

# Klippel-Feil Syndrome "Plus"

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## Abstract

We report a case with Klippel-Feil (KFS) syndrome associated with hypertelorism, microtia, Sprengel deformity, hand and feet deformities, scoliosis, clinical manifestations of Klippel-Trenaunay syndrome, other anomalies, and severe arterial hypertension secondary to renal artery stenosis. This patient underwent for surgical revascularization unsuccessfully, we have hypothesized that for patients with KFS and unilateral renal artery stenosis medical treatment with ACE inhibitors can provide more benefits than surgery or percutaneous transluminal angioplasty. In order to get better results in the management of this patients all underlying problems should be properly identified before sending patient for any kind of surgery, it is important to bring these problems to the anesthesiologist's attention for a very careful manipulation of the neck and head during induction of anesthesia. The final results will be strongly related with the capacity of management of the underlying cardio-respiratory, renal, and nervous system problems but the family physician should decide in which order of priority surgical or medical intervention should be done. We propose the term of Klippel-Feil syndrome "Plus" for those patients with cervical vertebral fusion and many other associated deformities rather than to add another eponym to the long lists that already exist. From our knowledge this is novel combination not previously reported to the medical literature.

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## INTRODUCTION

Maurice Klippel and Andre Feil described Klippel-Feil syndrome (KFS) independently, in 1912. Later, Feil (1919) classified the syndrome in three different categories as follows: Type I (40%) is present when there is fusion in most of the vertebral bodies. Type II (45%) is present when the fusion of 1 or 2 vertebrae occurs, fusion of C2-3 is dominant and fusion C5-6 is recessive, when there are associated thoracic and lumbar spine anomalies, then it is type III (12%). KFS type IV (3%) has been proposed for associated sacral agenesis.<sup>2</sup>

Those cervical anomalies are due to a failure of normal segmentation of cervical somites during the third and eighth weeks of gestation. The incidence and prevalence of KFS have not been established and its etiology in spite of a great variety of hypotheses such as genetic, vascular, global fetal insult etc. remains unknown. Most of the patients present with decreased flexion and extension of the neck and almost complete inability to rotate the neck that is short on examination, and a low hairline is also observed. Various mechanisms of neural complications have been studied in the literature: medullary abnormality, spinal instability,

narrowing of the cervical canal, and vascular dysfunction.<sup>3</sup> Sometimes neurological problems due to craniocervical junction anomalies like Arnold Chiari malformations type I, platybasia, or basilar invagination can be seen. Other common problems associated to KFS are: scoliosis (60%), spinal bifida, cleft palate, ptosis of the eyes, Duane's eye contracture, lateral rectus palsy, facial nerve palsy and cleft palate, syndactyly, hypoplastic thumb, supernumerary digitis, hypoplasia of the upper extremity, cervical stenosis, C1-C2 hypermobility and instability, cervical dysraphism, diastematomyelia, intracranial tumors, spinal cord abnormalities (Syringomyelia 15%), traumatic paraplegia, deformity of Sprengel (36%), omovertebral bone, ear abnormalities, hearing loss (38%), torticollis and facial asymmetry (45%), craniosynostosis, congenital limb and fingers abnormalities, syngonesis-mirror motions (20%) which tends to decrease after age 5, multiple ribs fusions, craniofacial dysostosis, cardiovascular anomalies (interventricular septal defect: 20%) genito-urinary- Up to 65% to such as: hydronephrosis, renal ectopia, renal agenesis (most common), horseshoe kidney, double collecting system, bilateral tubular ectasies.

Several types of combined malformations such as: KFS + frontonasal dysplasia + Sprengel deformity + widely spaced nipples + postaxial hexadactyly of the left foot,<sup>4</sup> KFS +

malformations of laryngeal cartilages,<sup>5</sup> KFS + microtia + conductive hearing loss + bilateral restriction to supination and elbow flexion of the forearms,<sup>6</sup> KFS + Sprengel anomaly + omovertebral bone + thumb abnormalities + flexion-crease changes,<sup>7</sup> KSS + vertebral dissection,<sup>8</sup> KFS + cervicomedullary neuroschisis + mirror movements,<sup>9</sup> KFS + hypogonadotropism-anosmia (Kallmann syndrome),<sup>10</sup> KFS + deafness + ocular motility disturbances (abducens's paralysis and retraction or adduction (Duane's retraction) also known as cervico-oculo-acoustic or Wildervanck syndrome),<sup>11</sup> Klippel-Feil syndrome + azoospermia + renal abnormalities (analogue of MURCS),<sup>12</sup> among others, can be observed.

Medical and/or surgical treatments are dependent upon the congenital anomalies present in the syndrome. Undiagnosed hidden anomalies are close related with poor prognosis.

We report a case with some of the before-mentioned anomalies plus renal artery stenosis (RAS). From our knowledge this is novel combination no previously reported to the medical literature.

### CASE REPORT

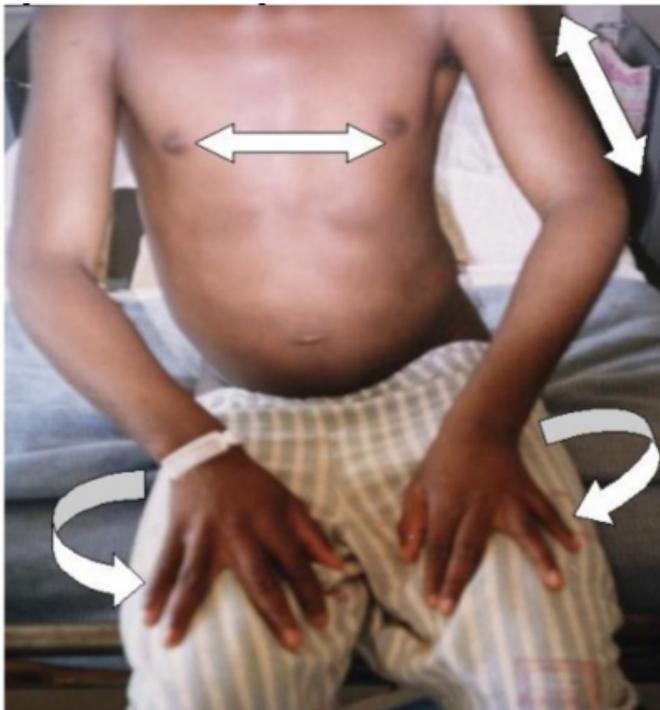
His family doctor refers a 15-years-old male patient to Neurology Out Patient Clinic. The referral doctor requested for this patient to be assessed for disability grand. The patient denied any complaint however is sent to admission because some physical anomalies were observed. The patient was born as the fourth child to healthy non-consanguineous parents. The family history was unremarkable. Pregnancy and birth were normal. When he was near the age of 4 years someone noticed a "funny elevation of the right shoulder" but no growth deficiency in stature is noticed. At admission his weight was 57 kg, his height 160 cm, and his head circumference 57 cm. On the face hypertelorism and mild micrognathia were observed, high narrow palate, bilateral microtia (incompletely formed ear), short neck, and low hairline were also seen (Figure 1 with patient consent).

Figure 1



General examination also showed a remarkable chest asymmetry with Kyphoscoliosis, muscle wasting on the left arm, hand, and wide separation between 3rd finger and 4th finger (Figure 2), On the lower limbs: mild gigantism of the right big toe, lymphedema of the feet and port-wine stain and "birthmark" (cutaneous capillary malformations) were well defined, the nails and teeth were normal. He was well orientated and no language or speech problems were detected, recent memory and sensory attention were altered, and mild-moderate mental retardation were confirmed, motor system examination showed a decreased muscle power in proximal region predominantly with symmetrical hypotrophy on the left arm, and muscle wasting on the right suprascapular area. Apart from BP 170/129 mmHg, cardiorespiratory system showed unremarkable clinical findings. The inferior border of the liver is palpated at 4 cm below the right inferior costal margin.

**Figure 2**



Complementary exams showed: Normal full blood count, urea and electrolytes, glucose, cretonne, liver function tests, thyroid function tests, kidney function tests, were within normal limits. Radiographic studies showed vertebral fusion between C6-7, moderate scoliosis, Springer deformity, left omovertebral bone, on X-Rays of the craniocervical region, the superior border of C2 is 6 mm above Chamberlain's line. CT Scan of the brain showed remarkable radiological signs of leucodystrophy in the cerebral hemispheres bilaterally. CT Angiography showed a right RAS (Figure 3); the patient is transferred to another hospital for surgical treatment where he died soon after operation.

**Figure 3**



### **ETHICAL CONSIDERATIONS**

Informed consent was obtained and confidentiality retained.

### **DISCUSSION**

Klippel-Trenaunay syndrome or Klippel-Trenaunay-Weber syndrome (KTWS), is generally accepted, when there are enlargement of the soft tissue, bony hypertrophy, port-wine stain, venous malformations and lymphatic abnormalities; in our patient we could not investigate arterio-venous fistulae by phlebography and arteriography because patient died before to do that. KTWS is an uncommon disease (around 310 cases have been published) due to a congenital malformation of the deep venous system with agenesis, hypoplasia or segmental atresia, the etiology is not clear however seems to be related with diffuse mesodermal abnormalities during fetal development and genetic mutations. In 1993, one patient with associated renal artery aneurysm is reported.<sup>13</sup> We can not proof what relationship exist between KFS and KTWS, if there is any, but we know that KFS is associated to different other anomalies, reason why we prefer to nominate it as KFS "plus." considering that it is an anecdotic coincidence.

Hypertelorism (Hp) presents as abnormal increase in distance between the eyes due to development arrest the greater wings of the sphenoid bone, which is sometimes associated to Sprengel deformity, and some other anomalies of the skull. It is often incorrectly diagnosed when a flat nasal bridge, epicanthal folds, external strabismus, widely spaced eyebrows, blepharophimosis, or some combination of these is present. Our patient presented a combination of anomalies not described in Greig's ocular hypertelorism

syndrome and Hp in G, Opitz-G, or BBB syndrome combine laryngotracheoesophageal cleft, cleft of lip, palate, and uvula; swallowing difficulty and horse cry, hypospadias or splayed labia majora, mental retardation, and congenital heart defects no present in our patient. Alagille syndrome with associated renovascular hypertension should also be distinguished, the association of at least three of the following five abnormalities characterizes it: chronic cholestasis, peripheral pulmonary stenosis, vertebra arch defects, embryotoxon, and typical facies. Tubulointerstitial nephritis, renal tubular acidosis, and renal artery stenosis have been noted in Alagille syndrome

Vascular Birthmarks present in this case was classified as vascular malformation (other category are hemangiomas) including Port Wine Stains associated with a deficiency in the nerve supply to the blood vessels.

### **KIDNEYS**

Abnormalities of the kidneys increase in frequency when there are auricular deformities, particularly when the patient is afflicted with other manifestations of facial underdevelopment; many patients have hypospadias or vaginal agenesis, and abnormalities of their collection systems. However, they can easily live with just one kidney, therefore to see patients with microtia and any life-threatening renal consequences from these system abnormalities is very uncommon, of course living with extremely high diastolic hypertension has a different prognosis. Cervical spine anomalies are more common in microtic patients if other "midline defects" exist, such as cardiac or renal disorders or cleft lip and palate but when associated neurological symptoms are not present, the frequency of these vertebral abnormalities are underestimated. We considered that microtia in our patient were not related with oculoauriculovertebral dysplasia (Goldenhar's syndrome) because he didn't had cleft palate and ocular dermoid among other differences. Because there are not Cleft Palate, breathing problems and glossoptosis (in spite of micrognathia), then Pierre Robin Malformation Sequence is ruled out. In absent of cleft palate and drooping of the lower eyelids for one side and a flat face, club feet, contracted muscles of the joints of the fingers and hands, and underdeveloped nose cartilage on the other, Miller Syndrome, Treacher-Collins Syndrome, and Freeman-Sheldon syndrome are can also be ruled out. Cataracts, retinal detachment, some degree of cleft palate, usually present in Stickler syndrome, Saethre-Chatzen syndrome, Apert Syndrome, and Pfeiffer Syndrome were also excluded.

Because no evidence of ventricular septal defects and conduction-system abnormalities were detected, we ruled out Holt-Oram syndrome.

### **HYPERTENSION AND RAS**

Inverse situation like postural hypotension in patient with cervical cord compression (C2-C3) and selective damage of the descending autonomic fibers due to craniocervical anomaly and KFS, has been reported.<sup>14</sup>

Approximately one-fifth of the South African population has hypertension; the national prevalence rate of 21 % is equivalent to other industrialized countries and greater than that many developing countries; nearly half South African population still rural and much of the African urban population now rapidly adopting Western lifestyle habits therefore prevalence rates will increase with time.<sup>15</sup>

Prevalence of secondary hypertension remains unknown and severe hypertension due to RAS and an associated KFS had not been before-cited; to the best of our knowledge this is the first report on this type of association in the medical literature. Constriction of the renal artery leads to a cascade of important hemodynamic and humoral events within the affected kidney, stenosis of the renal artery reduces perfusion pressure releasing rennin, augmenting intrarenal angiotensin II production which increase systemic vasoconstriction and aldosterone secretion

The optimal treatment for arterial hypertension due RAS is controversial. Current treatment options are medical therapy (angiotensin convertin enzyme inhibitors), percutaneous transluminal angioplasty with or without stenting, and surgical reconstruction. Renovascular hypertension must be distinguished from RAS, in true renovascular hypertension, the kidneys takes charge of the blood pressure and will do what it takes to push blood pressure high enough to force blood through the blocked artery. Some experts favor surgical revascularisation because of occasional angioplasty failure and the risk of deterioration of renal function after angioplasty.<sup>16</sup> Has been clearly established that for those patients who have atherosclerotic RAS with normal or mildly impaired renal function, primary angioplasty was not more effective than antihypertensive drugs alone for reducing blood pressure or limiting disease progression.<sup>17</sup> Has been accepted that angioplasty and stenting of stenosed renal arteries normalizes renin secretion by both treated and contralateral kidneys and improve the function of the treated kidney but for young patients with non-atherosclerotic RAS the chance for reducing blood pressure by angioplasty is and

is not certain; considering that other vascular lesions could be present (Takayasu's disease) is not, however when there is not coexisting renal parenchyma disease, when there is not progression to renal artery occlusion, no loss of renal mass, and no result in renal failure, those patients respond to angioplasty.<sup>18</sup> Paulsen et al performed 591 renal angioplasties in 419 patients with significant renal artery stenosis with better results in patients with fibromuscular dysplasia and concluded: angioplasty can be done in selected patients.<sup>19</sup>

Because renovascular hypertension remains raised despite surgery, although antihypertensive consumption declines some authors have postulated that uncorrected media/lumen ratio in resistance arteries does not cause hypertension.<sup>20</sup> Surgical reconstruction of the stenosed renal artery take time under anesthesia and the patient's body is forcibly moved in turning maneuvers including the head and neck for inducing anesthesia therefore risk of provoke complications increase with, mainly in those patients who the 100 % of underlying problems had not been previously identified. It is important to realize that if the congenital anomalies are picked up at an early stage, the damage is less harsh during any intervention. Although the following situation has not been reported yet, if any patient with bilateral renal artery stenosis (ACE inhibitors are contraindicated) undergo for surgery then anesthetic consideration should be discussed.<sup>21</sup> for patients with KFS and unilateral renal artery stenosis the treatment of choice is medical with ACE inhibitors until proven otherwise. We also propose the term of Klippel-Feil syndrome "plus" for those patients with cervical vertebral fusion and other associated deformities rather than to add another eponym to the long list that already exist.

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### References

1. Gunderson CH, Grennspan RH, Glaser GH, Lubs HA. The Klippel-Feil syndrome: genetic and clinical reevaluation of cervical fusion. *Medicine* 1967;46:491-512.
2. Rass-Rothschild A, Goodman RM, Grunbaum M, Berger I, Mimouni M. Klippel-Feil anomaly with sacral agenesis: an additional subtype, type IV. *J Craniofac. Genet. Dev. Biol.* 1988;8:197-301.
3. Rouvreau P, Glorion C, Langalais J, Noury H, Pouliquen JC. Assessment and neurological involvement of patients with cervical spine congenital synostosis as in Klippel-Feil syndrome: study of 19 cases. *J Pediatr OrthopB* 1998;7(3):179-85.
4. Fragoso R, Cid-Garcia A, Hernandez A, Nazara Z, Cantu JM. Frontonasal dysplasia in the Klippel-Feil syndrome: a new associated malformations. *Clin. Genet.* 1982; 22:270-273.
5. Clarke RA, Davis PJ, Tonkin J. Klippel-Feil syndrome associated with malformed larynx: case report. *Ann Oto.Rhinol.Laryng.* 1994;103:201-207.
6. Clarke RA, Singh S, McKenzie H, Kearsley JH, Yip MY. Familial Klippel-Feil syndrome and paracentric inversion inv (8)(q22.2q23.3). *Am J.Hum Genet.* 1995;57:1364-1370.
7. Larson AR, Josephon KD, Pauli RM, Optiz JM, William MS. Klippel-Feil anomaly with Sprengel anomaly, omovertebral boen, thumb abnormalities, and flexion-crease changes: novel association or syndrome? *Am J Med Genet* 2001 Jun 15;101:158-162.
8. Hasan I, Wapnick S, Kutscher L, Couldwell T. Vertebral dissection associated with Klippel-Feil syndrome in a child. *Childs Nerv Syst* 2002 Feb;18(1):67-70.
9. Royal SA, Tubbs RS, D'Antonio MG, Rauzzino MJ, Oakes W. Investigations into the association between cervicomedullary neuroschisis and mirror movements in patients with Klippel-Feil syndrome. *AJNR Am J Neuroradiol* 2002 Apr;23(4):724-729.
10. Zenteno JC, Venegas C, Santiago E, Kofman-Alfaro S. Kallmann syndrome (hypogonadotropism-anosmia) and Klippel-Feil anomaly in the same patient. *Clin.Dysmorphol* 2000 Jan;9(1):69-70.
11. Wang Y, Shi X, Wang Z. Wildervanck or cervico-oculo-acoustic syndrome Lin Chuang Er Bi Yan Hou Ke Za Zhi 1997Nov;11(110):499-501.
12. Meschede D, Kliesch S, Hortst J, Nieschlag E. Azoospermia and segmentation abnormalities of the cervicothoracic spine ('MURCS in the male') *Clin Dysmorphol* 1998 Jan;7(1):59-60.
13. Ogden CW, Jackson JE. The Klippel-Treanunay syndrome associated with renal artery aneurysm. *Br. J. Urol* 1993 May;71(5):617-618.
14. Misra UK, Kalita J, Kapoor R. Postural hypotension in a patient with cervical myelopathy due to craniocervical anomaly. *Cli Auton Res* 1997 Oct;7(5):223-226.
15. Steyn K, Thomas AG, Bradshaw, Laubscher R and Fourier J. Hypertension in South Africa adults: results from the Demographic and Health Survey, 1998. *Journal of Hypertension* 2001;19:1717-1725.
16. Spence JD. Treatment options for renovascular hypertension. *Expert Opin Pharmacother* 2002 Apr;3(4):411-416.
17. Van Jaarsveld BC, Krijnen P, Pieterman H. et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. *N Engl J Med.* 2002 Apr6: 342:1007-1014.
18. Edwards JM Zaccardi M, Strandness DE. A preliminary study of the role of duplex scanning in defining the adequacy of treatment of patients with renal artery fibromuscular dysplasia. *Vasc Surg* 1992; 15:604-609.
19. Paulsen D, Klow NE, Lien B, Fauchald P. Treatment of renal artery stenosis. *Tidsskr Nor Laegeforen* 2001Nov 20; 121(28): 3264-3269.
20. Renovascular hypertension remains raised following surgery.
21. Greener M. Renovascular hypertension remains raised following surgery. URL:<http://www.cardiosource.com/journal/journal/article?acronym=CARRES%format=abstract&uid=PHS00086636301003662>.
22. Sukanya M, Gombar KS, Charu D, Das A. Anesthetic management of a patient with Klippel-Feil syndrome. *J Anesth* 2001;15:53-56.

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