Radiographic characterization of the hands in Ritscher-Schinzel/3-C syndrome

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Abstract

Ritscher-Schinzel Syndrome (RSS) is a clinically variable, autosomal recessive disorder, involving cardiac, cerebellar and craniofacial abnormalities. Numerous reports describe hand changes in RSS patients; however, a detailed characterization of the hands has not previously been performed.

Objective: The purpose of this study was to identify whether specific radiographic hand changes were characteristic of RSS and could serve as a diagnostic tool.

Materials and methods: We performed a detailed radiographic hand characterization of 8 RSS patients. The patient population consisted of 5 males and 3 females from ages one month to 26 years, 7 months. The hands were characterized using metacarpophalangeal pattern (MCPP) profiles, carpal height and bone age analyses and assessment of bone morphology.

Results: There was generalized brachydactyly with the second ray being the most severely affected. There was significant shortening of the first metacarpal and the fifth distal phalanx. The MCPP profile generated showed a consistent wavy pattern with average Z-scores ranging from -0.15 (4th proximal phalanx) to -2.13 (1st metacarpal) and 0.53 (4th middle phalanx) to -1.73 (2nd proximal phalanx) for the left and right hands, respectively. Six of eight patients showed a decreased carpal height. Bone age was within normal limits for all patients. Our study population showed consistent radiographic changes including: overtubulation of the bones (especially metacarpals 2-4), prominent tufts of the distal phalanges and a hypoplastic fifth distal phalanx.

Conclusion: The hand findings identified in this study can provide helpful diagnostic tools to clinicians when the diagnosis of RSS is being considered.

Keywords: Ritscher-Schinzel syndrome; 3-C syndrome; Metacarpophalangeal pattern (MCPP); Profile; Carpal height; Phenotype

Introduction

Ritscher-Schinzel Syndrome (RSS) is a rare, autosomal recessive disorder first described by Ritscher et al. (Ritscher et al. 1987) who reported two sisters with similar craniofacial, cerebellar, and cardiac abnormalities. It is also commonly referred to as “3C syndrome” and is clinically heterogeneous (Leonardi et al. 2001). We have been following a large cohort of RSS patients who are First Nations from Northern Manitoba (Marles et al. 1995; Rusnak et al. 2008; Elliott et al. 2013). Seven of the eight patients included in this study have been previously reported (Marles et al. 1995; Elliott et al. 2013).

In addition to the craniofacial, cardiac, and cerebellar defects, numerous reports have discussed abnormalities involving the hands. Reported findings include: brachydactyly, camptodactyly, clinodactyly, syndactyly, single transverse creases, bilaterally adducted thumbs, absent flexion creases, proximally inserted thumbs, cutaneous syndactyly, and hypoplastic fingernails (Marles et al. 1995; Rusnak et al. 2008; Kosaki et al. 1997; Wheeler et al. 1999; DeScipio et al. 2005; Seidahmed et al. 2011). Despite clinical reports of hand anomalies, a detailed radiographic characterization of hand findings in RSS patients has not previously been performed.
Metacarpophalangeal pattern (MCPP) profiles have been used to aid in the diagnosis of congenital malformations and bone dysplasias since 1972. MCPP profiles are available for Turner Syndrome, hypochondroplasia, dyschondrostosis, Marfan syndrome, and numerous other genetic disorders (Dijkstra et al. 1994; Laurencikas et al. 2006). MCPP profile analysis offers an objective and statistical method of identifying characteristic patterns in bone lengths that are unique to different syndromes. This method allows the unbiased comparison of patients of different ages and genders. The MCPP profile is a characteristic and relatively constant feature which remains unchanged with increasing age and can enable early diagnosis when a distinct MCPP profile has been identified (Laurencikas et al. 2006). Each profile has the ability to identify a developmental pattern that could help guide further molecular genetic analysis. MCPP profile analysis can be particularly useful in genetic syndromes and skeletal dysplasias with subtle clinical and radiological abnormalities, such as RSS.

Carpal height is a radiographic ratio with clinical significance in many syndromes and has been used as a diagnostic tool as well as to evaluate the severity and progression of a disease, such as arthritis (Poznanski et al. 1978; Keats et al. 1985) and was assessed by determining a standard deviation from the expected ratio between the second metacarpal (MC2) and the carpal height for a patient’s age and gender. The general morphology of the bones was also documented. The bone age was assessed by comparing the patient's radiographs to standard radiographs for the corresponding age and gender of the patient (Greulich & Pyle 1959). These analyses were performed with a paediatric radiologist.

Results
Clinical findings
Table 1 reflects the variability in RSS. The craniofacial phenotype is consistent and distinctive in our patient population (Elliott et al. 2013). All of our patients have intellectual disability. There is variability with respect to the cardiac and cerebellar involvement.

MCPP profiles
The MCPP profiles of the left and right hands are represented in Figure 1a, b respectively.

Average MCPP profiles
The mean MCPP profiles of the left and right hands are represented in Figure 2a, b respectively. The mean Z-scores are a result of averaging the Z-scores of eight patients for the left hand MCPP profile and seven patients for the right hand MCPP profile. The average Z-scores of the left hands ranged from a minimum -2.13 (1st metacarpal [MC1]) to maximum of -0.15 (4th proximal phalanx [PP]). The average Z-scores of the right hand were higher than those of the left hand with a minimum of -1.73 (PP2) and a maximum of 0.53 (4th middle phalanx [MP4]). Both graphs indicate brachydactyly with a significant shortening of the second ray. There is also notable shortening of the bones in the first ray. The Z-score of the fifth distal phalanx (DP5) and analysis of patient radiographs both indicate a significant abnormality. DP5 has one of the lowest Z-scores in both
| Patient | RSSH01 (Patient III)* | RSSH02 (Patient VI)* | RSSH03 (Patient VIII)* | RSSH04 | RSSH05 | RSSH06 | RSSH07 | RSSH08 |
|---------|-----------------------|----------------------|------------------------|--------|--------|--------|--------|--------|
| Gender  | F                     | M                    | F                      | M      | M      | F      | M      | M      |
| Age at time of radiography | 15 yrs 3 months | 21 yrs 11 months | 26 yrs 7 months | 24 yrs 1 month | 7 yrs 7 months | 13 yrs 6 months | 1 yr 8 months | 1 month |
| Craniofacies |                     |                      |                        |        |        |        |        |        |
| Macropcephaly | +               | +                    | +                      | +      | +      | -      | -      | -      |
| Prominent Forehead | +               | +                    | +                      | +      | +      | +      | +      | +      |
| Brachycephaly | +                 | +                    | +                      | +      | +      | +      | +      | +      |
| Low posterior hairline | +            | +                    | +                      | +      | +      | +      | +      | +      |
| Wide palpebral fissures | +             | +                    | +                      | +      | +      | +      | +      | +      |
| Hypertelorism | +                | +                    | +                      | +      | +      | +      | +      | +      |
| Coloboma | +                  | -                    | -                      | ND    | ND    | -      | ND    | -      |
| Low set ears | +               | +                    | +                      | +      | +      | +      | +      | +      |
| CNS Finding | Cranial ultrasound-no abnormality detected | Dandy-Walker cyst with hypoplasia of the vermis, abnormal gyri of cerebral cortex | Extra-axial fluid over cerebral hemispheres | Not imaged | Dandy-Walker variant with cerebellar vermis hypoplasia, hydrocephaly | Third, fourth and lateral ventricles prominent. Mild amount of extra-axial fluid within both frontal regions | Heterotopic grey matter adjacent to the occipital horn of both the left and right ventricles | Hypoplasia of the cerebellar vermis with associated dilatation of the 4th ventricle, consistent with a Dandy-Walker variant |
| Intellectual Disability | +                | +                    | +                      | +      | +      | +      | +      | +      |
| Cardiac Finding | ASD/VSD, aberrant right subclavial artery, left sided superior vena cava joined at the coronary sinus | Muscular VSD with right ventricular hypertrophy | - | Limited study. No clinical evidence of cardiac disease. | ASD,VSD | Biventricular hypertrophy, intra-arterial defect | Large perimembranous VSD + small PDA | - |
| Brachydactyly | +                | +                    | +                      | +      | -      | +      | +      | -      |

*Marles et al. (1995) Am J Med Genet 56:343-350. ND = not documented, ASD = atrial septal defect, VSD = ventricular septal defect, PDA = patent ductus arteriosus. Patients RSSH02-06 and RSSH08 were included in the molecular analysis (Elliott et al., 2013).
graphs and radiographic interpretation revealed it to be hypoplastic.

**Carpal height ratio and bone age**
Figure 3 displays the standard deviations of the carpal height ratio in the patient population. Six out of eight patients were below average (between -2 and -4 standard deviations). Two patients had an average carpal height. The bone ages were not significantly different from normal for all patients.

**General morphology of hands**
Phenotypic analysis of the radiographs indicated similar findings including: bilateral prominent tufts of the DPs (5/8 patients), bilateral overtubulation of bones (especially MCs 2-4) (6/8 patients) and bilateral hypoplastic fifth DPs (5/8 patients) (Figure 4a and b).

**Discussion**

**Clinical findings**
Not all three systems are involved in all RSS patients (Leonardi et al. 2001; Elliott et al. 2013). An explanation for the diversity of cardiac malformations as evidenced in Table 1 has been proposed as a “shift” of the threshold (Lurie & Ferencz 1996). Six of the patients in Table 1 (RSSH02-06 and RSSH08) were included in a molecular study and were homozygous for the same mutation in the KIAA0196 gene, which encodes a highly conserved protein, strumpellin (Elliott et al. 2013).

**MCPP profile of RSS patients and comparison**
The MCPP profile revealed a distinctive wavy pattern (Figure 1a, b). In general, the average MCPP profile demonstrated brachydactyly with significant shortening in particular bones. The first MC, the second PP, and the fifth DP were the most shortened. The tubular bones of the second ray, also affected, resulting in a shortened index finger and can be a helpful clinical sign. The bones of the first ray become less affected from MC to DP, while the bones of the fifth ray become more affected from MC to DP. The DP s of the third and fourth rays were also affected. RSSH05 was a significant outlier due to increased values however; the overall pattern was similar. All growth parameters (height, weight, head circumference) for this patient were increased. Although he lacked ocular coloboma, he showed the craniofacial features typical of RSS, intellectual disability, Dandy-Walker variant with cerebellar vermis hypoplasia, atrial septal defect and ventricular septal defect (Table 1).
Furthermore, this patient was confirmed to have the same molecular defect (Elliott et al. 2013).

The pattern displayed by our patient population was distinct from that of other genetic syndromes such as Turner Syndrome, which also displays syndromic brachydactyly but demonstrates a bone-shortening gradient with increasing shortening from DPs to MCs in all rays (Laurencikas et al. 2005). Leri-Weill Dyschondrosteosis and Noonan Syndrome also show syndromic brachydactyly however each displays characteristic patterns (Butler et al. 2000; Laurencikas et al. 2005).

The patients in this study demonstrated brachydactyly. Brachydactyly can be isolated or syndromic. The isolated brachydactylies have been characterized into five groups, A-E, including several subgroups (Mundlos 2009). Analysis of different types of brachydactyly can provide insight into potential developmental pathways disrupted in RSS. Although all tubular bones are affected in RSS patients, the second ray is the most significantly affected followed by the first and fifth rays. Brachydactyly B2 exhibits some characteristics displayed by our RSS patient population including: hypoplasia/aplasia of the distal phalanges and proximally inserted thumbs as a result of a shortened first metacarpal and is caused by a missense mutation in Noggin (NOG), which under normal circumstances forms a homodimer which binds to bone morphogenic proteins (BMP). Like RSS, Brachydactyly E demonstrates a shortening of all the metacarpals. Overall, the pattern observed in the RSS population is distinctive from the isolated or syndromic brachydactylies. The osseous hand and skull involvement in RSS patients suggests a potential role of the strumpellin protein in chondrogenesis.

Carpal height ratio analysis
The average standard deviation of our RSS patients was negative indicating a decrease in carpal height. In our study, the second metacarpal (MC2) was shortened. This bone is utilized when calculating the ratio. A shortened MC2 would have the tendency to skew the result toward a greater carpal height (increased standard deviation). This was not the case for our patient cohort. Decreased carpal height and other carpal abnormalities have been found in other genetic syndromes such as Poland Syndrome (Friedman et al. 2009). The overall morphology of the carpals was normal despite the decrease in carpal height. Although this finding does not contribute to further understanding of the pathogenesis of the disorder, it can be utilized as a phenotypic marker for RSS.

Bone Age and radiographic features
The bone ages of the study population were not significantly different from expected. Zankl et al. performed a follow up study of the original patients (Zankl et al., 2003). One of the sisters appeared to have a delayed bone age. Our RSS study population showed normal bone ages, indicating that this is not a consistent feature in all RSS patients.
The observed radiographic features of our RSS patients included: bilateral prominent tufts of the DPs, bilateral overtubulation of bones (especially MCs 2-4), and bilateral hypoplastic fifth DPs.

Conclusion
The wavy MCP profile, with a shortened second ray, MC1 and DP5, decreased carpal height and other radiographic features identified in this study offer new diagnostic tools for clinicians when a diagnosis of RSS is being considered.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
AME designed the study. Clinical phenotypes were determined by BNC, AEC and AME. KJF, MHR and AME performed the analyses. KJF and AME wrote the manuscript. All authors read and approved the final manuscript.

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