Olmsted syndrome: clinical, molecular and therapeutic aspects

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Abstract
Olmsted syndrome (OS) is a rare genodermatosis classically characterized by the combination of bilateral mutulating transgradient palmoplantar keratoderma (PPK) and periorificial keratotic plaques, but which shows considerable clinical heterogeneity. The disease starts usually at birth or in early childhood. About 73 cases have been reported worldwide. OS is observed in both sexes, although male cases are more frequent. The most suggestive symptoms associate PPK with pseudoainhum and periorificial keratotic plaques. Frequently associated features include hair and nail abnormalities, leukokeratosis, corneal default and recurrent infections. Pain and itching are variable but can be severe. Most of reported OS cases are sporadic, although familial cases with different mode of inheritance were also described. Mutations in TRPV3 (Transient receptor potential vanilloid-3) gene have recently been identified as a cause of autosomal dominant (gain-of-function mutations) or recessive OS. Mutations in MBTPS2 (membrane-bound transcription factor protease, site 2) gene were identified in a recessive X-linked form. The diagnosis relies mainly on clinical features associating severe PPK and periorificial keratotic plaques, but can be challenging in patients with incomplete phenotype or atypical features. OS has to be differentiated from other severe forms of PPK including Vohwinkel, Clouston, Papillon-Lefèvre or Haim-Munk syndromes, Mal de Meleda, pachyonychia congenita, Tyrosinemia type II and acrodermatitis enteropathica. When differential diagnoses are difficult to exclude, genetic studies are essential to search for a TRPV3 or MBTPS2 mutation. However, additional genes remain to be identified. No specific and satisfactory therapy is currently available for OS. Current treatments of hyperkeratosis (mainly emollients, keratolytics, retinoids or corticosteroids), either topical or systemic, are symptomatic and offer only temporary partial relief. Specific management of pain and itching is important to reduce the morbidity of the disease. The disease is debilitating and progressive keratoderma and auto-amputation of digits can prevent patients from grasping and walking, and confine them to a wheelchair. New therapeutic options are therefore crucial and are expected from a better understanding of the disease mechanisms. The use of TRPV3 antagonists would represent such a targeted and potentially powerful strategy.

Keywords: Olmsted syndrome, Palmoplantar keratoderma, Periorificial keratotic plaques, Clinical heterogeneity, TRPV3, MBTPS2

Résumé
Le syndrome d’Olmsted (SO) est une génodermatose rare et sévère, classiquement caractérisée par une kératodermie palmo-plantaire (KPP) bilatérale transgradiente et mutilante associée à des plaques kératosiques périorificielles. Il existe une grande hétérogénéité clinique. Des anomalies des cheveux et des ongles, une leukokeratose, des anomalies de la cornée et de fréquentes infections peuvent être associées. La douleur et le prurit sont variables, mais peuvent être sévères. La maladie (Continued on next page)

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Introduction
Olmsted syndrome (OS) is a rare genodermatosis belonging to the heterogeneous group of palmoplantar keratoderma (PPK). OS shows marked clinical and genetic heterogeneity. The aim of this article is to give an updated review of clinical features, genetics, pathological mechanisms, diagnostic criteria, differential diagnosis and current treatment.

Methods
Literature review
This review is based on a literature search using PubMed. To identify all publications related to Olmsted syndrome and summarize reported cases, a comprehensive search of PubMed was performed for all studies published prior to December 1, 2014, using the search terms “Olmsted syndrome”, “mutilating palmoplantar keratoderma” or “periorificial keratoderma”. We then checked the bibliography of each article to identify additional references. Altogether, 59 reports containing a total of 73 OS were identified from 1927 until December 1, 2014.

Review
Disease name and synonyms
Mutilating palmoplantar keratoderma with periorificial keratotic plaques (ORPHA659, MIM #614594 and #300918)
Olmsted Syndrome (OS)
Palmoplantar and periorificial keratoderma

Definition
Olmsted syndrome is a rare keratinizing disorder characterized by the combination of bilateral mutilating gradient palmoplantar keratoderma and periorificial keratotic plaques. This syndrome was first described in 1927 by Olmsted [1]. Since that date, similar cases have been reported in the literature under the heading of Olmsted syndrome.

Epidemiology
Olmsted syndrome is a rare genodermatosis. The prevalence of the syndrome is unknown. To date, about 73 cases have been reported in the literature (Table 1). Although the number of cases is probably underestimated, the prevalence is likely to be less then 1/100000.

The disease seems to occur worldwide and is observed in both sexes, although male cases (~63% of OS patients) have been predominantly reported (Table 1).

Clinical description
The classical clinical phenotype of OS consists of bilateral mutilating palmoplantar keratoderma and periorificial keratotic plaques. However, OS shows high clinical variability and a wide range of inconsistent clinical manifestations have been reported [36,44]. Other features associated with this condition have been described subsequently and continue to be reported. Clinical manifestations described in detail below are not specific for OS, they can be rarely observed and can also vary in severity. In addition, some features observed in OS patients may be fortuitous and not a part of this syndrome. The disease starts usually at birth, in neonatal period or in early childhood, when the child starts to walk and grasp, and worsens over time. The disease has a slow but progressive course.

Skin
Initially, the hallmarks for the diagnosis of OS are bilateral mutilating palmoplantar keratoderma (Figure 1A) associated with periorificial keratotic plaques (mouth, nose, eyes, genital, anal, ears, navel) (Figure 1B) [1]. Indeed, progression of the keratoderma may lead to flexion deformities,
| Reference | Number of cases | Sex | Mutation |
|-----------|----------------|-----|----------|
| Olmsted, 1927 [1] | 1 | Male | Not reported |
| Costa, 1962 [2] | 1 | ? | Not reported |
| Keir, 1967 [3] | 1 | Female | Not reported |
| Ruiz-Maldonado et al., 1972 [4] | 1 | Female | Not reported |
| Michalowski, 1983 [5] | 1 | Male | Not reported |
| Poulin et al., 1984 [6] | 1 | Male | Not reported |
| Barnett et al., 1985 [7] | 1 | Male | Not reported |
| Harms et al., 1985 [8] | 1 | Male | Not reported |
| Rivers et al., 1985 [9] | 4 (child, father, paternal aunt and grandmother) | 2 females, 2 males | Not reported |
| Battini et al., 1989 [10] | 1 | Male | Not reported |
| Georgii et al., 1989 [11] | 1 | Female | Not reported |
| Atherton et al., 1990 [12] and Armstrong et al., 1997 [13] | 1 (son of case reported in Keir, 1967 [3]) | Male | Not reported |
| Judge et al., 1991 [14] | 1 | Male | Not reported |
| Hausser et al., 1993 [15] | 1 | ? | Not reported |
| Ueda et al., 1993 [16] and Yoshizaki et al., 2001 [17] | 1 | Male | Not reported |
| Lucker et al., 1994 [18] | 1 | Male | Not reported |
| Cambiaghi et al., 1995 [19] | 2 (twins) | Male | Not reported |
| Kress et al., 1996 [20] and Raskin and Tu, 1997 [21] | 1 | Female | Not reported |
| Dogra et al., 1997 [22] | 1 | Male | Not reported |
| Frias-Iniesta et al., 1997 [23] | 1 | Male | Not reported |
| Santos et al., 1997 [24] | 1 | Male | Not reported |
| Sirk et al., 1999 [25] | 1 | Male | Not reported |
| Larregue et al., 2000 [26] | 2 | Male | Not reported |
| Fonseca et al., 2001 [27] | 1 | Female | Not reported |
| Koch et al., 2001 [28] | 1 | Female | Not reported |
| Requena et al., 2001 [29] | 1 | Male | Not reported |
| Bergonse et al., 2003 [30] | 2 | Male | Not reported |
| Dessureault et al., 2003 [31] | 1 | Female | Not reported |
| Ogawa et al., 2003 [32] | 1 | Female | LOR excluded |
| Batra and Shah, 2004 [33] | 1 | Male | Not reported |
| Inamadar et al., 2004 [34] | 1 | Male | Not reported |
| Al-Mutairi et al., 2005 [35] | 1 | Female | Not reported |
| Mevorah et al., 2005 [36] and Eytan et al., 2014 [37] | 1 | Male | TRPV3 p.Trp521Ser |
| Ziaaddini et al., 2006 [38] | 1 | Male | Not reported |
| Ali et al., 2007 [39] | 3 (2 brothers) | 2 Males, 1 ? | Not reported |
| Yaghoobi et al., 2007 [40] and Haghighi et al., 2012 [41] | 2 (uncle, nephew) | Male | MBTPS2 p.Phe464Ser |
| Bedard et al., 2008 [42] | 2 | Female | Not reported |
| Kumar et al., 2008 [43] | 1 | Female | Not reported |
| Tao et al., 2008 [44] | 1 | Male | Not reported |
| Nofal et al., 2010 [45] | 2 (sister) | Female | Not reported |
| Vosynioti et al., 2010 [46] | 1 | Male | Not reported |
| Tharini et al., 2011 [47] | 2 | Female | Not reported |
constrictions of digital bands and even spontaneous digit amputations. However, this pseudoainhum feature is in fact inconsistently reported in OS patient [45]. In addition, in rare cases, periorificial keratotic plaques are absent [55,56]. Keratoderma is initially focal and distributed on the pressure points, gradually extends to most of the surface and becomes diffuse, massive and thicker with time with painful deep fissures. The keratotic lesions are pruritic and can be painful with pressure. Some cases present with focal or punctuate keratoderma [45,57]. A clear improvement of the keratoderma during febrile diseases may occur [19]. Other patients are reported with nonperiorificial keratotic lesions involving the thighs, arms, elbows, knees and intertriginous folds. Hyperkeratotic linear streaks [45,52], follicular keratosis [40], pachyderma, cheilitis [47], ichthyotic lesions or chronic blepharitis [14,23,40] may be also observed.

Pain and itching
Slight to severe pain with variable intensity is a frequent feature of OS [6,9,18,36,44,45]. Painful PPK is reported in around 50% of OS cases, it can be disabling causing most of the time the patient to avoid walking and grasping. In the less severe patients, only slight pain not interfering with hand and feet activities (walking, writing, grasping objects) is mentioned [45].

Itch has also been reported, although less frequently [36,44]. Pruritus, which can be severe, is mentioned in around 16% of OS cases. Thus, pain and itch represent major causes of morbidity resulting in insomnia and interfering with walking and grasping.

Atypical OS, with nonmutilating PPK and no periorificial keratotic plaques, associated with erythromelalgia is rarely observed [55,56]. Pain and itching are reported to be particularly severe in uncommon OS patients with erythromelalgia which lead to acute flares of hyperalgesia, severe itch, erythema, vasodilatation and warmth of the legs and extremities (hands, feet and ears) [55,56]. Erythromelalgia is triggered by heat and pain and is reduced by immersion in cold water. In these patients presenting with dysesthesia (tingling or burning sensations) and allodynia with increased sensitivity to thermal and mechanical stimuli, the pain has clearly features of neuropathic pain. The extend to which similar but less

| Table 1 Reported Olmsted syndrome cases in the literature (Continued) |
|---------------------------------------------------------------|
| Elise Tonoli et al., 2012 [48] | 1 | Female | Not reported |
| Lai-Cheong et al., 2012 [49] | 1 | Male | TRPV3 p.Gly573Ser |
| Lin et al., 2012 [50] | 6 | 5 females, 1 male | TRPV3 p.Gly573Ser (4 cases), p.Gly573Cys (1 patient) and p.Trp692Gly (1 case) |
| Tang et al., 2012 [51] | 1 | Male | Not reported |
| Attia et al., 2013 [52] | 1 | Male | Not reported |
| Danso-Abeam et al., 2013 [53] | 1 | Female | TRPV3 p.Gly573Ala |
| Aloitaibi et al., 2014 [54] | 1 | Male | Not reported |
| Duchatelet et al., 2014a [55] | 1 | Female | TRPV3 p.Leu673Phe |
| Duchatelet et al., 2014b [56] | 2 (brother) | Male | TRPV3 p.Gly568Cys and p.Gln216_Gly262del |
| He et al., 2014 [57] | 2 (father and son) | Male | TRPV3 p.Gln580Pro |
| Kariminejad et al., 2014 [58] | 1 | Male | TRPV3 p.Trp692Cys |
| Wang et al., 2014 [59] | 1 | Male | MBTPS2 c.671-9 T > G |
| Total | 73 | 26 Females, 44 Males | 14 TRPV3 mutations \ 2 MBTPS2 mutations |

Figure 1 Clinical features. A. Diffuse and transgredient, inflammatory plantar keratosis in a 2 year of age child. B. Periauricular keratosis in a 2 year of age child.
severe features could be present in other cases of OS remains to be evaluated.

Hair and nails
The vast majority of patients present with hair abnormalities including alopecia (diffuse, universal or patchy), hypotrichosis, sparse, thinning, curly, woolly, coarse, dry or easily broken hair [22,36,44,47,51]. Microscopic Hair examination may show pili torti, trichorrhexis nodosa type defects, reduced pigment, as well as longitudinalridges and transverse fractures of the hair shaft [19,22,36]. Rare OS cases have normal hair.

Sparse and thin eyebrows and eyelashes but also madarosis are also reported [19,40]. In contrast, eyelash trichomegaly is also observed in OS patients [56]. OS patients often show nails abnormalities including dystrophic, lusterless, ridged, rough nails, hyperkeratosis, onychogryphosis, leukonychia, irregular curvatures, onycholysis, paronychia, subungal hyperkeratosis and even absence of nails [22,32,36,43–45,60].

Oral cavity
Leukokeratosis of the tongue or buccal mucosa have been noted [2,6,11,16,24,27,33,36].

Sweating
Sweating abnormalities such as palmoplantar hyperhidrosis or anhidrosis, acral hyperhidrosis are reported in OS patients [29,61].

Eye
Eyes lesions are frequently described in OS patients, including corneal dystrophy, epithelial dysplasia and opacity [10,14,40]. Inflamed lacrimal glands/ducts or meibomian glands dysfunction are also observed.

Growth
Delayed physical development leading to short stature is frequently described in OS patient [32,36,59].

Recurrent infections
OS patients are prone to recurrent bacterial or candidal infections in keratotic areas [11,14,20,26,27,30]. Perionychial infections are also mentioned.

Immunity
The immunological phenotype was assessed in one OS patient and demonstrated immune dysregulation leading to frequent dermal infections, inflammatory infiltrate in the affected areas, hyper IgE production and elevated follicular T cells and eosinophils in the peripheral blood [53]. Immunodeficiency of an unknown origin has been also reported in another patient [11].

Predisposition to malignancies
OS patients may have a higher susceptibility to develop malignant tumors in keratotic areas such as verrucous carcinoma (a squamous cell carcinoma) and its variant epithelioma cuniculatum located on the sole of the foot, and malignant melanoma [7,15,17,31,32,62].

Teeth
Abnormal dentition with absence of premolar teeth [6], mammilations on the free margins of the incisors [34] or peridontal disease leading to premature teeth loss [54] are mentioned.

Hearing
Hearing loss for high frequencies and congenital deafmutism are noted in few OS patients [6,11,29,48].

Bone
Deformed lower extremities (bow legs) as well as ankylosis (knee and ankles joints), likely resulting from long-term impeded mobility due to painful hyperkeratosis, are described [51]. Osteoporosis and osteolysis of hands and feet [2,3,6,24,26,32] have been also reported.

Other abnormalities
Other abnormalities including joint laxity [6,11,16,26], primary sclerosing cholangitis [11], intellectual disability [1,12] and haemangioma [35] are also rarely observed in OS patients.

Thus, OS syndrome may result from multiple defects in embryonic structures with a major ectodermal involvement as found in ectodermal dysplasia, with possible minor mesodermal abnormality as manifested by hyperlaxity of joints in some cases.

Aetiology

Genetics
Most reported OS cases are sporadic, although familial cases with different modes of inheritance (dominant or recessive autosomal or X-linked inheritance) were also reported.

Recently, the genetic basis has been partially elucidated by the identification of mutations in TRPV3 (Transient receptor potential vanilloid-3) in 14 OS patients with different genetic background (Chinese, Indian, Iranian, Arabic, Caucasian) [37,49,50,53–58]. TRPV3 has been reported as a thermosensitive cation non selective channel, activated by temperature and several chemical ligands, predominately expressed in keratinocytes, and in sensory neurons [63,64]. TRPV3 is a transmembrane channel belonging to the family of TRP (Transient receptor potential) [63,64] and consists of 6 transmembrane domains with cytoplasmic N and C-termini, assembling as tetramers. TRPV3 mutations are responsible for autosomal dominant but also
recessive OS (Figure 2). To date, 7 dominant mutations (p.Gly573Ser in 5 unrelated patients, p.Gly573Cys, p.Gly573Ala, p.Gln580Pro, p.Leu673Phe, p.Trp692Gly and p.Trp692Cys each in an unique case) have been reported (Figure 2). Several dominant mutations were demonstrated to be gain-of-function mutations leading to an increased intracellular Ca$^{2+}$ [50,57]. Three recessive mutations (p.Trp521Ser in a homozygous state in one patient, and p.Gly568Cys and p.Gln216-Gly262del in a compound heterozygote state in two brothers) were also reported (Figure 2) [37,49,50,53,55–58]. Thus, the Gly573 residue, and Trp692 to a lesser extent, are recurrently mutated. In addition, all mutations, except for two recessive mutations, are located in the S4-5 linker or in the C-terminal part of the protein (Figure 2). The recessive p.Trp521Ser and p.Gln216-Gly262del (resulting from the splicing site mutation c.784 + 1G > A) mutations are located in the S2-3 linker and in the N-terminal part of the protein respectively (Figure 2). OS caused by TRPV3 mutations shows clinical heterogeneity. Indeed, OS patients with TRPV3 mutations present either with typical OS hallmarks or incomplete phenotype with atypical features. Genotype-phenotype correlations are difficult to establish at present because of the few reported cases. However, the 5 patients with the same p.Gly573Ser mutation present with a similar phenotype including mutilating PPK with variable severity, hair abnormalities (from dry hair to alopecia) and keratotic plaques (periorificial or only in the natal cleft). In the other hand, other mutations, located in the same part or in different domains of the protein, are associated by atypical features (Figure 2). The p.Leu673Phe (dominant), p.Gly568Cys (recessive) and p.Gln216-Gly526del (recessive) mutations lead to atypical OS, with nonmutilating PPK and no periorificial keratotic plaques, associated with erythromelalgia [55,56]. The patient with the p.Gly573Ala presents with immune dysregulation [53]. The 2 related patients with the p.Gln580Pro mutation have a very mild phenotype with only focal PPK even at 37-year-old for the father [57].

Mutations in MBTPS2 (membrane-bound transcription factor protease, site 2) gene (p.Phe464Ser and c.671-9 T > G), encoding a zinc metalloprotease essential for cholesterol homeostasis and endoplasmic reticulum stress response, have also been reported in recessive X-linked OS [41,59]. Mutations in MBTPS2 also lead to IFAP (Ichthyosis follicularis - atrichia - photophobia) syndrome with or without BRESHECK syndrome (MIM #308205, ORPHA2273) [65]. BRESHECK syndrome is a multiple congenital malformation characterized by intellectual disability, brain anomalies, Hirschsprung disease, corneal opacifications, kidney dysplasia, cryptorchidism, cleft palate, and skeletal malformations, particularly of the vertebrae. The OS patient with the c.671-9 T > G mutation also presents with classic IFAP syndrome [59], whereas previously reported patients with the same mutation in MBTPS2 has no OS features. The mechanism by which MBTPS2 mutations lead to IFAP or OS is currently unclear.

There is no obvious clinical difference between OS caused by TRPV3 and MBTPS2 mutations despite the mode of inheritance. In addition, clinical variability is observed even in patients from the same family or unrelated patients harbouring the same mutation, suggesting the implication of modifier genes, epigenetics and/or environmental factors.
Finally, some patients do not carry detectable mutations in either gene, indicating further genetic heterogeneity.

**Pathogenesis**

The pathogenesis of OS is poorly understood. However, a defect in the expression of mature epidermal keratins (1 and 10) and persistence of basal keratins (5 and 14) was reported [20,21,27,45], as well as increased expression of Ki-67, a mitotic activity marker in basal and suprabasal layers [29,44,48]. Thus, involved areas remain in an immature state and continue to proliferate in an improper fashion. This excessive epithelial proliferation may result in hyperkeratosis. The mechanism by which TRPV3 mutations lead to OS pathogenesis is unknown. Functional studies of four TRPV3 mutations (p.Gly573Ser, p.Gly573Cys, p.Trp692Gly and p.Gln580Pro) using patch clamp analysis on transfected HEK293 cells expressing TRPV3 mutants were performed [50,57]. These studies have shown that these mutations lead to much larger inward currents probably because of the constitutive opening of the mutants [50]. Thus, these mutations are gain-of-function mutations and result in elevated intracellular Ca\(^{2+}\) inducing increased apoptosis, suggesting that enhanced cell-death could drive OS [50]. In addition, murine models have shown that TRPV3 is also associated with TGF-α/EGFR signaling, which plays a role in keratinocyte differentiation control [66]. Reported immune dysregulation in OS suggests a primary (as TRPV3 is expressed by Langerhans cells) or secondary role of immunological processes in OS pathogenesis [53]. Transcriptomic and proteomic investigation in patients with the p.Gln580Pro mutation, leading only to focal PPK, showed decreased expression of proteins involved in keratinocyte differentiation, in gap junction, tight junction and desmosome formation, but increased expression of proteins involved in keratinocyte proliferation and cell death [57]. Thus, the TRPV3 p.Gln580Pro gain-of-function mutation disrupts the balance between keratinocyte proliferation and differentiation, and compromises cell adhesion. In addition, previous studies on murine models have also demonstrated that TRPV3 mediates release of pro-inflammatory cytokines including interleukin IL-1α [67], an important mediator of cutaneous inflammation, but also prostaglandin E2 [68]. Of note, TRPV3 is expressed in nociceptive neurons. Thus, it is also likely that TRPV3 over-activation leads to local overproduction of inflammatory cytokines which could affect the somatosensory system, leading to a peripheral neuropathic pain.

**Diagnosis and diagnostic methods**

Olmsted syndrome diagnosis relies on the clinical presentation. Initially, the diagnostic hallmarks of OS are the association of bilateral transgredient mutilating palmoplantar keratoderma and periorificial keratotic plaques (mouth, nose, eyes, genital, anal, ears, navel) which allows exclusion of other hyperkeratotic related disorders. However, subsequent reports showed that this full-blown OS is not always observed, making the diagnosis challenging for patients with partial cutaneous expression of OS. Unfortunately, the histopathology of skin sections shows epidermal hyperplasia, ortho/hyperkeratosis, focal parakeratosis, hypergranulosis, acanthosis, and inflammatory infiltration in upper dermis, which are unspecific and of limited use to orientate the diagnosis. In the absence of specific biologic markers, molecular genetics is the most powerful approach to establish the diagnosis when the clinical presentation is unusual.

**Differential diagnosis**

The diagnosis of Olmsted syndrome is supported by clinical criteria that require the exclusion of other diseases. OS has to be differentiated from other severe forms of PPK, such as Vohwinkel syndrome (MIM#124500 and 604117, ORPHA494 and ORPHA79395), Mal de Meleda (MIM#248300, ORPHA87503), Clouston syndrome (MIM#129500, ORPHA189), Papillon-Lefèvre syndrome (MIM#245000, ORPHA678), pachyonychia congenita (MIM#167200 and 167210, ORPHA2309), Tyrosinemia type II (MIM#276600, ORPHA28378) and Haim-Munk syndrome (MIM#245010, ORPHA2342) (Table 2) [52]. The periorificial involvement is the unique characteristic of OS that allows exclusion of the above syndromes. However, because of periorificial involvement, OS is easily confused with acrodermatitis enteropathica (MIM#201100, ORPHA37) which however can be excluded by measurement of zinc levels. Indeed, low plasma level of zinc is diagnostic of acrodermatitis enteropathica which shows improvement after oral zinc therapy, unlike OS. Thus, the full-blown OS with its typical association of mutilating bilateral PPK and periorificial keratotic plaques is distinctive enough to lead to the correct diagnosis.

**Table 2 Differential diagnosis and underlying molecular basis**

| Disease              | Gene     | Mode of inheritance |
|----------------------|----------|---------------------|
| Vohwinkel syndrome   | GJB2, LOR| Autosomal dominant  |
| Mal de Meleda        | SLURP1   | Autosomal recessive |
| Papillon-Lefèvre syndrome | CTSC    | Autosomal recessive |
| Clouston syndrome    | GJB6     | Autosomal dominant  |
| Pachyonychia congenita| KRT6A, KRT6B, KRT16 and KRT17 | Autosomal dominant |
| Tyrosinemia type II  | TAT      | Autosomal recessive |
| Haim-Munk syndrome   | CTSC     | Autosomal recessive |
| Acrodermatitis enteropathica | SLC39A4 | Autosomal recessive |
However, the diagnosis becomes challenging for patients with partial and moderate cutaneous expression because of clinical overlap with other PPK mentioned above. In this case, OS diagnosis should be considered and molecular genetics and the mode of inheritance may help to discriminate these disorders (Table 2). The difficult clinical and histopathological distinction between different PPK makes genetic testing important in the diagnostic approach to these patients.

Genetic counselling and antenatal diagnosis
Most reported OS cases are sporadic, although familial cases were also reported. For familial cases, the mode of inheritance of OS has not been clearly established. Thus, different modes of inheritance have been suggested including dominant or recessive autosomal pattern but also dominant or recessive X-linked inheritance.

As with all severe genetic disorders, genetic counselling and psychological support are appropriate and requested for the families, to discuss the aetiology, the probability of occurrence in future pregnancies, the possibilities of early prenatal diagnosis and current treatment available.

Management including treatment
There is currently no specific nor satisfactory treatment for OS. Skin lesions are usually refractory to therapy. Different treatments have been tried with varying success to reduce hyperkeratosis. Topical treatments including emollients (white petrolatum), keratolytics (urea, salicylic acid), wet dressing, boric acid, tar, retinoid acid, shale oil, corticosteroids, steroids are attempted with poor to moderate improvement. In several OS patients, systemic retinoids (acitretin, etretinate), corticosteroid or methotrexate were used with poor to moderate relief [9,15,16,51]. Repeated partial excision of palmoplantar keratosis or full-thickness excision with skin grafting have been also performed for few patients but was usually followed by recurrence of the hyperkeratosis after initial improvement [42].

Until now, treatments either topical or systemic only offer temporary partial symptomatic relief of pain and fissures by reducing the thickness keratotic palmoplantar skin lesions. Specific treatments of pain and itching are essential to reduce the morbidity of the disease. Painkillers and topical lidocaine can be effective, but for patients with severe pain and especially when erythromelalgia and/or neuropathic pain are present, anti-inflammatory drugs, anticonvulsants (carbamazepine, gabapentin, pregabalin), tricyclic antidepressants (amitriptyline, nortriptyline) and lastly opioid analgesics (tramadol) are required to alleviate the pain of these patients. Prolonged soaking of the affected parts in cold water may reduce pain. However, these treatments are ineffective in arresting the course of the disease. The identification of TRPV3 gain-of-function mutations indicates that TRPV3 antagonists may be an effective therapeutic approach to treat the OS patients harbouring such mutations.

Prognosis
The natural history of the disease can lead to severe morbidities. Progressive keratoderma and auto-amputation of digits worsens the disability by preventing patients from grasping and walking, and can confine them to a wheelchair. Severe pruritus and pain increase the discomfort and can result in insomnia. Corneal dystrophy can cause blindness. In addition, OS patients may have a higher susceptibility to develop tumors in keratotic areas. No reduced life expectancy has been reported.

Unresolved questions
There have been recently many major advances in our understanding of the genetic basis of OS, with the identification of TRPV3 and MBTPS2 mutations, although other causal genes remain to be identified. Several questions remain unanswered with regards to the great variability of clinical expression of the disease, the lack of phenotype/genotype correlation and the exact physiological mechanism(s) underlying OS. The broad spectrum of OS clinical features raises the question whether atypical reported cases really belong to OS. Mutations within TRPV3 can cause both typical and atypical OS cases. Thus, OS may be a heterogeneous syndrome with variable clinical features.

Conclusion
For 87 years after its first description, around 73 OS cases have been reported, increasing the spectrum of clinical features associated with this condition and disclosing variable clinical expression. OS diagnosis may be challenging in the absence of the full-blown cutaneous phenotype associating bilateral mutilating PPK and periorificial keratotic plaques. The recent advances in the genetics of OS has lead to a better understanding of the aetiology of the disease and make possible the use of diagnostic genetic testing. Currently available drugs are nonspecific and poorly effective. The identification of the molecular basis of OS will permit the development of specific therapeutic strategies such as TRPV3 antagonists, and better patient management. However, other genes remain to be identified and next generation sequencing is likely to permit to further elucidate the genetics of OS and its clinical spectrum in patients with no TRPV3 or MBTPS2 mutation.

Abbreviations
OS: Olmsted syndrome; PPK: Palmoplantar keratoderma; TRPV3:Transient receptor potential vanilloid-3; MBTPS2: Membrane-bound transcription factor protease, site 2; IFAP: Ichthyosis follicularis atrichia photophobia.

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