



# Cornelia de Lange Syndrome with Hypernatremia: Two Case Reports

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## Abstract

Cornelia de Lange syndrome (CdLS), is a genetical syndrome which can be seen as hereditary, or sporadically. Characteristical appearance is very crucial for diagnosis. Although almost all patient shave characteristical face appearance, depending on the severity of the cases, some accompanying symptoms could be skeletal and extremity defects, gastrointestinal system diseases, central nervous system anomalies and related diseases, genitourinary system anomalies, or heart defects, vision and hearing problems. In this paper, two patients with holoprosencephaly and recurrent episodes of hypernatremia are minded us to reconsider CdLS as a differential diagnosis of hypernatremia. We also point out some important steps in the treatment of the hypernatremia.

**Keywords:** Cornelia de Lange syndrome, hypernatremia, holoprosencephaly

## INTRODUCTION

Cornelia de Lange syndrome (CdLS), also known as Brachmann de Lange syndrome, was first as reported by W. Brachmann in 1916, and it was described by CdLS in 1933 (1). CdLS has been defined as a syndrome that includes microcephaly, synophysis (lush and thick, curved eyebrows in the midline), long lashes, deep orbital arch, small and blunt nose, antevert nostrils, long philtrum, thin upper lip, wide-spaced small teeth, small chin, big ears, posterior or low anterior hairline, bushy hair, distinctive phenotypic features, mental retardation or learning disabilities, intrauterine growth retardation, prematurity, retardation of postnatal growth and development, developmental anomalies of hands and feet, widespread or regional hypertrichosis, heart defects, eye and genitourinary anomalies, hearing loss, gastro esophageal dysfunction (2,3). According to phenotypic properties, type 2, CdLS classic type (type 1) and mild type (type 2) have been identified. Type 2, which shows mild phenotypic characteristics, has a better prognosis than the classical type (2,4,5). Two cases

presenting with hypernatremia and diagnosed with CdLS were presented here.

## CASE PRESENTATIONS

### Case 1

The eleven-month-old girl was admitted to the pediatric emergency outpatient clinic with symptoms of vomiting, coughing, wheezing and weakness. Twenty five-year-old mother's follow-up without problems as the first baby after 41 weeks of uncomplicated pregnancy by cesarean section and she weighted 4,000 gr. It was learned that she had a convulsion on the second day after birth and stayed in the neonatal intensive care unit for 2 months due to the neonatal jaundice.

When she applied to the clinic, the general condition was medium-bad, severe dehydrated appearance, turgor tone decreased, Glasgow Coma score 11, fever 37 °C, respiratory rate 50-55/min, pulse 146/min, blood pressure 60/45 mmHg, SpO<sub>2</sub>=98 (% with



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**Cite this article as:** Kurul E, Sazak S, Bektaşoğlu İ, Dursun H. Cornelia de Lange Syndrome with Hypernatremia: Two Case Reports. Eur Arch Med Res 2020;36(3):218-21

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European Archives of Medical Research published by Galenos Publishing House.

**Received:** 25.09.2017

**Accepted:** 12.03.2019

21 O<sub>2</sub>), and the capillary filling time was under 3 seconds. On physical examination, facial appearance characteristic of CdLS compatible with synophris, long eyelashes, blunt nose, antevert nose, big ears, low hairline, and bushy hair, small discrete teeth, micrognathia, hypertrichosis, transfers lines in palms were seen (Figure 1). Body weight 7.5 kg (<3 p), height 68 cm (<3 p), head circumference 42.5 cm (median of first age), pulse rate as 110 per minute and respiration rate as 23 per minute were measured. On arrival, the patient's routine laboratory tests received hemoglobin 8.5 g/dL (11 to 16 g/dL, hematocrit 34.3% (37-54%), leukocyte 33.000  $\mu$ L (4-103  $\mu$ L), platelet 601,000 mm<sup>3</sup> (100,000-300,000 mm<sup>3</sup>), glucose 152 mg/dL (74-106 mg/dL), urea: 172 mg/dL (8.4 and 25.8 mg/dL) creatinine 1.76 mg/dL (0.31 to 0.98 mg/dL), sodium 186 mEq/L (136-146 mEq/L), potassium 6.6 mEq/L (3.5-5.1 mEq/L), C-reactive protein 40 mg/L (<5 mg/L), fractional excretion of sodium 0.14%, pH: 7.23 (7.35-7.45), pCO<sub>2</sub>: 55 mmHg (35-48 mmHg), HCO<sub>3</sub> 20 mEq/L (22.5-26.9 mEq/L), pO<sub>2</sub> 55 mmHg (83-108 mmHg), base deficit -5 were detected in blood gas. The patient was admitted for further examination and treatment, and intravenous fluid treatment was initiated by admitting severe hypernatremic dehydration. Desmopressin HCl was started by considering the syndrome-induced central diabetes insipidus due to high urine output, hypernatremic dehydration attacks in the past history, low urine density and high sodium in the follow-up. On the third day of treatment, blood sodium, urea

and creatinine values returned to normal limits. The patient was discharged after scheduled outpatient follow-up.

### Case 2

A five-and-a-half-year-old girl was referred to the pediatric nephrology outpatient clinic due to an increase in serum sodium values. The patient was born from the first pregnancy of the 31-year-old mother, born with cesarean as 4.500 gr in the term, there was no kinship between the parents, and she was treated for hypernatremia at the centers where she applied due to complaints of fatigue, inability to move her feet, and tendency to sleep when she was four months old. It was learned that cranial computed tomography and magnetic resonance examinations revealed holoprosencephaly, that she was treated for hypernatremia in the intensive care unit of another hospital before she was admitted to our outpatient clinic and was discharged the day before.

Body weight was measured at 10,250 kg (<3 p), height 87 cm (<3 p), head circumference 46 cm (1.5 median median) pulse rate was 110 per minute and breath count was 23 per minute. In his physical examination, synophrosis, long eyelashes, blunt nose, antevert nostrils, big ears, low forehead hairline, bushy hair, small split teeth, micrognathia, hypertrichosis, and transverse lines were seen in the palm (Figure 2). There was no walking and speaking, but he could understand simple sentences. Oral



**Figure 1.** In case 1, Cornelia de Lange phenotypic features such as synophysis, long eyelashes, blunt snout, antevert nostrils, long philtrum, thin upper lip, wide-spaced small teeth, micrognathia, bushy hair



**Figure 2.** In case 2, Cornelia de Lange phenotypic features such as synophysis, long eyelashes, blunt nose, antevert nostrils, long philtrum, thin upper lip, wide-spaced small teeth, micrognathia, bushy hair

mucosa was dry, skin turgor was impaired and there were evident signs of dehydration. Mild tachycardia was present in the cardiovascular system examination. Respiratory system and abdominal examination were normal.

Serum sodium level 162 mEq/L (136-146 mEq/L), antidiuretic hormone (ADH) level 0.5 pmol/L (0.0-13 pmol/L) and creatinine level 0.55 mg/dL (0.31-0.98 mg/dL) were detected in laboratory studies. Urine creatinine levels were 127 mg/dL (40-278 mg/dL) and sodium 41 mEq/L (20-69 mEq/L). Fractional sodium excretion was 0.12%. Serum osmolarity was 335 mOsm/L (275-295 mOsm/L). With these findings, hyponatremia due to CdLS and prosencephaly were considered. Intravenous and oral fluid treatment was initiated and serum sodium values returned to normal limits on the second day of treatment. The patient has been discharged. Seven days later, when she came to the checkup, hyponatremia (serum sodium 162 mEq/L) was found to have recurred and the family did not provide the recommended liquid. The patient was again given intravenous and oral fluid treatment and serum sodium levels were restored to normal. The family was given genetic counseling, but genetic mutation analysis could not be done and the patient was discharged with oral hydration and serum sodium levels were stable during the sixth month of follow-up.

## DISCUSSION

CdLS is a syndrome that is often diagnosed with characteristic facial appearance, and it is not common in the literature to have holoprosencephaly and surviving cases such as those presented in the case (3-6). Holoprosencephaly is an anomaly resulting from the inability of dividing the prosencephalon bilaterally to form the cerebral hemispheres. Patients with holoprosencephaly who have severe and complex anomalies die in the intrauterine period, and the incidence of living holoprosencephaly cases has been reported as 12/100,000 (2). Some of the complications of holoprosencephaly are adipsy, hypopituitarism, diabetes insipidus, neurogenic hyponatremia, and patients are therefore able to apply with the clinical picture of hyponatremic dehydration (7,8). Our patients also have hyponatremia episodes due to dehydration.

A mutation in the Nipped-B-like protein gene has been reported on the 5<sup>th</sup> chromosome in 50% of typical cases (type 1). Furthermore, the X-transitive form of the syndrome (type 2) has been reported to occur with a mutation in *structural maintenance of chromosomes protein 1A (SMC1A)* gene on the 10<sup>th</sup> chromosome, and the type 3 form has been reported to occur with a mutation in the *SMC3* gene on the 10<sup>th</sup> chromosome

(9,10). For this reason, although chromosome and gene mutation analysis were not performed on our patients, families were given genetic counseling.

When plasma osmolarity in hyponatremia rises to 285 mOsm/kg, the first physiological response is increased ADH secretion and a feeling of thirst. These mechanisms do not work in infants, unconscious patients, or in cases where the brain does not develop, such as in our patients, so water retention or water intake in the kidneys can not be increased. When sodium intake increases, fractional sodium excretion increases while hyponatremic dehydration decreases (11-13). In these cases, fractional sodium excretion of 0.14% and 0.12% support non-renal fluid loss. In hyponatremic dehydration, the clinical signs are mostly due to water and electrolyte imbalance between the body's liquid compartments. These patients are presented with various clinical statements such as convulsions, lethargy, hyperthermia, coma and encephalopathy. When sodium concentration is gradually increased in the blood, neurons synthesize a number of substances that raise intracellular osmotic pressure, called "idiogenic osmol", to prevent the loss of water going through the cell to the blood (12,13). Since serum sodium values were chronically high in our cases, serum sodium values reached 170 mEq/L, but central nervous system findings such as lethargy, coma were not observed.

Adipsy is a disease characterized by the absence of thirst sensation despite dehydration or excess of salt, which can be one of the rare causes of hyponatremic dehydration (11,12). The first physiological stimuli for thirst are increased osmolarity and hypovolemia. Osmoreceptors in the anterior wall of the third ventricle, the osmotic regulator of thirst, stimulate ADH secretion from the anterior hypothalamus. This warning is known as osmotic thirst. Any congenital or acquired lesion affecting the anterior hypothalamus or third ventricle can cause loss of sensation of thirst. These patients are presented with a combination of adipsy and central diabetes insipidus (11-13). ADH secretion may be unaffected, partially affected or completely affected in adipsy. Rarely, some children may experience adipsia without a structural lesion. Although there was a structural abnormality in our cases, serum ADH value was within normal limits.

## CONCLUSION

As a result, CdLS should be considered in patients with mental retardation, suspicious dysmorphic facial appearance and recurrent episodes of hyponatremia, care should be taken in their treatment and most importantly, the family should

be informed to ensure that the patient does not become dehydrated.

### Ethics

**Informed Consent:** Oral consent has been obtained from the patient and her relatives.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: H.D., Design: S.S., İ.B., Data Collection or Processing: H.D., E.K., Analysis or Interpretation: H.D., E.K., Literature Search: H.D., E.K., Writing: H.D., E.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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