias [14], but not specific posterior rib-gap defects, except in the case of CCMS. Infants born with atelosteogenesis type I and campomelic dysplasia have also small, narrow thorax at birth [16, 18], but very distinctive other clinical and radiological features.

Literature data indicate that in about 35–50% of CCMS cases, death occurs during the first year of life [12]. Nagasawa et al. [2] classified CCMS according to severity into the following three types: lethal CCMS, where death occurs during the first month of life; severe type, where death occurs between the first and 12th month of life; and mild type, where patients live more than a year. Analyzing the descriptions of previously published cases, the same authors concluded that patients with severe type of CCMS had respiratory infections significantly more often than patients with a mild type [2]. Poor respiratory functions and frequent respiratory infections present the main causes of death in infants with severe CCMS. Their origin lies in underventilation of lungs, lying position in bed, and often microaspirations because of feeding difficulties. Special

issues are infections with multiresistant hospital strains in hospitalized patients with CCMS [19]. In our patient, there were deformities of tracheal cartilages and of thoracic spine. Combination of micrognathia, rib and spine deformities, and deformities of tracheal cartilages caused air-way disturbances and flail chest, with consequent respiratory distress. Exacerbations coincided with respiratory infection, causing a vicious circle, which eventually led to fatal outcome.

In several other case reports of CCMS, there were some other anomalies: ear anomalies [21], conductive hearing loss [7], cardiac anomalies [12], renal cysts [12], central nervous system anomalies [5], mycrocephaly [5], occult spina bifida [2], other bone deformities – except ribs and mandible [5], arthrogryposis [21], and urogenital anomalies [5]. All these deformities are sporadic and have low incidence [6, 11].

Mental deficiency was found in a considerable number of cases with CCMS [4, 7, 8, 9, 11], but there were also reports of normal intelligence [8, 12]. At first, it was considered that mental retardation is inherited, and, as such, a part of this syndrome; hence the "cerebro" part of the acronym. Recently, most authors see mental deficiency as a consequence of neonatal hypoxic brain injury [8], with the exception of cases accompanied with mycrocephaly, cerebral abnormalities or extensive perivascular calcification as a basis for mental retardation [5, 20].

At birth, head circumference is normally greater than chest circumference, and equalization of these two measures takes place at the age of about six months [22]. In our patient, chest circumference was considerably smaller than head circumference at birth. This difference was even greater at the age of six months. Chest deformity played an important role in reduction of respiratory capacity. This is obvious from subsequent chest X-rays (Figure 1), as well as from simple observation of the infant over time (Figure 3).

Figueroa et al. [23] postulated that a certain number of infants with micrognathia show accelerated growth of the mandible during the first year of life, thus resolving airway obstruction. In our patient, micrognathia seemed to be even more pronounced at the age of six months than at birth (Figure 2). In some other cases of CCMS, authors also noticed lack of mandibular catch-up growth over time [2].

Maintenance of airway patency is a key point in early treatment of infants with CCMS. Depending on the nature and severity of respiratory distress, one should try conservative methods first – prone positioning, nasopharyngeal airway, laryngeal mask [24], or continuous positive airway pressure via nasal mask, as applied in our patient. If and when these measures become insufficient, surgical interventions must be considered. Tracheotomy was performed in our patient, considering artificial ventilation dependence and pneumonia present at the time. Finding of the abnormalities of tracheal cartilages during the intervention confirmed that it was a right decision. In several other reported cases, tracheotomy was performed in patients with CCMS [12, 13, 21, 25]. In some other cases, a tongue-lip adhesion operation [24] and bilateral mandibular osteostomy and osteogenic distraction [8] were succesfully performed, but in infants without airway narrowing below the tongue base.

In conclusion, CCMS should be considered in every infant with micrognathia and rib-gap defects on chest X-ray. These infants need careful monitoring of respiratory functions, and surveillance of respiratory infections. Furthermore, their physical and psychomotor development requires frequent assessment. Rapid and accurate diagnosis is basic for proper information for parents' expectations regarding health problems and life span of the child, as well as for genetic counseling in subsequent pregnancies.

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## Случај тешког облика цереброкосто-мандибуларног синдрома


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**КРАТАК САДРЖАЈ**

**Увод** Цереброкосто-мандибуларни синдром (*CCMS*) редак је поремећај. До сада је описано 75 случајева. Главна карактеристика овог синдрома је удружено присуство микрогнатије и мултиплих специфичних дефеката ребара. У значајном броју случајева *CCMS* је удружен са менталним дефицитом, а понекада са неким другим аномалијама и проблемима: деформитети кичме, аномалије мозга, срца, бубрега и ува, тешкоће у храњењу, успорен психомоторни развој, заостатак у расту. У зависности од тежине деформитета и последичне респираторне инсуфицијенције, *CCMS* у око 35–50% случајева доводи до смртног исхода у првој години живота. Такви случајеви спадају у тежак облик *CCMS*.
**Приказ болесника** У овом раду приказујемо женско одојче са тешким обликом *CCMS*. Дијагноза је постављена у првом дану живота, на основу постојања микрогнатије и специфичних дефеката ребара на рендгенском снимку грудног коша, праћених диспнејом. Прогресивни поремећај респираторне функције, узрокован деформитетима грудног коша и дисајних путева и погоршан епизодама пнеумоније, довео је до респираторне инсуфицијенције и смрти у узрасту од 7,5 месеци.
**Закључак** Дијагнозу *CCMS* треба имати на уму код сваког одојчета са микрогнатијом и специфичним дефектима ребара на рендгенском снимку грудног коша.



**Кључне речи:** цереброкосто-мандибуларни синдром; дефекти ребара са микрогнатијом; микрогнатизам; респираторна инсуфицијенција; ребра; урођене абнормалности

**Примљен • Received:** 10/08/2015 **Ревизија • Revision:** 02/11/2015 **Прихваћен • Accepted:** 10/11/2015