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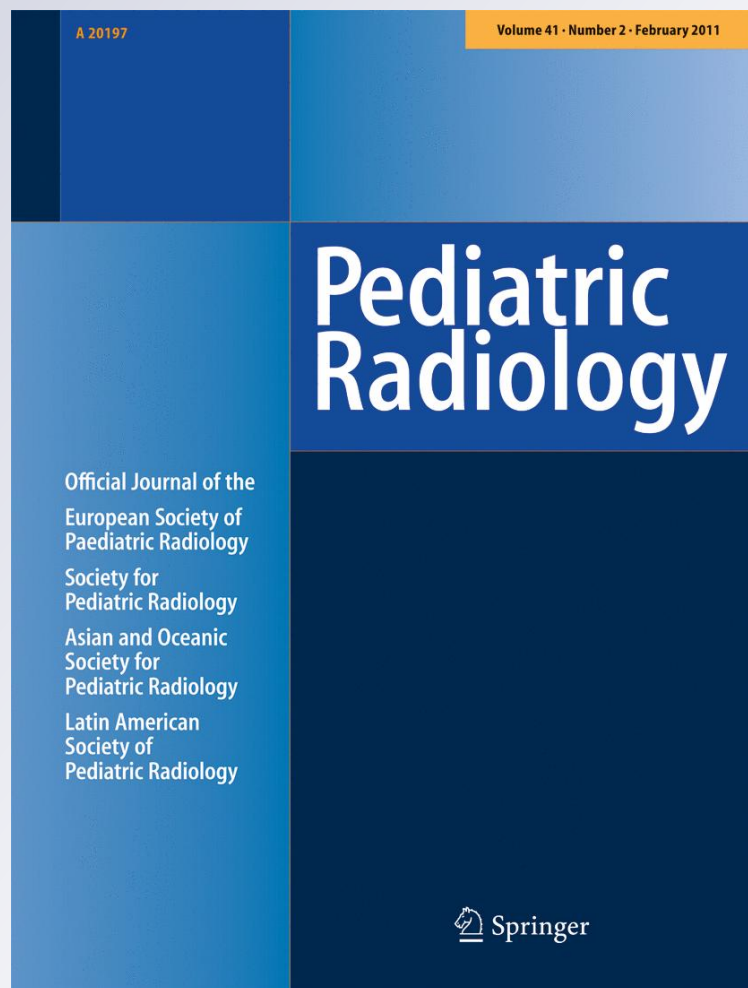
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Williams-Beuren syndrome: historical aspects

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Abstract Williams syndrome, also known as Williams-Beuren syndrome (OMIM database entry 194050), is now known to be commonly associated with a hemizygous chromosomal deletion at 7.q11.23. The way in which the condition came to be recognized historically is reviewed along with some biographical details of the people involved.

Keywords Williams · Beuren · Supravalvular aortic stenosis · Hypercalcemia

Introduction

Williams syndrome, also known as Williams-Beuren syndrome (OMIM database entry 194050), is a generalized disorder characterized by unusual facies, abnormal behavioral abilities, cardiovascular anomalies, especially supravalvular

aortic stenosis (SVAS), renal and other abnormalities [1, 2]. Some or all of these features may be present to a variable degree. Initial appreciation of the syndrome came from two seemingly unrelated disorders, one largely the domain of pediatricians (idiopathic hypercalcemia of infancy), the other that of cardiologists (SVAS). They were later shown to be aspects of the same syndrome that is named after John Williams of New Zealand (Fig. 1) and Alois Beuren of Germany (Fig. 2).

History of the disorder

In the 1950s, there was increasing awareness among pediatricians of a disorder referred to as idiopathic hypercalcemia of infancy [3]. Attention became focused on the policy in Britain (where most cases were recognized) of fortification of infant formulas and cereals that resulted in infants receiving up to ten times the recommended daily requirement of calcium but did not lead to a simple etiological explanation. Initial observations of the severe form by Guido Fanconi (Fig. 3) in Switzerland and Bernard Schlesinger (Fig. 4) in England [4] included failure to thrive, hypercalcemia and abnormal facies later referred to as “elfin” [5, 6]. The hypercalcemia and some other features were transient, but the abnormal facies persisted and there was frequently developmental delay and mental retardation in these children.

SVAS is a relatively rare form of aortic stenosis with the narrowing occurring above the aortic valve (Fig. 5). It was seldom recognized prior to 1958, when investigative methods enabled its differentiation from other types of aortic stenosis [7]. In addition to being a common finding in Williams syndrome, SVAS is also seen as a familial condition with normal intelligence [8] or as an isolated

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Fig. 1 John C.P. Williams, born 1922, death unknown. First author on paper from Green Lane Hospital, New Zealand, to describe supra-valvular aortic stenosis associated with unusual facies and reduced IQ. He did not publish again on this subject. Some biographical details are to be found in the associated paper [25] (Photograph courtesy of the Mayo Historical Unit, Mayo Clinic, Rochester, MN, USA)

finding and is associated with peripheral pulmonary and other arterial stenoses.

In 1961, Williams, Barratt-Boyes and Lowe [9] reported on four unrelated patients with SVAS associated with mental retardation and an unusual facial appearance. In three of these patients, the diagnosis of SVAS was suggested by their close facial resemblance to the initial patient. Similar independent observations were made by Beuren and his colleagues in Germany, who also commented on the friendly endearing nature exhibited by their patients [10].

The similarity between the facies seen in some children previously affected by idiopathic hypercalcemia of infancy and in other patients with SVAS was recognized by Hooft, Vermassen and Blancquaert [11] in Belgium (Fig. 6) and subsequently by Black and Bonham-Carter [12] in England.

The first case report of documented idiopathic hypercalcemia in infancy with abnormal facies and supra-valvular aortic (and pulmonary) stenosis appeared in 1964 [13], and in 1965 Black et al. [14] reported the autopsy findings of SVAS in their original patient with proven idiopathic hypercalcemia and an unusual facial appearance.

The syndrome has been referred to as Williams-Beuren syndrome [15], or Williams syndrome [16], and also as “elfin facies syndrome,” or various combinations thereof. The shorter eponym reflecting the first author of the 1961 paper is commonly used [17].

Assessment of individuals with the syndrome led to recognition of many associated findings [1]. Although it was presumed that all had hypercalcemia in infancy, which had resolved when presenting at an older age, not all who had serum calcium measured in the first year of life were found to be hypercalcemic [18].

Standard IQ testing in Williams syndrome shows reduced scores in most, but this does not reflect the complex behavioral patterns that have been extensively investigated. The friendly, outgoing, socially engaging behavior has long been recognized [10, 19] but it has become apparent that performance is better in areas such as language and considerably less good in spatial and other skills [1]. As a group, those with Williams syndrome are drawn toward music, with many displaying a range of musical abilities often well beyond what might be expected from their overall cognitive function (Fig. 7) [20].

In the 1990s, advances in genetics research led to the recognition of a hemizygous microdeletion in chromosome 7q11.23 in individuals with Williams syndrome, which involves the elastin as well as adjacent genes [21]. In familial



Fig. 2 Alois Beuren 1919–1984. German physician who became interested in cardiac research, which led to his becoming a fellow in Pediatric Cardiology at Johns Hopkins Hospital (Baltimore, MD, USA). On returning to Germany, he developed the Department of Pediatric Cardiology at the University of Göttingen [26]. He also noted the association between supra-valvular aortic stenosis and an unusual facies. In addition, he commented on the behavioral characteristics of the three children he described. “All have the same kind of friendly nature.” A later paper detailed the association of peripheral pulmonary stenoses and typical dental anomalies (reprinted with permission [26])

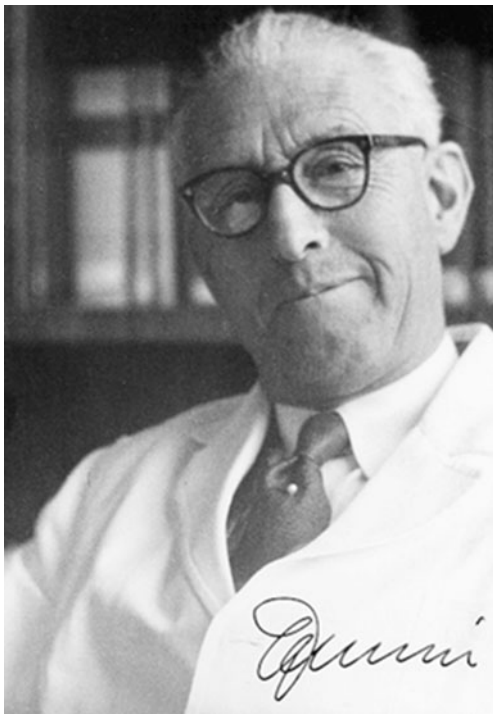


Fig. 3 Guido Fanconi 1892–1979. Swiss pediatrician, professor of pediatrics at University of Zurich, who brought together the scientific methodology of biochemistry and physiology to the investigation of clinical disease. He published more than 200 papers including three on idiopathic hypercalcemia of infancy, made major contributions to pediatric hematology, and many disease states are associated with his name [27] (Photograph by Ze'ev Aleksandrowicz, Wikimedia Commons)



Fig. 4 Bernard Schlesinger 1896–1984. British pediatrician at Great Ormond Street Hospital in London, with an active interest in kidney diseases. A wide variety of pediatric conditions were the subject of more than 80 papers including three on idiopathic hypercalcemia of infancy [28] (Photograph courtesy of Nick Baldwin, Great Ormond Street Hospital)

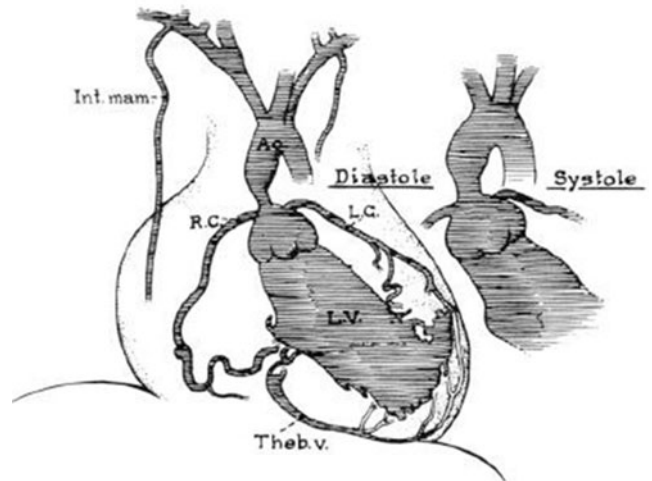
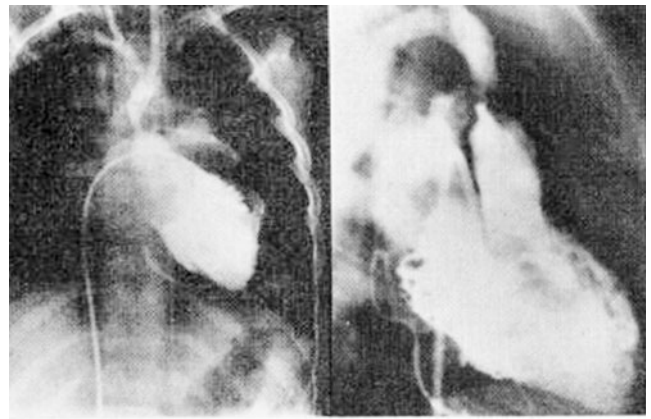


Fig. 5 Angiogram of supravalvular aortic stenosis (reprinted with permission [10])

supravalvular aortic stenosis, there may be either mutation or deletion of the elastin gene but deletions are considerably less extensive than those seen in Williams syndrome [22, 23].

In recent years, functional MRI of the brain in those who have Williams syndrome has demonstrated changes linked to the behavioral characteristics of this condition. As an example, pattern construction, block design and drawing are methods of measuring ability in visuospatial construction. The visual cortex of the primate is organized into two processing pathways, a ventral stream for processing an object (“what”) and a dorsal pathway for spatial processing (“where”). In those who have Williams syndrome, functional MRI demonstrates an abnormal dorsal pathway [24]. These and other studies with functional MRI encourage further research into the effects of missing genes on neural function.

Investigation of patients with Williams syndrome has led not only to an understanding of some of the mechanisms involved in this disorder, but also insights into seemingly unrelated matters. Ongoing investigation might well shed further light on the neurobehavioral characteristics of Williams syndrome and of other neurobehavioral and connective-tissue disorders.

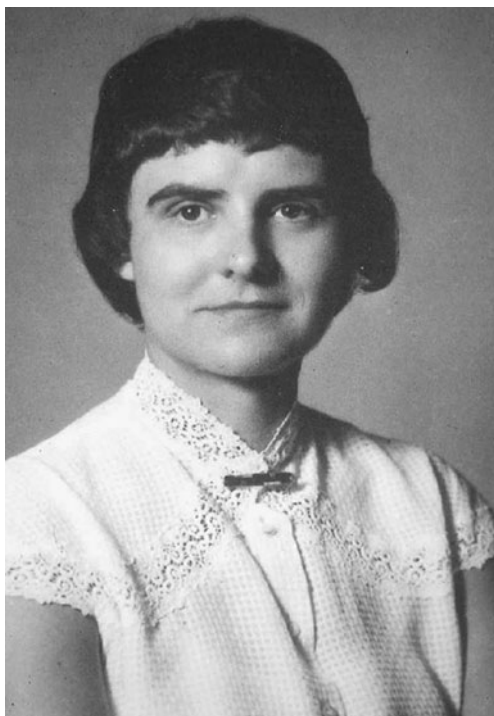


Fig. 6 Anna Blancquaert 1922–2001. Belgian pediatric cardiologist who, with her colleagues, was the first to point out the similarity of the facies in patients with idiopathic hypercalcaemia of infancy and those with supravalvular aortic stenosis and mental retardation [29] (reprinted with permission [29])



Fig. 7 Gloria Lenhoff, one of a number of music savants who have Williams syndrome. This photograph was taken in 1961 when she was age 6. Gloria was diagnosed with Williams syndrome in 1993 and is the subject of a book “The (strangest) song: One Father’s Quest to Find His Daughter’s Voice” [30] (Photograph courtesy of the Lenhoff family)

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