Long Term Follow-Up of Four Patients With Keutel Syndrome

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Keutel syndrome (KS) [OMIM 245150] is an autosomal recessive hereditary syndrome characterized by multiple peripheral pulmonary stenoses (PPS), brachytelephalangia, inner ear deafness, and abnormal cartilage ossification or calcification. Mutations in the matrix Gla protein (MGP) gene have been reported in different unrelated families with KS previously. MGP is an extracellular matrix protein and calcification inhibitor; mutations in its encoding gene result in cartilage ossification or calcification, the main presenting feature of KS. This report describes the findings of four sisters with KS born to consanguineous parents were followed for 26 years in an irregular fashion. During follow-up of the patients over the years the complications appear to be mostly involving the respiratory system. Permanent skin rashes, papillary microcarcinoma of the thyroid, asthma, massive bullous pulmonary emphysema, severe systemic arterial hypertension, and short term memory loss were observed during long term follow-up. The fertility status of the patients were also observed and infertility was observed in one of three married patients.

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Key words: keutel syndrome; long term follow-up; ossification of cartilage tissue; tracheobronchial stenosis

INTRODUCTION

Keutel syndrome (KS), is an autosomal recessive hereditary syndrome with an estimated prevalence of 1:1,000,000. It was first described by Keutel in 1971 and is characterized by multiple peripheral pulmonary stenoses (PPS), brachytelephalangia, inner ear deafness, and ossification or calcification of cartilages [Keutel et al., 1971]. Fryns et al. [1984] reported a 13 year old slightly mentally retarded female patient with diffuse calcification of the cartilage, brachytelephalangy, mixed hearing loss and peripheral pulmonary stenosis and confirmed the existence of Keutel syndrome as a distinct syndrome [Fryns et al., 1984]. Khosroshahi et al. [1989] reported four additional cases of KS in sisters of consanguineous parents. At the time of diagnosis the patients were 14, 11, 10, and 8 years old and clinical manifestations included typical facial appearance, abnormal cartilage ossification, multiple PPS, brachytelephalangism, subnormal IQ (borderline in Patients 1, 2, and 4, low average in patient 3), repeated respiratory infections, otitis media, and hearing loss. Based on auricular cartilage biopsy, authors underlined direct ossification without tissue reaction or calcification of auricular cartilage tissue in KS [Khosroshahi et al., 1989].

Homozygous mutations in the gene encoding MGP, a member of the Gla protein family which includes osteocalcin and some coagulation factors [Munroe et al., 1999] are main cause of KS. MGP is a vitamin K-dependent protein synthesized primarily by chondrocytes and vascular smooth muscle cells. It is found in a variety of tissues such as the lung, heart, kidney, cartilage, and bone [Hur et al., 2005]. It has been demonstrated that deficiency of MGP, which also acts as a local inhibitor of calcification [Theuwissen et al., 2012], may cause massive calcification of the arterial tunica media [Luo et al., 1997] and that MGP carboxylation would have a beneficial effect in preventing the development of arterial calcification [Cranenburg et al., 2011].

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Data on the long term outcomes in patients with KS are limited. Meier et al. [2001] reported a 20-year follow-up of two patients originally reported by Keutel et al. [1971]. Post-mortem examination of these two patients revealed tracheobronchial stenosis, and calcification of pulmonary, coronary, hepatic, renal, meningeal, and cerebral arteries [Meier et al., 2001]. A 14-year follow-up of a 27-year-old patient who suffered from transient patchy alopecia, dyspnea, and mild mental retardation during follow-up, has also been reported [Devriendt et al., 1999].

We followed the course of the disease in the aforementioned sisters for 26 years, (Patient 2 for 24 years) between 1988 and 2014. In this article, we report on the social and educational status and clinical findings of the four patients recorded during the follow-up period.

CLINICAL REPORT

During the final review in March 2014, Patients 1, 3, and 4 were 40, 36, and 34 years old, respectively. Patient 2 died in 2012 at 37 years of age after giving birth to her second baby by cesarean (C/S). We previously described the findings of the patients at the time of diagnosis in 1989, which included typical face, PPS, ossification of auricular cartilage, calcification/ossification of epiglottis, trachea, and alae nasi with short terminal phalanges [Khosroshahi et al., 1989].

Social and Occupational Status

All four patients completed high school. Patient 1 has received an applied course on echocardiography and currently works as echocardiography technician at a university. After receiving high school diploma, Patient 2 started to work as secretary in a furniture store. Patients 3 and 4 finished some digital design and computer software program courses and presently are working in related jobs respectively.

Physical Examination

The signs and symptoms of the patients are summarized in Table I and physical findings are presented in Table II. All patients developed hypertension before 20 years of age, which was controlled with appropriate medical (Perindopril terbutaline 10 mg/day/P.O., Amlodipin besilat 10 mg/day/P.O., Nifedipine 30 mg/day/P.O.) treatment. Hypertension in Patient 4, who had a tendency to neglect medication, was particularly high compared with the other patients. Losartan potassium had little effect on controlling the hypertension in Patient 4.

| TABLE I. Consistent Sign and Symptoms of Patients During Follow up |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Amnesia                 | No                      | Yes                     | Yes                     | Slightly                |
| Arthralgia              | No                      | Yes                     | No                      | Yes                     |
| Bleeding (Nasal, tooth extraction) | No | Yes                     | No                      | Yes                     |
| Delayed wound healing   | Yes (severe)            | Yes                     | No                      | Yes (mild)              |
| Easy fatigue/Dyspnea    | Severe                  | Moderate                | Moderate                | Severe                  |
| Headache                | Severe                  | No                      | No                      | Unilaterally lost       |
| Hearing                 | No                      | Yes                     | No                      | Yes                     |
| Irregular menstruation  | Yes                     | No                      | Yes                     | Yes                     |
| Phobia/Obsession/Panic  | Yes                     | No                      | No                      | No                      |

| TABLE II. Physical Findings* |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Patient                     | 1                          | 2                          | 3                          | 4                          |
| Age (years)                 | 41                         | 37                         | 36                         | 34                         |
| Body mass index (Kg/m²)     | 24                         | 31,1                       | 31,4                       | 25,8                       |
| Anemia                      | No                         | Yes                        | No                         | Yes                        |
| Blood pressure (mm Hg) †    | 140/80†                    | 160–170/90†                | 130/80                     | 220/115†                  |
| Barrel chest                | Yes                        | Yes                        | Yes                        | Yes                        |
| Cardiac murmur              | Yes                        | Yes                        | Yes                        | Yes                        |
| Eyelid ptosis               | Yes (left eye)             | No                         | No                         | Yes (left eye)             |
| Respiratory sound           | Obstructive                | Obstructive                | Obstructive                | Obstructive                |
| Skin lesion                 | Yes                        | Yes                        | Yes                        | Yes (slight)               |

*Basic findings has been reported previously [Khosroshahi et al., 1989].
†Under medication.
‡Measured at last visit.
Facial appearance of all patients showed premature aging with deepening of nasolabial folds, puffy and droopy upper eyelids, puffy and loose cheeks, and a prominent puffy double chin (Figs. 1–3).

**Facial Appearances**

Facial appearance of all patients showed premature aging with deepening of nasolabial folds, puffy and droopy upper eyelids, puffy and loose cheeks, and a prominent puffy double chin (Figs. 1–3).
Skin Lesion

All patients developed multiple erythematous, irregularly bordered macular skin lesions without induration typically after the age of 30 years. These lesions were located on the dorsum of hands, elbows, the neck and sternal region, and the entire trunk (Figs. 4–7). The first biopsy of the skin lesions of Patient 1 taken in 2008, showed mild increased melanin pigment in the epidermis, presence of mild melanin incontinence, and capillary proliferation along with minimal perivascular mononuclear inflammatory cell proliferation in the superficial dermis. Microscopic examination of the second skin biopsy of the same patient in 2013 revealed orthokeratosis at the surface, mild irregular acanthosis at the epidermis and few macrophage infiltrations in the superficial dermis. Perivascular mild lymphocytic infiltration with the presence of plasma cells in the superficial and deep dermis was observed along with mild vascular proliferation. Histochemical examination with Elastika van Gieson dye revealed the absence of elastic fibers in papillary dermis but the presence of structurally preserved elastic fibers in the reticular dermis (Figs. 8–10).

Ossification/Calcification of Upper and Lower Airways Cartilage

All patients suffered from recurrent upper and lower respiratory tract diseases, chronic sinusitis, chronic obstructive pulmonary disease, asthma, and emphysema. The chest x-ray of patients demonstrated widespread micro-densities all over the lungs. Pulmonary functional tests revealed obstructive lung disease pattern.
without bronchodilator response. FEV1/FVC values were 0.57; 0.53; 0.79, and 0.73 in Patients 1, 2, 3, and 4, respectively (Obstruction is defined as a FEV1/FVC ratio of less than 0.7).

Progressive laryngotracheobronchial ossification/calcification was evident in all patients (Figs. 11 and 12). The pulmonary CT scan of Patients 1 and 3 taken during the last visit showed severe bullous emphysema (Fig. 13). The cervical x-ray was also evident for laryngotracheal ossification/calcification (Fig. 14).

Although Patient 2 had not experienced any respiratory difficulties when she gave birth to her first child when she was 19 years old (see below), however she was unable to regain consciousness for up to 4 hr following general anesthesia for curettage after spontaneous

![Pulmonary CT scanning showing tracheobronchial ossification/calcification of Patient 1.](image1)

![Pulmonary CT scanning showing tracheobronchial ossification/calcification of Patient 3.](image2)
abortion of a fetus at 10 weeks of gestational age at the age of 34. In 2012, she gave birth to her second live born baby by C/S. During this operation, due to laryngotracheal rigidity, she experienced tracheal intubation difficulties. Following the operation she developed respiratory failure, and was unable to wake up from general anesthesia for approximately one hour and died at the age of 37.

Patient 4 also experienced the same difficulties when she underwent surgery for thyroid papillary microcarcinoma and tracheostomy was required.

Thyroid Nodule, Thyroid Carcinoma
All patients developed thyroid nodules. In three of the patients, the nodules were small in size; however, in patient 4, the nodule was large enough to warrant biopsy. The nodule was identified as papillary microcarcinoma of the thyroid gland, and as noted above, the patient underwent surgery; she was 31 years old at the time.

Fertility Status
Patient 1 was unmarried and there is no documentation regarding her fertility status. Patient 2 married when she was 17 years old and gave birth to two healthy boys when she was 19 and 37 years old. The first born is now a healthy young man and the second baby is a 2½-year-old healthy child. Patient 3 married and gave birth to a healthy baby boy by C/S in February 2014. Patient 4 did not show any abnormalities with menstruation, ovulation and hormonal levels; however, she could not conceive. In vitro fertilization was attempted several times, but all unsuccessful.

Amnesia
All cases, with the exception of Patient 1, have complaint of having short-term memory loss, which did not interfere with their daily lives. This complaint has not been tested formally yet. The patients are following up in this regard and further investigation will be carried out.

Hearing Loss
At the time of the diagnosis the hearing loss was only present in Patient 2 and was mild (40 dB). Progressive hearing loss was observed in all patients during the follow-up. Patients 1 and 2 exhibited a mild hearing loss (about 35–40 dB) in one ear and profound (above 90 dB) in the other. The unilateral hearing loss is moderate (about 40–50 dB) in Patient 3.

Laboratory Findings
At the last visit, values were all within normal limits for the followings: Fe, Fe binding capacity, ferritin, vitamin B12 and folate, blood urea nitrogen and creatinine, creatine kinase, fasting blood sugar, thyroid-stimulating hormone, free T3 and T4, liver function tests, active partial thromboplastin time, prothrombin time, and international normalized ratio. Patient 4 showed mild hypochromic and microcytic anemia.

Medical Imaging
Chest x-ray in all patients showed diffuse micro-radiodensities all over the chest. Renal arterial Doppler, carotid Doppler and abdominal ultrasound results were all within normal limits. Transthoracic echocardiography revealed mild mitral regurgitation in Patients 3 and 4, and mild pulmonary insufficiency in Patient 3. The chest computed tomography of Patients 1 and 3 revealed hyperdensity of laryngotracheobronchial cartilage with diffuse and massive bullous emphysema. Abdominal computed tomography of Patients 1 and 3 revealed hiatus hernia.

DISCUSSION
In 1989 Khosroshahi et al. reported four cases of KS. The cases were four sisters of consanguineous parents. At the time, clinical man-
i festations included abnormal cartilage ossification of ears, epiglo-
tis and alae nasi, multiple PPS, brachytelephalangism (Fig. 15),
subnormal IQ (borderline in Patients 1, 2, and 4, low average in
Patient 3), repeated respiratory infections, otitis media, and hearing
loss. Based on auricular cartilage biopsy, the ossification but not
the calcification of the auricular cartilage tissue (Fig. 16) in KS had
been underlined [Khosroshahi et al., 1989]. Over the last 26 years
of follow-up, all findings were progressive in nature. Obstructive
pulmonary disease dominated clinical presentation and had an
impact on the clinical findings. Skin lesions in all patients developed
typically after the age of 30.

The genetic analysis of our four patients carried out by Munroe
et al. [1999], revealed the homozygosity for a deletion of cDNA
nucleotide 69, a G, of the \textit{MGP} gene. A mutation in the \textit{MGP}
gene (IVS2 + 1G > A) in a consanguineous Arab family with KS has been
reported by Hur et al. [2005]. A novel homozygous \textit{MGP} mutation
(c.61 + 1G > A) in a patient with KS without signs of arterial
calcification has also described [Cranenburg et al., 2011]. Recently
a new \textit{MGP} mutation (c.79G > T, which predicts p.E27X) and a
partial deletion of exon 4 has reported [Weaver et al., 2014].

Upper and lower respiratory cartilage tissue calcification/ossifi-
cation has a major impact on symptoms, clinical findings, progno-
sis, and the natural history of KS. Tracheobronchial and subglottic
stenosis may develop in patients with KS [Buchsteiner et al., 1998;
Meier et al., 2001; Ozdemir et al., 2006; Sun and Chen, 2012].
Indeed, progressive tracheobronchial cartilage ossification/calcifi-
cation of our patients may have played a leading causative role in the
development of chronic and progressive obstructive respiratory
disease in all of our patients.

Meier et al. [2001] reported thickened skin with livid maculae in
their 34 year-old patient whose skin biopsy showed calcification of
elastic interna of the arteries of soft tissue and ossification in the
dermis [Meier et al., 2001]. Nanda et al. [2006] reported four
patients with KS (an infant, and three children, ages 3½, 6½, and
8 years old) with clinical findings mimicking cutis laxa in which
skin biopsies revealed elastolysis not restricted to the atrophic
patches (Patient 1) and secondary anetoderma (Patient 2) [Nanda
et al., 2006]. Extravascular ossifications and elastic fiber calcifica-
tion in the dermis and calcium deposition along the elastic fibers in
the aortic media was demonstrated in patients with KS [Cranen-
burg et al., 2011].

Multiple erythematous, irregularly bordered macular skin
lesions without induration developed in all of our patients typically
after the age of 30. Skin biopsies of Patient 1 performed 5 years apart
failed to demonstrate calcification or ossification in the dermal
tissue. There was a loss of elastic fibers through the papillary dermis
but not in the reticular dermis. Absence of elastic tissue in the
mid-dermis of a patient with KS has been previously reported [Hur
et al., 2005].

It is known that the mother of a patient with KS had experienced
several miscarriages [Gilbert and Lacombe, 1999]. We were unable
to find any report regarding the fertility status of the female
patients with KS. One third of our married patients showed
infertility (Patient 4), and one experienced spontaneous abortion
(Patient 2). Patient 2 gave birth to two healthy boys; Patient 3 gave
birth to a healthy boy; Patient 4 could not conceive despite lack of
any evident abnormality in reproductive function and in vitro
fertilization was unsuccessful. Although the miscarriage and
infertility are relatively common problems in the population,
we think infertility should be kept in mind while following patients
with KS.

The role and prognostic value of \textit{MGP} gene expression in cases
of breast cancer, renal-cell carcinomas, prostate carcinomas, and
testicular germ-cell tumors have been reviewed [Chen et al., 1990;
Levedakou et al., 1992; Yoshimura et al., 2009]. The loss of \textit{MGP}
gene expression may be associated with tumor progression and
metastasis [Levedakou et al., 1992]. Mediastinal seminoma in a
patient with KS has been also reported previously [Meier
et al., 2001]. All our patients developed thyroid nodules and Patient
4 developed papillary microcarcinoma. The mutation in the human
\textit{MGP} gene may play causative role in developing thyroid papillary
carcinoma in our patient.
It is known that renal arterial calcification resulting from MGP inactivation may cause renal dysfunction and systemic hypertension, which predisposes the patients to unfavorable prognosis [Meier et al., 2001]. All our patients suffered from systemic hypertension. Although all renal Doppler, carotid Doppler and ultrasonography tests of our patients were within normal range, we suggest that the renal arterial microcalcification may be the cause of systemic hypertension in our patients.

Pineal calcification has been demonstrated by brain MRI and MRA in four patients with KS recently [Thangamadhan et al., 2014]. The cerebral calcification and microinfarcts also have been reported in some cases of KS [Luo et al., 1997; Teebi et al., 1998; Meier et al., 2001]. We were unable to demonstrate such calcifications in our patients yet. But it is presumptive whether such cerebral calcifications may play causative role in developing of short term memory loss in our patients. Further investigations need to be carried out.

We suggest that laryngotracheal rigidity and tracheobronchial stenosis, bullous emphysema, skin lesions, progressive hearing loss, hypertension, malignancies like thyroid gland papillar microcarcinoma should also be considered as part of the long-term clinical picture of patients with KS. We also suggest that patients with KS should be followed-up regarding miscarriage, infertility, and short term memory loss.

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