

Research Article

Distinctive Cranial Abnormalities in Children with Early Infancy Insulin Dependent Diabetes in Connection with Wolcott-Rallison Syndrome

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Abstract

Background: Abnormal craniofacial contour and deformities of the appendicular skeleton of the lower limbs can occur in connection with a long list of skeletal dysplasia. The natural history of chronic/unusual disorders can be a precise key factor towards a successful diagnostic process.

Material and Methods: Three unrelated children aged 18-months, 2 and 7 year (two boys and one girl) presented with generalised skeletal mal-development compatible with multiple epiphyseal dysplasia. However, in the early months of life these children have been diagnosed with early infancy insulin dependent diabetes. Strikingly, all manifested Wormian bones over the lambdoid sutures. In addition to Progressive malalignment of the lower limbs and thoracic kyphosis associated with significant growth deficiency were the major skeletal abnormalities. Endochondral ossification was diffusely affected associated with multiple epiphyseal dysplasia and appearance of irregular and fragmented epiphyses.

Results: Based on early permanent neonatal or early-infancy insulin-dependent diabetes, associated with the clinical and radiological phenotypic characterizations of multiple epiphyseal dysplasia and growth retardation as the major abnormalities in these children. Wolcott-Rallison syndrome was the highly likely diagnosis. The most interesting findings in this study; The Wormian bones, not only involved the lambdoid sutures, but also extended to involve the occipitomastoid suture. We confirmed our diagnosis via sequence analysis which revealed a homozygous nonsense gene mutation (EIF2AK3) resulting in a premature stop codon (c.2707 C>T, p.R903X). Parents in two families were identified as heterozygous carriers of this mutation.

Conclusion: The significance of this study is to point out the importance of analysing the skull bones in children with skeletal dysplasia. Interestingly, for the first time we detected the downward bulging of the occiput because of the abundance of the Wormian bones (sites of maximal skull bone fragility) along the lambdoid and the occipito-mastoid sutures is by itself a highly alarming sign of progressive weakness of the weight-bearing zone (which is represented by the lambdoid and the occipitomastoid

sutures). The exerting load of the cerebrum on these vulnerable and soft sutures can lead to brain swelling (a serious condition). Despite that lower limb defects in children are the most frequent deformities encountered in the departments of paediatric orthopaedics, because of the real or apparent detrimental effect that they have on gait and upright activity, and it draw immediate and alarming attention to parents. But, nevertheless, it is the responsibility of physicians to pay prompt attention for the necessity to scrutinize the skulls and the craniocervical junction in patients with long term bone disorders.

Keywords: Cranial Abnormalities; Cerebrum; Diabetes; Insulin; Limb

Introduction

Wolcott-Rallison Syndrome (WRS) (OMIM 226980) is a rare autosomal-recessive disorder characterized by the association of permanent neonatal or early-infancy insulin-dependent diabetes, multiple epiphyseal dysplasias and growth retardation, and other variable multisystemic clinical manifestations. The main features are multiple epiphyseal/spondyloepiphyseal dysplasia and diabetes mellitus. Onset is in early infancy; the diabetes may precede the bone dysplasia. Clinically WRS is characterized by disproportionately short trunk compared to the limbs. Wide thorax with pigeon chest, prominent abdomen, large liver and hyperlordotic lumbar spine are the main features. Radiological features such as diffuse osteoporosis with possible fractures, and generalized platyspondyly with maximal intensity over the thoracic vertebrae. The epiphyses are irregular with poor ossification associated with irregular carpal bones. Defective metaphyseal remodeling of the small tubular bones of the extremities is characteristic. Biochemically, hyperglycaemia, acetonuria and glycosuria are frequent findings. However, occasional biochemical findings such as increased creatinemia and reduced creatine clearance do occur as well [1,2,3].

The clinical and the radiological phenotypic characterizations features in our present patients were suggestive of Wolcott-Rallison syndrome. In our patients the radiographic features showed significant irregular and fragmented carpal bones, dysplastic femoral heads, and metaphyseal expansion associated with spinal end-plate ossification mimicking multiple epiphyseal dysplasia/ spondyloepiphyseal dysplasia. The irregular ossification of the tubular bone epiphyses, short bones, and spine were distinctive. Endochondral ossification was diffusely altered with a combination of epiphyseal dysplasia associated with acceleration and early fusion. WRS is caused by mutations in the gene encoding Eukaryotic Translation Initiation Factor 2 α Kinase 3 (EIF2AK3), also known as PKR-like Endoplasmic Reticulum Kinase (PERK). Delepine, et al., mapped the gene to 2p12 in one consanguineous family of Tunisian origin and another of Pakistani origin. Mutations in the EIF2AK3 gene encoding the eukaryotic translation initiation factor 2-alpha kinase 3 were found [4]. Further EIF2AK3 mutations were reported by Brickwood, et al., and Durocher, et al., [5,6].

Material and Methods

The study protocol was approved by Ethics Committee of the (Ilizarov Scientific Research Institute, No.4(50)/13.12.2016, Kurgan, Russia). Informed consents were obtained from the patient's Guardians. Three children aged 18 months, 2 and 7 year (two boys and one girl) have been enrolled in this study. We fully documented these children through detailed clinical and radiological phenotypic characterizations at the Osteogenetische ambulanzen in orthopaedic Hospital of Speising (Paediatric department) and through the scientific collaboration of the first author with Ilizarov Center, Kurgan, Russia. All children presented to our paediatric orthopaedic department showed growth deficiency associated with a history of early infancy with total insulin dependent diabetes mellitus. Birth weight of these children was almost within normal range. All children were followed up via abdominal ultrasound to guard against hepatomegaly and or renal damage and through periodic assessment of the liver enzymes and renal functions particularly during episodes of respiratory infections. The latter may cause elevated bilirubin, hypoglycaemia and possibly coma. None, of these events have been recorded until writing this paper (there was no icterus, nor signs of hepatitis, the spleen was normal, as was Doppler ultrasound examination of the kidneys and the glomerular filtration rate). Review of the family members over three generations revealed several family subjects manifested short stature, osteoarthritis and scoliosis associated with adult onset type II diabetes mellitus. Global developmental retardation was a landmark, particularly in acquiring the skills of gross motor development. The follow-ups of these children showed waddling gait accompanied with bilateral, irritable groin and ankle pain. The children were referred to our orthopaedic department because of abnormal gait and progressive malalignment of the lower limbs.

Clinical examination showed growth retardation of (-3 to -4SD) associated with minor facial dysmorphic features. The neck was short as well as the trunk in comparison with the limbs. The joints were stiff and the spine showed remarkable thoracic kyphosis and a pigeon chest. Articular stiffness associated with loss of the physiological lumbar lordosis was present. Short hands and flat valgus feet and significant genu valgum (knock knees) were present in one child (7-years old). Sequence analysis revealed a homozygous nonsense gene mutation (EIF2AK3) resulting in a premature stop codon (c.2707 C>T, p.R903X). Two parents were identified as heterozygous carriers of this mutation.

On the bases of skeletal survey; Lateral skull radiograph of a 18-months-old-boy disproportion between the small facial bones and the large cranium. Note progressive disorganized ossification of the cranium with islands of osteolytic changes. Particularly

the early development of Wormian bones along the lambdoid sutures. Atlanto-axial instability in connection with dysplastic atlas and odontoid dysplasia (white arrow). Wormian bones along the lambdoid sutures causing downward bulging of the occiput possibly due to mixed disorganized ossification and osteolytic changes of these sutures (arrow head). Persistent open anterior fontanelle, J-shaped sella turcica and hyperostosis of the skull base (arrow head). Atlanto-axial instability in connection with dysplastic atlas and odontoid dysplasia (white arrow). Wormian bones along the lambdoid sutures causing downward bulging of the occiput possibly due to mixed disorganized ossification and osteolytic changes of these sutures (arrow head) (Fig. 1). Full extension lateral cervical spine radiograph of a -2-years-old- girl with WRS note, the disorganized calcification of the cranium with islands of osteolytic changes associated with mild hyperostosis of the skull base (arrow), Wormian bones (red arrow) associated with downward bulging of the occiput along the lambdoid and the occipito-mastoid sutures. Atlanto-axial instability in connection with odontoid hypoplasia (red arrow) (Fig. 1). Lateral skull radiograph of a-7-years-old-boy with WRS showed large cranium and small facial bones. The cranium showed distinctive pathological expansion associated with progressive downward bulging of the occiput which is overwhelmed with massive areas of Wormian bones along the lambdoid and the occipitomastoid sutures (white arrow). Hyperostosis of the skull base (arrow head), very small sella turcica and obtuse angle of the mandible (red arrow head) with overcrowding of the teeth (Fig. 2). Enlarging the occipital parts of the skull in two unrelated children with (WRS) aged 18 months and 7 years. Note, the distinctive progressive expansion of the occiput along the lambdoid and the occipitomastoid sutures respectively (arrows). These changes reflecting the progressive fragility of the lambdoid and the occipitomastoid sutures. The overload of the cerebrum over these fragile sutures can easily leads to morbid /mortal brain concussion, particularly when a force of whatever magnitude is directed to this part of the skull. In addition the downward sliding of the occipitomastoid part onto the craniocervical junction can exerts additional anatomical disruption (Fig. 3).

AP pelvis radiograph of the same boy showed bilateral and symmetrical dysplastic capital femoral epiphyses associated with metaphyseal expansion, dysplastic and sloping acetabulae amid apparent osteoporosis (Fig. 4).

This child at the age of eight years surgical intervention to re-align his lower because of his progressive knock knees (genu valgum). AP standing lower limbs radiograph showed genu valgum. At the age of 8 years, we performed a bilateral temporary hemiepiphyseodesis against valgus deformity of the knees using 8-plates at the distal medial femur and the proximal medial tibia. The outcome was encouraging after removal of the staples and re-alignment has been approached (Fig. 5). We choose this technique as an alternative to acute correction to avoid shortening of the bones by closing-wedge osteotomy. Enlarging the occipital parts of the skull in two unrelated children with (WRS) aged 18 months and 7 years. Note, the distinctive progressive expansion of the occiput along the lambdoid and the occipitomastoid sutures respectively (arrows). These changes reflecting the progressive fragility of the lambdoid and the occipitomastoid sutures. The overload of the cerebrum over these fragile sutures can easily leads to morbid /mortal brain concussion, particularly when a force of whatever magnitude is directed to this part of the skull. In addition, the downward sliding of the occipitomastoid part onto the craniocervical junction can exerts additional anatomical disruption.

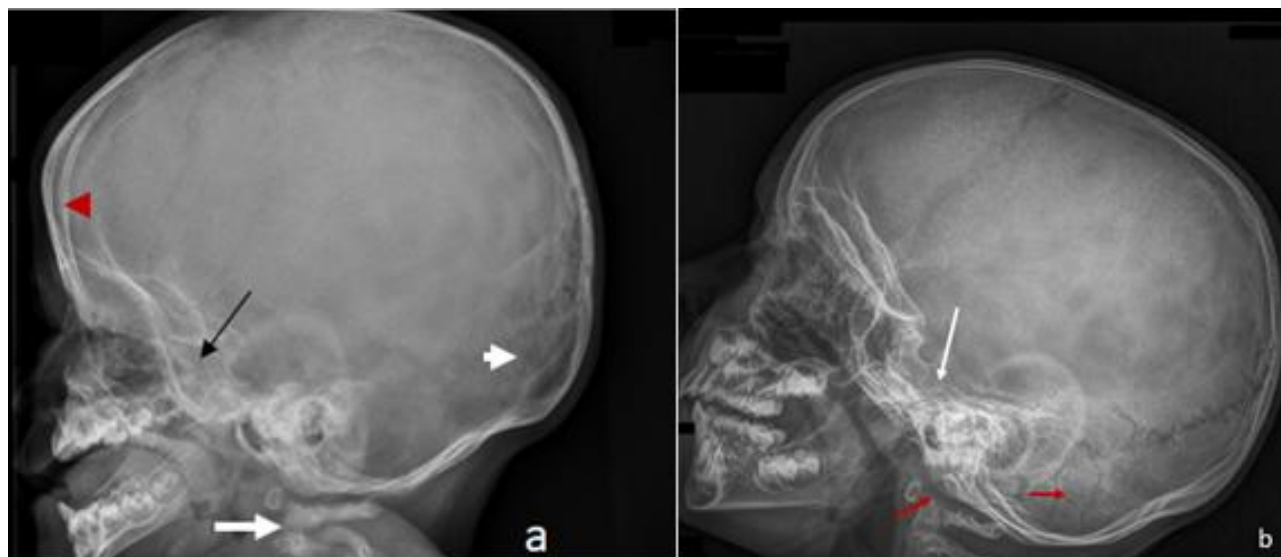


Figure 1: (a,b): Lateral skull radiograph of a 18-months-old-boy disproportion between the small facial bones and the large cranium. Note progressive disorganized ossification of the cranium with islands of osteolytic changes. Particularly the early development of Wormian bones along the lambdoid sutures. Atlanto-axial instability in connection with dysplastic atlas and odontoid dysplasia (white arrow). Wormian bones along the lambdoid sutures causing downward bulging of the occiput possibly due to mixed disorganized ossification and osteolytic changes of these sutures (arrow head). Persistent open anterior fontanelle, J-shaped sella turcica and hyperostosis of the skull base (arrow head). Atlanto-axial instability in connection with dysplastic atlas and odontoid dysplasia (white arrow). Wormian bones along the lambdoid sutures causing downward bulging of the occiput possibly due to mixed disorganized ossification and osteolytic changes of these sutures (arrow head) (Fig. 1, a).

Full extension lateral cervical spine radiograph of a -2-years-old- girl with WRS note, the disorganized calcification of the cranium with islands of osteolytic changes associated with mild hyperostosis of the skull base (arrow), Wormian bones (red arrow) associated with downward bulging of the occiput along the lambdoid and the occipito-mastoid sutures. Atlanto-axial instability in connection with odontoid hypoplasia (red arrow) (b).

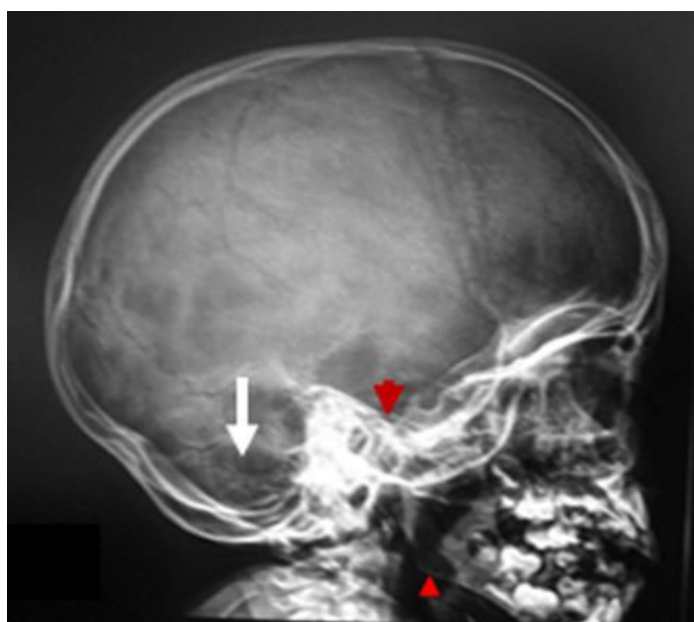


Figure 2: Lateral skull radiograph of a 7-years-old-boy with WRS showed large cranium and small facial bones. The cranium showed distinctive pathological expansion associated with progressive downward bulging of the occiput which is overwhelmed with massive areas of Wormian bones along the lambdoid and the occipitomastoid sutures (white arrow). Hyperostosis of the skull base (arrow head), very small sella turcica and obtuse angle of the mandible (red arrow head) with overcrowding of the teeth.

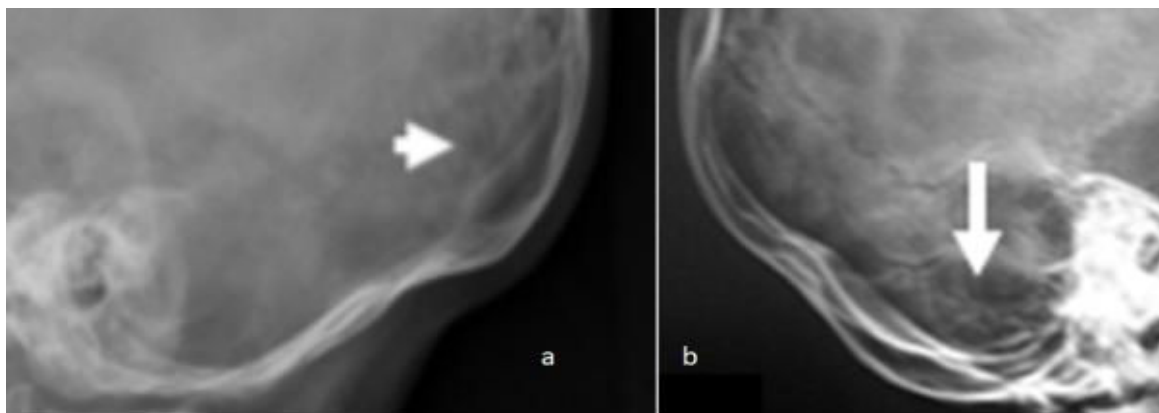


Figure 3: (a,b): Enlarging the occipital parts of the skull in two unrelated children with (WRS) aged 18 months and 7 years. Note, the distinctive progressive expansion of the occiput along the lambdoid and the occipitomastoid sutures respectively (arrows). These changes reflecting the progressive fragility of the lambdoid and the occipitomastoid sutures. The overload of the cerebrum over these fragile sutures can easily leads to morbid /mortal brain concussion, particularly when a force of whatever magnitude is directed to this part of the skull. In addition, the downward sliding of the occipitomastoid part onto the craniocervical junction can exerts additional anatomical disruption.

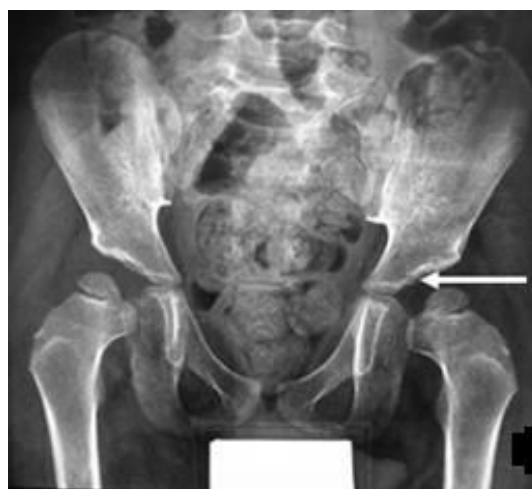


Figure 4: AP pelvis radiograph of the same boy showed bilateral and symmetrical dysplastic capital femoral epiphyses associated with metaphyseal expansion, dysplastic and sloping acetabulae amid apparent osteoporosis.



Figure 5: (a,b): AP standing lower limbs radiograph showed genu valgum. At the age of 8 years we performed a bilateral temporary hemiepiphysodesis against valgus deformity of the knees using 8-plates at the distal medial femur and the proximal medial tibia. The outcome was encouraging after removal of the staples and re-alignment has been approached (a,b). We choose this technique as an alternative to acute correction to avoid shortening of the bones by closing-wedge osteotomy.

Discussion

Wolcott-Rallison Syndrome (WRS) is a rare autosomal-recessive disorder characterized by the association of permanent neonatal or early-infancy insulin-dependent diabetes, multiple epiphyseal dysplasia and growth retardation, and other variable multisystem clinical manifestations. Wolcott and Rallison described 2 brothers and a sister with infancy-onset diabetes mellitus and multiple epiphyseal dysplasias [1]. Demineralisation of bone with multiple fractures, tooth discoloration, and skin abnormalities were also noted. The parents were not related.

Goumy, et al., described two sibs and Stoss, et al., also described two sibs [2,3]. The main features are multiple epiphyseal/spondyloepiphyseal dysplasia and diabetes mellitus. Onset is in early infancy; the diabetes may precede the bone dysplasia. One patient of Stoss, et al., was microcephalic and mentally retarded, but he was apparently in a diabetic coma for five days at the age of 10 weeks. Three patients developed renal insufficiency. Al-Gazali, et al., described two sibs with WSR [4-7]. Diabetes developed within the first 2 months of life in each. This has been the case in other reported patients. Castelnau, et al., reported a case with endocrine and exocrine pancreatic insufficiency. Bin-Abbas, et al., reported two sibs with the condition and central hypothyroidism [8,9]. Thornton, et al., described a family in which the proband, born to first-cousin parents, died at 2 years of age from the sequelae of poorly controlled diabetes [10]. The child had gray-blue sclerae, high-arched palate and absent teeth. There was thoracolumbar kyphosis and bowing of the femora with under tubulation and thin cortices of the long bones with osteopenia. In addition, there was severe brachycephaly and poor ossification of the skull and Wormian bones. Stewart, et al., reported a three-and-a-half-year-old female with features of the condition [11]. She died at four years of age after an episode of hypoglycaemia. At post-mortem examination endocardial fibroelastosis, a stenotic larynx, a markedly hypoplastic pancreas and arhinencephaly were found. A 15q deletion was found in 65% of lymphocytes but the significance of this was not certain [11-12].

None of the above-mentioned studies mentioned the necessity of skull radiographs in children with WSR. Except a brief report by Thornton, et al., and Dias, et al., described Os odontoideum, as a cervical spine abnormality not previously reported in associated with WSR [12].

Unfortunately, defective ossification of the cranium or any other observation regarding the skull is almost always receive no interest by the vast majority in the departments of paediatric orthopaedics. But nevertheless, it was our fixed adopted strategy applied to all patients with skeletal dysplasia /syndromic association or any form of long-term osseous ailment. From within our experience of hundreds of children and families with variable forms of syndromic and non-syndromic long-term entities, the skull images can speak and illustrates unnoticed abnormalities. The vast majority of the studies on patients with WSR focused on the skeletal and the visceral complications of early infancy insulin dependent diabetes. None, took into account the necessity to scrutinize the cranium. Hyperostosis of the skull base means that the cranial nerve foraminae of the optic and the auditory are at high risk of being obliterated and leads to blindness and hearing loss. The downward bulging of the occiput because of the abundancy of the Wormian bones along the lambdoid and the occipito-mastoid sutures is by itself is a highly alarming sign of progressive weakness of the weight-bearing zone within the lambdoid sutures. Therefore, the exerting load of the cerebrum along the weight bearing zone which is represented by the lambdoid sutures, made this area as the most vulnerable i.e., any minor trauma in this soft area can lead to a highly hazardous fatal brain swelling with subsequent damage. The traditional definition of Wormian bones is small bones that are often found within the sutures and fontanelles of the skulls [13]. We extensively studied previous publications regarding (WRS). The vast majority of publications regarding WRS has been addressed chiefly towards the phenotype and the genotype. What we have observed in this paper concerning (WRS) is totally different from what has been published. The skull radiographs in our patients illustrated the grades of severity of Wormian bones in correlation with age of the patients.

Al Kaissi, et al., for the first time refuted what has been identified as Wormian bones in the medical literature. Al Kaissi and co-workers were able to put the words on the right authentic aetiology understanding in medicine, changing the traditional conception of Wormian bones into high scoring scientific words [14].

Conflict of Interest

The authors have no conflict of interest to declare.

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