

CASE REPORT

Silver–Russell syndrome associated with type-I Chiari malformation. A case report

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Email: babar_naeem@hotmail.com**Abstract**

Comprehensive medical evaluation is important for patients with SRS to identify associated medical conditions and provide timely interventions. Clinicians should remain vigilant for potential neurological manifestations in SRS patients.

KEYWORDS

case report, Chiari malformation, Russell-Silver syndrome, short stature, Silver-Russell syndrome

1 | INTRODUCTION

Silver–Russell syndrome (SRS) is one of the rare conditions characterized by both prenatal and postnatal growth retardation.¹ While the exact incidence of SRS is unknown, the global estimate suggests SRS incidence ranges between 1:3000 and 1:100,000.² Diagnosis of SRS remains very challenging due to the prevailing heterogeneity in the presentation of SRS.¹ While most of the clinical features of SRS remain non-specific such as growth failure at birth without catch-up growth, macrocephaly, clinodactyly, asymmetry, and hemihypertrophy, are considered typical features of this syndrome.¹ However, neurological involvement is very rare in patients with SRS. To the knowledge of the authors, only two published reports are available that show neurological findings associated with SRS, such as low conus medullaris³ and tethered cord.⁴ Only one previous case of SRS has been described in the literature in association with Chiari malformation.⁵ Here, we report a case of SRS in conjunction with type-I Chiari malformation.

2 | CASE REPORT

A 13-year-old male born to consanguineous parents was presented to the pediatric neurology at The Children's Hospital and the Institute of Child Health, Lahore, with chief complaints of lethargy and fits. He was delivered at term via spontaneous vaginal delivery with a birth weight of 1.3 kilograms (that corresponds to less than the third percentile for age). Intrauterine growth failure was detected in the fifth month of gestation on the antenatal scan. He has had a poor appetite and feeding difficulties since childhood. He achieved all the milestones normally, but his weight and height remained below the average. He has one brother with normal stature and a sister with short stature and characteristic facial features who expired at the age of 7 years with measles and pneumonia. He was diagnosed as a case of Silver–Russell syndrome by a consultant endocrinologist on the clinical ground 2 years ago.

On examination, he was a thin, short, and well-looking child with a weight of 12.5 kg, a head circumference of 43.5 cm, and a length of 122 cm. All of these

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FIGURE 1 Showing characteristic features of RSR.

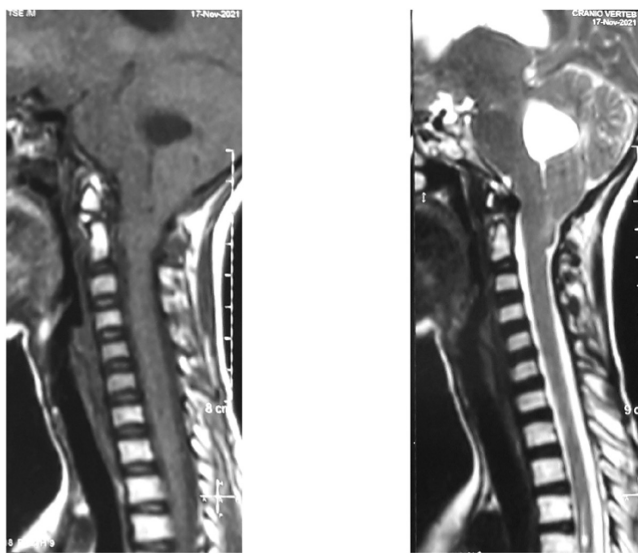


FIGURE 2 T1/T2 sagittal images showing downward herniation of cerebellar tonsils and medulla oblongata with hydrocephalus suggestive of Arnold Chiari malformation type 1.

anthropometric measures are below for age. He had triangular facies, micrognathia, deep-seated eyes, a broad forehead, undescended testis, and clinodactyly of the feet. (Figure 1) There was no asymmetry or hemihypertrophy of the limb or face. Neurological examination revealed

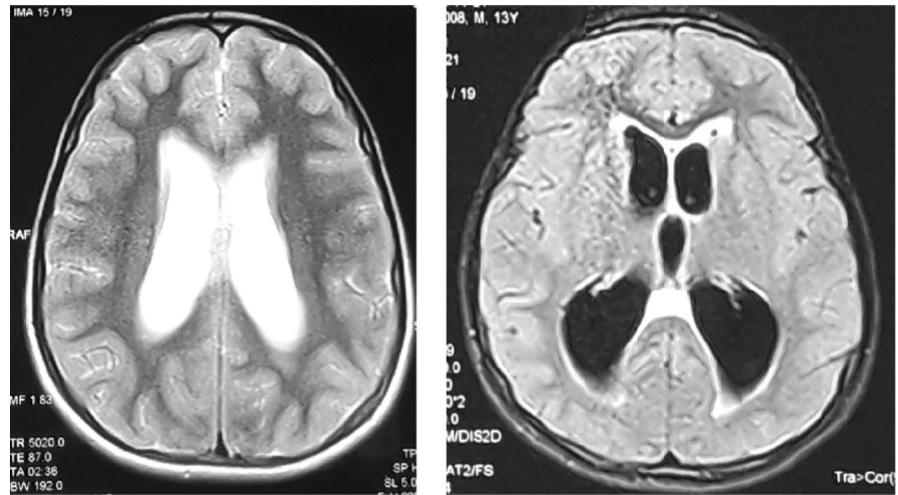
normal gait, speech, cranial nerves, and motor functioning. The rest of the systemic examination was normal. All routine investigations, including renal function tests, serum electrolytes, fasting lipid profile, and EEG, were normal. Thyroid stimulating hormone (TSH) level was 1.6 mIU/ml (Reference range 4.5–6.2), and insulin-like growth factor-1 was 167 ng/mL (reference range 27–245). Karyotyping was normal but genetic testing could not be performed due to unavailability. CT scan showed dilated third, fourth, and lateral ventricles. MRI showed >13 mm descent of the cerebellar tonsils through the foramen magnum into the upper cervical canal. Features of the MRI were suggestive of type-1 Chiari malformations (Figures 2 and 3). He was referred to neurosurgery for ventriculoperitoneal shunting. Unfortunately, the patient was lost to follow-up.

3 | DISCUSSION

Silver–Russell syndrome is a heterogeneous disorder with a broad spectrum of symptomatology. The genetic etiology of the SRS is very complex, and different potential genetic bases have been described. Methylation defect on chromosome number 11 is the most common defect and is found in about 50% of patients. Chromosomes 5 and 11 are among the most commonly described chromosomes.⁶ About 10% of the patients with SRS have maternal uniparental disomy (UPD) of chromosome 7. However, it should be noted that no genetic defect was detected in 40% of the patients with SRS.⁷

Currently, SRS is mainly diagnosed based on clinical signs and symptoms. Molecular tests are used for the confirmation of the diagnosis. The diagnosis can be challenging for a physician unfamiliar with SRS due to the wide variability in the phenotype. Netchine Harbison (NH) Scoring system is the most sensitive criteria for the diagnosis of SRS and was developed by Netchine et al.⁸ This scoring system contains clinical criteria, and if a patient meets any four criteria, then the diagnosis of SRS is considered likely. This criterion lists short for gestation at birth (SGS), postnatal growth failure, preservation of the occipitofrontal circumference at birth, body asymmetry, protruding forehead, and feeding difficulties as the 6 points for the clinical criteria. NH clinical scoring system has 98% sensitivity and 89% specificity for diagnosing the SRS.⁷ Additional facial features not included in the NH scoring system include the triangular face, clinodactyly, micrognathia, low muscle mass, downturned mouth, and low set ears. Our patient exhibited several features, including SGA, postnatal growth failure, protruding forehead during early childhood, feeding difficulties, and cryptorchidism. Cryptorchidism is also classified as a variety of

FIGURE 3 T2/FLAIR axial images showing hydrocephalus.



body asymmetry.^{9,13} Our patient fulfilled five out of the six clinical criteria for diagnosing the SRS.

Neurological manifestations are very infrequent in patients with SRS. Tubbs et al. reported a 20-year-old patient with Silver–Russell syndrome and tethered cord syndrome.¹³ Larisa et al. described a 2-year-old male with clinically diagnosed SRS with low conus medullaris. MRI scan in that patient showed a conus medullaris at the lower border of the L3 vertebrae and a vertebral fusion defect between L5–S1. To the best of our knowledge, no report of Chiari malformation associated with SRS has been described in the literature to date.

Chiari malformation is the herniation of the cerebellar tonsils through the foramen magnum (equal to or greater than 5 mm), resulting in disruption of normal cerebrospinal (CSF) flow between the cranium and the spine. The fourth ventricle and brainstem retain their normal anatomical position. The exact pathogenesis of the Chiari malformation is not known, but it has been postulated that it occurs due to the overcrowding of the posterior fossa due to underdeveloped occipital bones.¹⁰ Treatment options for Chiari Malformation include ventriculoperitoneal (VP) shunting and surgical decompression of the Foramen magnum.¹¹

Treatment of SRS is mainly supportive and consists of nutritional support and physiotherapy. Recombinant growth hormone (cGH) is offered to improve final adult height. However, the use of cGH in patients with Chiari malformation is highly debated. Naftel et al. reported two cases of Chiari malformation who were treated with growth hormone and experienced progression of the disease. Surgical intervention was required in these cases due to the development of syringomyelia.¹² Harrison et al. also reported that 42.9% of the patient experienced an increase in tonsillar descent after growth hormone administration; however, clinically significant progression of the disease

was not seen.¹³ Growth hormone therapy was offered to our patient before the diagnosis of Chiari malformation but was refused by parents due to the cost and associated risks. Therefore we do not have any information regarding the impact of cGH therapy associated with SRS patients with Chiari malformation. However, based on the reports, it may be helpful for pediatricians to examine for the presence of Chiari malformation in SRS patients before advising cGH therapy.

4 | CONCLUSION AND LESSONS LEARNED

Silver–Russell syndrome is a rare disorder with various genotypes and clinical manifestations. Neurological findings are not frequently encountered in patients with SRS. The incidence of Chiari malformation is high in patients with growth hormone deficiency; however, there are no reported cases of Chiari malformations associated with SRS. This case highlights the importance of comprehensive medical evaluation in patients with SRS to identify associated medical conditions such as Chiari malformation and provide timely interventions. It also emphasized the need for appropriate follow-up care in patients with genetic disorders to prevent complications and optimize clinical outcomes. It also highlights the importance of prenatal screening and genetic counseling to identify and manage potential genetic risks in families with consanguinity. Further research is required to confirm the association between SRS and Chiari malformation before definitive recommendations can be made. Nonetheless, clinicians should remain vigilant for potential neurological manifestations in patients with SRS and consider the possibility of associated medical conditions.

ACKNOWLEDGEMENT

The authors are grateful to Dr. Pradeep MK Nair for reviewing their article. They would also like to express their appreciation to Dr. M. Zia Ur Rehman (Pediatric Neurology, The Children's Hospital and Institute of Child Health) for his contribution to the diagnosis of Chiari malformation and to Dr. Somayya Aftab (Pediatric Endocrinology, The Children's Hospital and Institute of Child Health) for her contribution to the diagnosis of Russell Silver Syndrome.

AUTHOR CONTRIBUTIONS

Babar Naeem: Conceptualization; investigation; methodology; validation; writing – original draft; writing – review and editing. **Javeria Nasim:** Supervision; writing – review and editing. **Tipu Sultan:** Investigation; supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Naeem B, Nasim J, Sultan T. Silver–Russell syndrome associated with type-I Chiari malformation. A case report. *Clin Case Rep.* 2023;11:e7203. doi:10.1002/ccr3.7203