Cystic fibrosis and Silver–Russell syndrome due to a partial maternal isodisomy of chromosome 7

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Case History

A 3-week-old female newborn presented at our pediatric pulmonology department after she tested positive for the CFTR mutation F508del on neonatal screening. She was the second child of nonconsanguineous parents. Both her parents and her brother were healthy. She was born after an uneventful pregnancy at a gestational age of 36 weeks and 6 days. She had a birth weight of 2344 g (−1 SD score). Length was not measured at birth. On physical examination, we observed a relatively small child without apparent dysmorphic features or CF-related symptomatology. Her length was 45 cm (−3.5 SD score according to postnatal norms, and −2.8 SD score according to intrauterine norms).

A positive sweat test and a line probe assay confirmed the diagnosis of CF. Subsequently, she commenced with pancreatic enzymes, fat-soluble vitamins, and salt supplementation. During the first months after initial presentation, she caught up in weight and length. From the age of 3 months, her weight started to lag behind, whereas her length remained stable (Fig. 1A and B). This pattern was accompanied by a poor appetite, with an estimated caloric intake of 700 kcal/day. Subsequently, she switched to an

Key Clinical Message
If an infant with cystic fibrosis exhibits failure to thrive, despite adequate disease management, Silver–Russell syndrome should be considered, given the locations of these conditions in the genome. However, an earlier clue to the diagnosis is small-for-gestational-age birth.

Keywords
Cystic fibrosis, growth disorders, Silver–Russell syndrome, small-for-gestational age, uniparental disomy.

Introduction
Silver–Russell syndrome (SRS) is a clinically heterogeneous disorder characterized by intrauterine and postnatal growth restriction, hemihypoplasia, relative macrocephaly, and (usually subtle) craniofacial anomalies, such as frontal bossing. Most patients exhibit severe feeding difficulties [1, 2].

Several genetic defects can underlie SRS. Sixty percent of cases have hypomethylation of the imprinting control region 1 (ICR1) in chromosomal region 11p15 [1, 2]. Five to 10% of cases could be explained by maternal uniparental disomy of chromosome 7 (mUPD7), which is segmental in a minority of individuals [2].

Chromosomal region 7q31.2 harbors the cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene, which is mutated in CF patients. Consequently, the co-existence of CF and SRS has been reported several times [3–7]. Moreover, the first reports on UPD in humans occurred after the identification of maternally inherited homozygous mutations in the CFTR gene as a cause of CF [4, 5]. This case report describes the clinical course of a patient with CF and mUPD7 of only a segment.
energy-enriched diet, and the dose of pancreatic enzymes was increased to 10,000 IU per kg body weight per day. To further improve fat digestion, a proton-pump inhibitor was added. Tube feeding was initiated at 9 months.

Due to persistent growth failure and clinical suspicion of gastroesophageal reflux disease (GERD), treatment with thickened feeds and a dopamine antagonist was initiated at 12 months. The deflection of the growth curve

Figure 1. The arrows indicate the timing of percutaneous endoscopic gastrostomy tube placement. Growth curves of our patient. (A) Weight, x-axis: age (years), y-axis: weight (kg). (B) Length/height, x-axis: age (years), y-axis: length/height (cm).
continued and, eventually, she lost weight (Fig. 1A). Therefore, at age 13 months, a percutaneous endoscopic gastrostomy (PEG) tube was placed.

At that time, segregation analysis revealed that the mother exclusively carried the CFTR F508del mutation. No paternal pathogenic mutation in or deletion of the CFTR gene was found. Moreover, the possibility of non-paternity was excluded. Therefore, a subsequent UPD analysis was performed using a PCR-based analysis with 11 variable number tandem repeat markers on chromosome 7. This test showed homozygosity for seven consecutive markers and maternal-only inheritance for three markers, indicative of partial mUPD7 that covered at least chromosomal region 7q31-q34 (Table 1). She was subsequently referred to a pediatric endocrinologist, who confirmed clinical suspicion of SRS [8]. She was likely born small-for-gestational age (SGA) for length and exhibited four of the five other criteria for SRS: postnatal growth restriction, relative macrocephaly, frontal bossing, and feeding difficulties. Body asymmetry was lacking. Thus, she fulfilled the criteria for SRS.

After PEG tube placement, a gradual improvement in weight was observed, whereas length remained stable between the −2 and −2.5 SD lines (Fig. 1A and B). Our patient is now 4 years of age. Her height is slightly below the −2 SD line according to Dutch norms (Fig. 1B) and at the +1.5 SD line for girls with SRS. Her weight is normal (Fig. 1A). There is a slight delay in her gross motor development. However, her fine motor skills and speech development are age appropriate.

### Discussion

We describe a patient who suffered from both CF and SRS due to a partial mUPD7. Although there was maternal isodisomy of only a segment of chromosome 7, which covered at least region 7q31-q34, our patient exhibited similar SRS-related symptoms as other patients with mUPD7, including intrauterine and postnatal growth restriction, relative macrocephaly, frontal bossing, and feeding difficulties. However, hemihypoplasia, which is a hallmark of SRS, was lacking in our patient. This finding is compatible with previous reports demonstrating that mUPD7 is associated with a milder SRS phenotype, including less hemihypoplasia, than in cases of ICR1 hypomethylation [1, 2].

Our patient with CF and SRS due to mUPD of only a segment of chromosome 7 had a clinical presentation that was no different from previously reported patients with CF and SRS due to mUPD7. It is unclear whether segmental mUPD7 was excluded in the previously reported cases [4–7]. Given that more recent evidence suggests that segmental mUPD7 is only noted in a minority of patients with SRS, with 7q31-qter being the most likely candidate region [9], it is conceivable that we have reported on the first patient to date with CF and SRS due to partial mUPD7.

The case presented in this report illustrates that SRS is accompanied by severe feeding difficulties, including poor appetite, GERD, and failure to thrive. This finding is of paramount importance in CF, where a lower weight or lower body mass index is associated with a more rapid deterioration in pulmonary function and increased mortality [10]. Therefore, the achievement and maintenance of an optimal nutritional status is one of the mainstays in CF treatment [11, 12]. Given the risks associated with a suboptimal nutritional status in CF, we would like to comment briefly on current practice guidelines. First, the CF Foundation consensus document for the management of infants with CF does not consider SRS, although rare, as a possibility in the work-up of patients with insufficient weight gain [11]. Although SRS is characterized by a set of relatively mild dysmorphic features that are easily overlooked at examination, an SGA birth should alert

| Marker   | Position | Patient | Father | Mother | Informative | Conclusion |
|----------|----------|---------|--------|--------|-------------|------------|
| D7S2201  | 7p22.1   | 104/108 | 104/108| 104/108| No          | –          |
| D7S1802  | 7p15.3   | 186/183 | 186/183| 178/183| Yes         | No UPD     |
| D7S1808  | 7p15.1   | 258/255 | 258/251| 269/255| Yes         | No UPD     |
| D7S1830  | 7p12.1   | 201/214 | 201/223| 214/214| Yes         | No UPD     |
| D7S2847  | 7q31.31  | 179/190 | 194/194| 194/194| Yes         | mUPD       |
| D7S1804  | 7q32.3   | 262/262 | 266/273| 269/262| Yes         | mUPD       |
| D7S1824  | 7q34     | 189/189 | 165/185| 185/189| Yes         | mUPD       |
| D7S2195  | 7q35     | 284/284 | 284/291| 287/284| No          | –          |
| D7S1805  | 7q36.1   | 213/213 | 213/209| 196/213| No          | –          |
| D7S550   | 7q36.3   | 191/191 | 191/187| 189/191| No          | –          |
| D7S559   | 7q36.3   | 195/195 | 195/199| 201/195| No          | –          |

VNTR, variable number tandem repeat.
clinicians to this possibility. Second, early initiation of tube feeding is warranted in patients with both conditions to avoid a suboptimal nutritional status and weight loss. However, this must be balanced against recent recommendations for patients with SRS, stating that caution should be exercised with nutritional management [8]. The dietary requirements of patients with SRS are typically lower given their relatively low muscle mass. Rapid weight gain is associated with increases in fat content and long-term cardiometabolic risks [8]. Third, growth hormone treatment is known for its anabolic effects and can be considered in children born SGA who remain short, including those with SRS [8]. However, its efficacy and safety in patients such as ours are unclear.

**Authorship**

LCG, EGH, MAH, and MJJF: performed the data acquisition and interpretation. LCG: prepared the figures. MAH: prepared the table. LCG and MJJF: drafted the manuscript. LCG, EGH, MAH, and MJJF: edited, reviewed, and approved the final version of the manuscript.

**Informed Consent**

Obtained from the parents.

**Conflict of Interest**

None declared.

**References**

1. Wakeling, E. L. 2011. Silver-Russel syndrome. Arch. Dis. Child. 96:1156–1161.
2. Rossignol, S., I. Netchine, Y. Le Bouc, and C. Gicquel. 2008. Epigenetics in Silver-Russel syndrome. Best Pract. Res. Clin. Endocrinol. Metab. 22:403–414.
3. Taussig, L. M., G. D. Braunstein, and B. J. White. 1973. Silver-Russel dwarfism and cystic fibrosis in a twin. Am. J. Dis. Child. 125:495–503.
4. Spence, J. E., R. G. Perciaccante, G. M. Greig, H. F. Willard, D. H. Ledbetter, J. F. Heijtmancik, et al. 1998. Uniparental disomy as a mechanism for human genetic disease. Am. J. Hum. Genet. 42:217–226.
5. Voss, R., E. Ben-Simon, A. Avital, S. Godfrey, J. Zlotogora, J. Dagan, et al. 1989. Isodisomy of chromosome 7 in a patient with cystic fibrosis: could uniparental disomy be common in humans? Am. J. Hum. Genet. 45:373–380.
6. Hehr, U., S. Dörr, M. Hagemann, U. Preiss, and S. Brömme. 2000. Silver-Russel syndrome and cystic fibrosis associated with maternal uniparental disomy 7. Am. J. Med. Genet. 91:237–239.
7. Sonnappa, S., K. Prescott, B. Adler, R. Dinwiddie, and C. Wallis. 2005. Cystic fibrosis and Russell-Silver syndrome in a child with maternal isodisomy of chromosome 7. Pediatr. Pulmonol. 40:166–168.
8. Wakeling, E. L., F. Brioude, O. Lokulo-Sodipe, S. M. O’Connell, J. Salem, J. Biek, et al. 2017. Diagnosis and management of Silver-Russel syndrome: first international consensus statement. Nat. Rev. Endocrinol. 13:105–124.
9. Hannula, K., M. Lipsanen-Nyman, T. Kontio, and J. Kere. 2001. A narrow segment of maternal uniparental disomy of chromosome 7q31-qter in Silver-Russel syndrome delimits a candidate gene region. Am. J. Hum. Genet. 13:247–253.
10. Stallings, V. A., L. J. Stark, K. A. Robinson, A. P. Feranchak, H. Quinton, and Clinical Practice Guidelines on Growth and Nutrition Subcommittee; Ad Hoc Working Group. 2008. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J. Am. Diet. Assoc. 108:832–839.
11. Cystic Fibrosis Foundation, D. Borowitz, K. A. Robinson, M. Rosenfeld, S. D. Davis, K. A. Sabadosa, S. L. Spear, et al. 2009. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J. Pediatr. 155(6 Suppl):S73–S93.
12. Lahiri, T., S. E. Hempstead, C. Brady, C. L. Cannon, K. Clark, M. E. Condren et al. 2016. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. Pediatrics 137:e20151784.