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Angiokeratoma: decision-making aid for the diagnosis of Fabry disease

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Summary

Isolated angiokeratomas are common benign cutaneous lesions, generally deemed unworthy of further investigation. In contrast, diffuse angiokeratomas should alert the physician to a possible diagnosis of Fabry disease, a rare X-linked lysosomal storage disorder, characterized by α-galactosidase deficiency. Glycosphingolipids accumulate in cells throughout the body resulting in progressive multi-organ failure. Difficulties are encountered when trying to interpret the significance of angiokeratomas because they may also occur in other lysosomal storage disorders and rarely in an isolated manner in Fabry disease. We present an algorithm for the classification of angiokeratomas which might prove useful for the diagnosis and management of Fabry disease. Assessment of the clinical features and location of the lesions, personal and family history, skin biopsy, dermoscopy and electron microscopy imaging are sequential steps in the diagnostic process. Assessing the deficiency of α-galactosidase enzyme activity is essential to confirm the diagnosis in males, while mutation analysis is always needed in females. Potentially this algorithm can change the current approach to patients when Fabry disease is suspected, thus improving the diagnostic strategy and management of this disorder. It remains to be decided whether the use of an algorithm might reduce the number of genetic consultations. As evidence has shown the efficacy of enzyme replacement therapy in halting progression of the disease before the onset of irreversible organ damage, it is advisable to aim at an early diagnosis in order to achieve timely initiation of effective treatment with benefits for patients and appropriate use of medical resources.

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Although present in other metabolic and nonmetabolic conditions, angiokeratomas (AGK) are considered the cutaneous hallmark of Fabry disease (Anderson–Fabry disease; OMIM 301 500, FD). This rare metabolic X-linked disorder is caused by partial or complete deficiency of the activity of the lysosomal enzyme α-galactosidase A. The estimated prevalence varies from 1 : 1250 to 1 : 883 000 inhabitants.[1,2] To date, 630 mutations affecting the *GLA* gene, including a lot of missense changes, have been reported [Human Gene Mutation Database (HGMD)] (http://www.hgmd.cf.ac.uk/, accessed 29 December 2011). A majority of them are private mutations, occurring in individuals or in a small number of families.[3] Absent or reduced activity of the enzyme causes a progressive accumulation of glycosphingolipids with terminal α-galactosyl residues, especially globotriaosylceramide (Gb3), within lysosomes of different cell types with a preferential involvement of endothelial cells. The clinical manifestations appear to be influenced by the residual enzyme activity depending on the

type of mutation, but a clear genotype–phenotype correlation has not been demonstrated.[4] Early manifestations include gastrointestinal disturbances, pain in the hands and feet, altered sweating and fever. These manifestations are thought to be due to capillary obstruction, small nerve fibre damage and autonomic neuropathy.[5–7] Hearing disturbances like tinnitus are also frequent in childhood while hearing loss is mostly observed later in life.[8] Cornea verticillata, a strong indicator of FD, may be observed very early in childhood.[9] In adulthood, morbidity is associated with cardiovascular, renal and central nervous system involvement; specifically, left ventricular hypertrophy,[10] proteinuria gradually progressing to end stage renal failure,[11,12] and stroke.[13,14] Average life expectancy is reduced to 50–55 years in males and 70 years in females.[15] As a result of random X inactivation, females may present with variable degrees of disease severity. A significant proportion of women are as severely affected as males, and need to be treated accordingly.[16,17]

Since 2001 intravenous enzyme replacement therapy (ERT) has been used to target the clearance of Gb3. Both currently available preparations, α-galactosidase A (Replagal®; Shire Human Genetic Therapies, Geneva, Switzerland) and α-galactosidase B (Fabrazyme®; Genzyme Europe B.V., Naarden, the Netherlands), have demonstrated efficacy in halting and even reversing the progressive multi-organ deterioration, if started early in life.[18–20] New orally administered active-site-specific chaperones (ASSCs) for FD resulting from missense mutations that cause misfolded proteins, are currently under investigation.[21–23] The iminosugar 1-deoxygalactonojirimycin (DGJ) acts as the most effective ASSC to increase residual enzyme activity in a mouse Fabry model and in cultures of human Fabry fibroblasts and lymphoblasts.[24–27]

FD symptoms are frequently misdiagnosed – especially in children, but also in adults – as manifestations of rheumatological diseases. The delay from the onset of symptoms to diagnosis is over 10 years. With currently available therapies there is a 'window of opportunity' for successfully treating patients with FD if the diagnosis is made before significant organ damage has occurred.[28] Skin examination to detect multiple AGK holds a key role in the diagnosis of FD.

Clinical suspicion and sufficient knowledge of lesions resembling AGK and of other metabolic and nonmetabolic disorders presenting with AGK, are usually required to alert the clinician to FD. In order to speed up the diagnostic process and to minimize delays in starting treatment, we propose an algorithm with which to approach patients presenting with angiokeratomas.

Angiokeratoma in Fabry disease

Angiokeratomas are present in 66% of male and 36% of female patients with FD.[29] Appearing as nonblanching red to blue-black lesions from 1 to 5 mm in diameter, they are not always covered by fine white scales as their name would suggest, being also macular or just palpable. In classically affected males, the earliest lesions are observed during childhood on the hands, knees, elbows and flanks. Their number increases during adolescence with lesions on the genitals, involving the penis, scrotum and groins in men (Fig. 1a), and the lumbosacral area, gluteal cleft and trunk in both sexes (Fig. 1b). Later in life AGK can appear on the lips (Fig. 1c), umbilicus (Fig. 1d), periungual areas and palms and there may be macular angiomas (Fig. 2a,b). More lesions are usually observed in men. Females frequently have AGK on the upper back and chest and rarely on the genitalia. Telangiectasiae are the second commonest skin manifestation and occur most commonly on photodamaged areas such as the face and the V of the neck. Occasionally, in patients with widespread AGK, they are found on sunprotected sites such as the flanks and antecubital fossae. In some patients, mucosal lesions on the inner aspect of the lips or tongue can be observed (Fig. 2c,d). Other less well recognized dermatological manifestations include

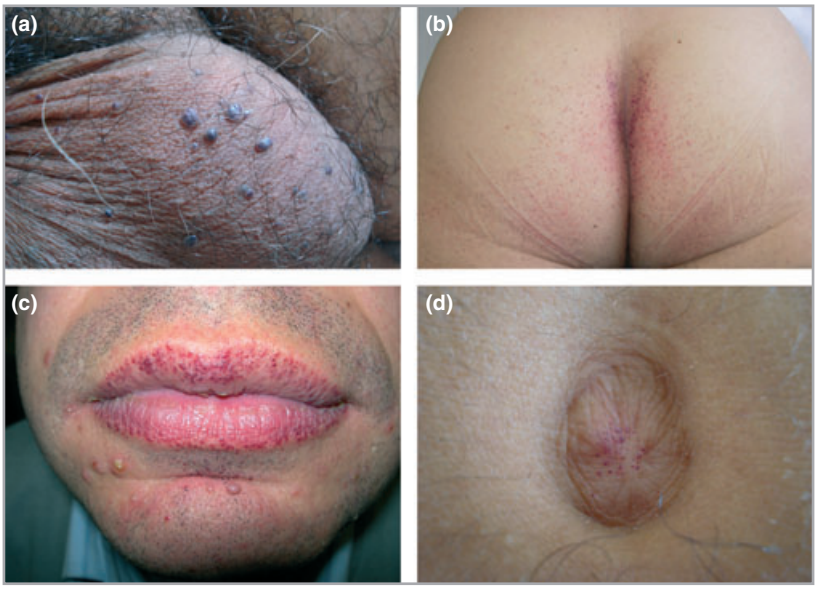

Fig 1. Skin angiokeratomas (AGK) of the scrotum (a) in a 43-year-old man with Fabry disease with a central nervous system involvement; AGK of the gluteal cleft in a 33-year-old female patient with Fabry disease (b). Further AGK on the lips (c) and AGK on the umbilicus in two other male patients (d).

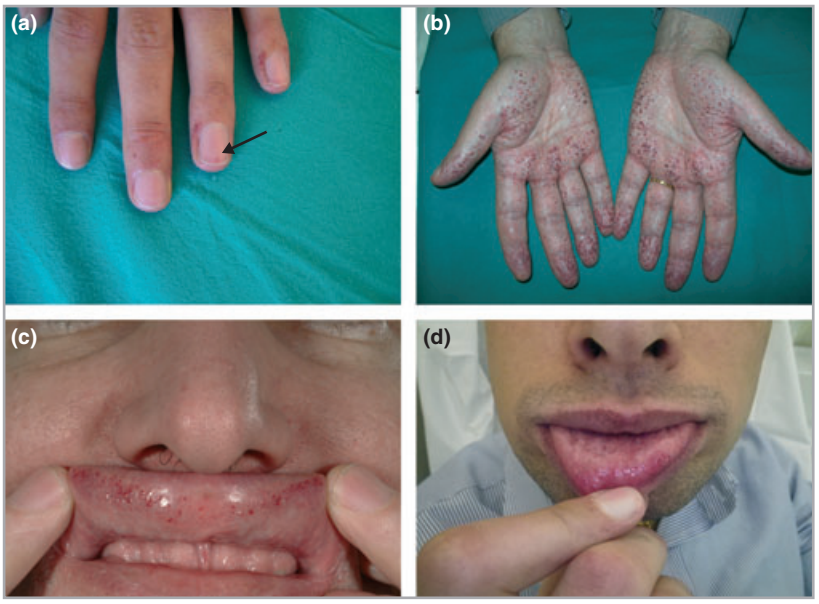

Fig 2. Details of angiokeratomas (AGK) of the periungual area (a) with a subungual AGK (arrow) in a 24-year-old patient with Fabry disease with no visceral involvement. AGK of the palms (b) in a 43-year-old male patient with a kidney transplant and Fabry disease. Involvement of the superior lip in a 52-year-old patient with Fabry disease with a history of stroke (c) and of AGK of the tongue (d).

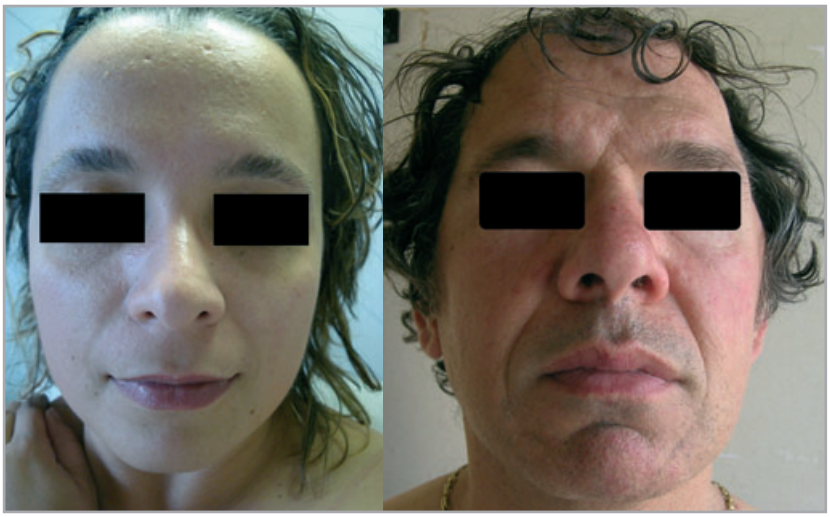

Fig 3. The so-called 'Fabry facies' is predominantly observed in male patients with Fabry disease but occasionally also in females. It is characterized by a recessed forehead, bushy eyebrows, prominent supraorbital ridges, widened nasal bridge, bulbous nasal tip, shallow midface, full lips, coarse features, posteriorly rotated ears and prognathism.

lymphoedema of the limbs[30] and sweating abnormalities, most frequently hypohidrosis, but occasionally palmoplantar or forehead hyperhidrosis.[31] The so-called 'Fabry facies' is reported predominantly in males (Fig. 3).[32]

Histology of skin angiokeratoma

The histology of AGK shows a vascular proliferation within the papillary dermis with an overlying acanthotic and orthokeratotic epidermis encircling thin-walled vascular channels occasionally filled with erythrocytes. Common cherry haemangiomas (CH) are usually more dome shaped with an associated oedematous or fibrotic stroma.[33] Histology can potentially differentiate AGK from CH but not from AGK of different pathogenesis because lipid inclusions are usually dissolved during the preparation of the sample.

Skin analysis of Fabry angiokeratomata by electron microscopy

Skin biopsies are usually fixed with 2·5% glutaraldehyde in phosphate-buffered saline (PBS) for 2 h at 25 °C. Samples are then post-fixed in 1% osmium tetroxide in veronal acetate buffer (pH 7·4) for 2 h at 25 °C and stained with uranyl acetate 2% (5 mg mL^{-1}), dehydrated in acetone then embedded in Epon 812. Thin sections can be examined post-stained with uranyl acetate and lead hydroxide. Electron microscopy (EM) shows lamellated intracytoplasmic vacuolar inclusions called 'zebra bodies' (Fig. 4). As previously reported, ultrastructural analysis of skin biopsies obtained from patients with Fabry disease after ERT, shows the disappearance of the intracytoplasmic Gb3 inclusions (Fig. 5a–h).[34]

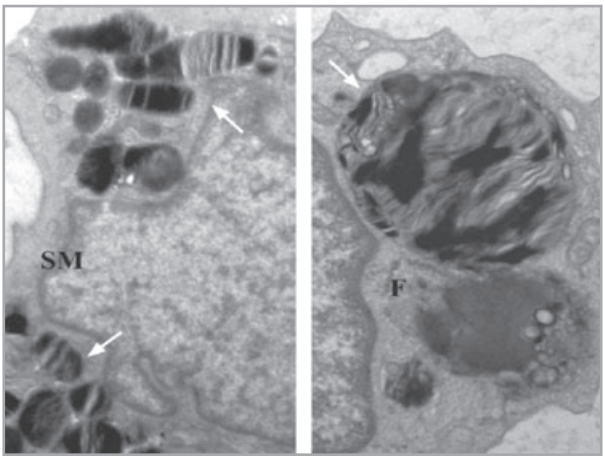

Fig 4. Electron microscopy of a skin biopsy from a patient with Fabry disease showing the typical 'zebra bodies'. These are lysosomes filled with abnormal lipid deposits that have alternating dark and light bands with a periodicity of 4–6 nm. Zebra bodies classically occur in several types of cells (endothelial cells, pericytes, macrophages, fibroblasts, sweat gland cells, smooth muscle cells, glomerular epithelial cells, neuronal cells) not only in FD but also in other metabolic disorders such as in Niemann–Pick disease and mucopolysaccharidoses.

Dermoscopy analysis

Dermoscopy usually shows sharply demarcated grouped vascular lacunae with a red to bluish-black colour sometimes with overlying yellowish keratotic areas. Dermoscopy can help physicians detect multiple AGK, not always visible to the naked eye, around an apparently single prominent lesion (Fig. 6a,b).

Angiokeratoma in other rare lysosomal storage disorders

Fucosidosis (OMIM 230000) is an autosomal recessive lysosomal storage disorder (LSD) due to a mutation on the *FUCA1* gene on chromosome 1p34, leading to α-L fucosidase deficiency and accumulation of fucose-containing glycolipids and glycoproteins in various tissues. Fewer than 100 patients have been described to date, the majority of cases being from southern Italy and the southwestern part of the U.S.A. Consanguinity was reported in 40% of the 45 identified families.[35] Type I fucosidosis evolves rapidly to progressive neurological deterioration and death before the second year of life. Type II fucosidosis progresses more slowly to neuromotor deterioration with seizures. Patients usually have coarse facial features, dysostosis multiplex, visceromegaly, recurrent respiratory infections, impaired growth and mild psychomotor retardation and diffuse AGK. The only available treatment to date is unrelated donor bone marrow transplantation.[36]

Sialidosis (*Mucolipidosis Type I*, OMIM 256550) is a total or partial deficiency of the lysosomal enzyme N-acetyl-α-neuraminidase (NEU1, sialidase), caused by genetic lesions in the sialidase *NEU1* gene on chromosome 6p21.3, which leads to this autosomal recessive disorder. Patients show abnormal accumulation of mucopolysaccharides in several tissues and organs including bone marrow. They also develop cherry-red retinal spots, myoclonus, learning difficulties, hepatosplenomegaly, and impaired kidney and bone marrow function.[37] The juvenile form, presenting between the ages of 2 and 20 years, is associated with diffuse AGK. No specific treatment is currently available.[38]

GM1 Gangliosidosis (*β-galactosidase deficiency*, OMIM 230500) is caused by deficiency of lysosomal enzyme β-galactosidase, due to mutations in the *GLB1* gene on chromosome 3p22.3. This results in the accumulation in cells of GM1 ganglioside, mucopolysaccharide keratan sulphate and their derivatives, with their excretion in urine. Clinical findings are macular dysplasia and coarse facial features in the infantile and juvenile form. The adult form is less severe with an extreme clinical variability starting from only focal neurological signs, such as dystonia, to a more severe involvement with extrapyramidal signs and learning difficulties. Diffuse AGK have been associated with the juvenile and adult forms.[39]

Galactosialidosis (OMIM 600419); mutations in the *CTSA* gene on chromosome 20q13.12 cause this autosomal recessive disorder characterized by the combined deficiency of lysosomal β-galactosidase and neuraminidase and resulting in a primary defect in the protective protein/cathepsin A (PPCA). It manifests with gargoylism, macular cherry-red spots, vertebral deformities, epilepsy, myoclonus and ataxia, and diffuse AGK.[40]

β-mannosidose (OMIM 248510); this rare autosomal recessive LSD is caused by deficient activity of β-mannosidase, an enzyme encoded by the *MANBA* gene on chromosome 4q22–q25. To date, only 20 cases have been described. The clinical manifestations are heterogeneous, from mild to moderately severe with diffuse AGK, skeletal abnormalities, facial dysmorphism and neurological findings such as learning difficulties, hearing loss and speech impairment, hypotonia, epilepsy and peripheral neuropathy.[41]

Schindler disease type II (*Kanzaki disease* OMIM 609242); total or partial deficiency of the lysosomal enzyme α-N-acetyl-α-D-galactosaminidase (NAGA), also known as α-galactosidase B, is caused by genetic lesions in the *NAGA* gene located on 22q13-qter. The prevalence remains unknown because only 12 cases have been reported. Two forms have been described of this autosomal recessive disorder: the infantile (Schindler type I) and the adult, Kanzaki disease (KD) (Schindler type II). The first shows severe to moderate neurological involvement; the second is a mild late-onset form. Both share the abnormal urinary excretion of specific oligosaccharides. Only KD is associated with diffuse AGK, gradual coarsening of facial features with or without mild intellectual impairment with signs and symptoms often absent under the age of 30 years.[42,43]

Aspartylglucosaminuria (OMIM 208400) is an autosomal recessive LSD due to a mutation in the *AGA* gene located on chromosome 4q34.3. It is very rare outside Finland, where 1

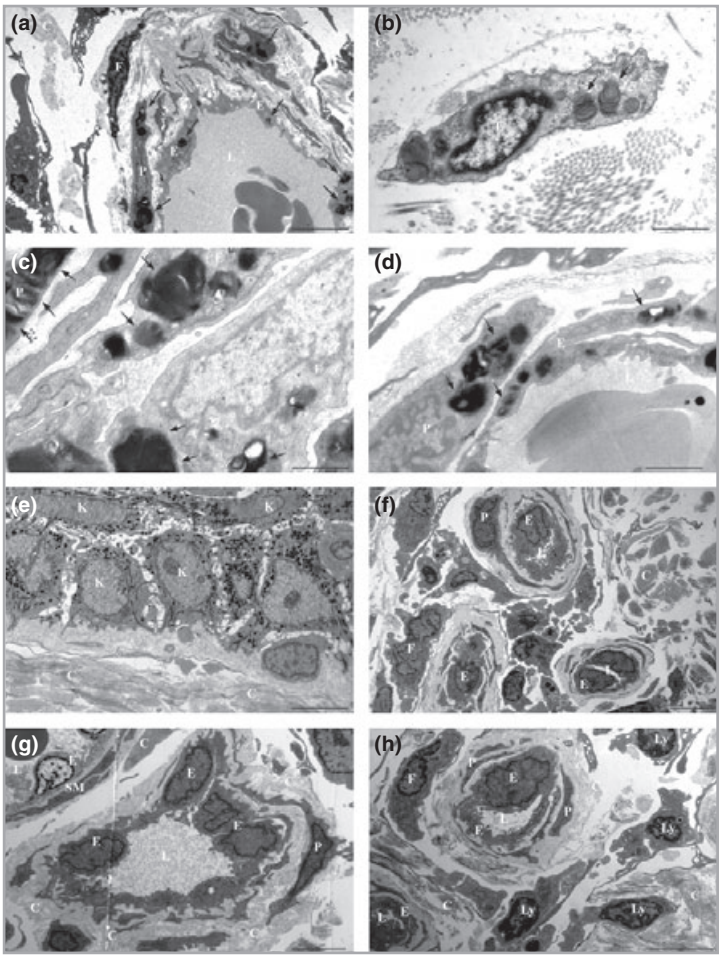

Fig 5. Ultrastructural imaging analysis of skin biopsies pre- (a–d) and post-enzyme replacement therapy (ERT) (e–h) collected from three patients with angiokeratomas respectively before and after 1, 2 and 6 years of ERT. (a) Cytoplasmic inclusion bodies are evident in different dermal cell types (arrows). At higher magnification fibroblasts (b), endothelial cells and pericytes (c, d) reveal the presence of 'zebra bodies' (arrows). After ERT (e–h) skin biopsies show a complete disappearance of lysosomal inclusions from fibroblasts, pericytes, superficial capillaries and smooth muscle cells, K, keratinocytes; F, fibroblasts; P, pericytes; E, endothelial cells; L, lumen; Ly, lymphocytes; SM, smooth muscle cells; C, collagen. Scale bars: (a) 5 μm; (b) 1 μm; (c) 0.5 μm; (d) 1 μm; (e–h) 5 μm.

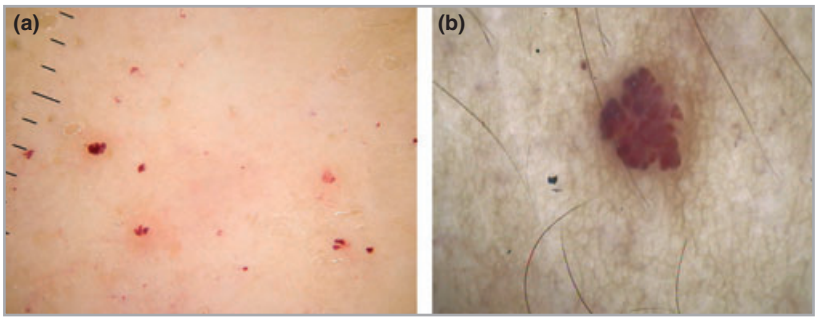

Fig 6. Dermoscopy of a group of angiokeratomas on the arm of a young female Fabry patient (a, 20 ×); the lesions were barely visible to the naked eye. The observation of a single lesion at a higher magnification (b, 50 ×) allows the detection of a vascular multilobular structure with the absence of the keratotic aspect.

in 17 000 people are affected. Aspartylglucosaminuria is characterized by the deficiency of the lysosomal enzyme glucosylasparaginase or aspartylglucosaminidase (AGA). This enzyme acts in the catabolism of N-linked oligosaccharides of glycoproteins and hydrolysis of the protein oligosaccharide linkage in Asn-linked glycoprotein substrates; the deficiency of AGA leads to the accumulation of abnormal breakdown products such as glycosyl asparagine units in the tissue lysosomes and body fluids. Patients present slowly progressive mental retardation, coarse facial features, kyphoscoliosis and diffuse AGK. Currently, the only available treatment is bone marrow allograft.[44]

Idiopathic angiokeratoma corporis diffusum (Fabry sine Fabry?); there are few reports of angiokeratoma corporis diffusum in the literature allegedly not associated with any underlying enzyme deficiency.[45–47]

Solitary and localized angiokeratoma; solitary AGK is a relatively common lesion occurring in both sexes, typically between the ages of 10 and 40 years. Its prevalence in the general popula-

tion is estimated to be around 0·16%. Solitary AGK typically measure between 2 and 10 mm, may occur at any site and frequently bleed or become thrombosed.[48]

Localized genital AGK, first described in 1860 by John Addison Fordyce, is reported in 15% of males over the age of 50 years and has been associated with varicocele or herniae, epididymal tumours, urinary tract tumours, trauma or thrombophlebitis.[49,50] Similar lesions are found in older women, where predisposing factors such as pregnancy, vulval varicosity and hysterectomy were found in 54% of the patients. Rare factors include vascular malformations or results of radiotherapy for genitourinary malignancy.[51]

Angiokeratoma of Mibelli usually presents as grouped asymptomatic blue-black papules on the dorsum of hands and feet in females, manifesting typically between 10 and 15 years of age. There may be a familial predisposition and an association with chilblains, acrocyanosis or trauma.[52]

Angiokeratoma circumscriptum naeviformis is rare, presenting as a unilateral localized plaque on a lower extremity or on the trunk in a band-like or segmental arrangement. In many cases, the lesions are present at birth, but may appear in childhood or adulthood, mainly in females, as asymptomatic small papules and plaques with irregular borders and associated pigmentation. It has been reported to coexist with AGK of Fordyce, AGK of the tongue, Cobb syndrome, Klippel–Trénaunay syndrome, naevus flammeus, cavernous haemangioma, haemangiectatic hypertrophy, traumatic arteriovenous fistulae.[53] It is not known whether this may represent mosaicism of the Fabry gene.

Angiokeratoma-like lesions

Cherry haemangiomas (CH); they are the most common vascular lesions in the general population, appearing often spontaneously in middle age, without any known underlying cause. They present as dome-shaped red-purple papules containing an abnormal proliferation of capillaries. Chemical compounds and drugs such as mustards, butoxyethanol, bromides, chloroquine and ciclosporin seem to induce them occasionally.[54] Enhanced activity of the enzyme carbonic anhydrase and an increased number of mast cells in comparison with normal skin have been reported.[55]

Connective tissue diseases Telangiectasia are observed on sun-exposed areas in connective tissue diseases such as systemic sclerosis, dermatomyositis and overlap syndromes. To date, one case presenting an association of Fabry and systemic lupus erythematosus has been reported.[56]

Hereditary haemorrhagic telangiectasia type I (HHT) (OMIM 187300), also known as Osler–Weber–Rendu syndrome, HHT type. HHT is an autosomal dominant vascular disorder charac-

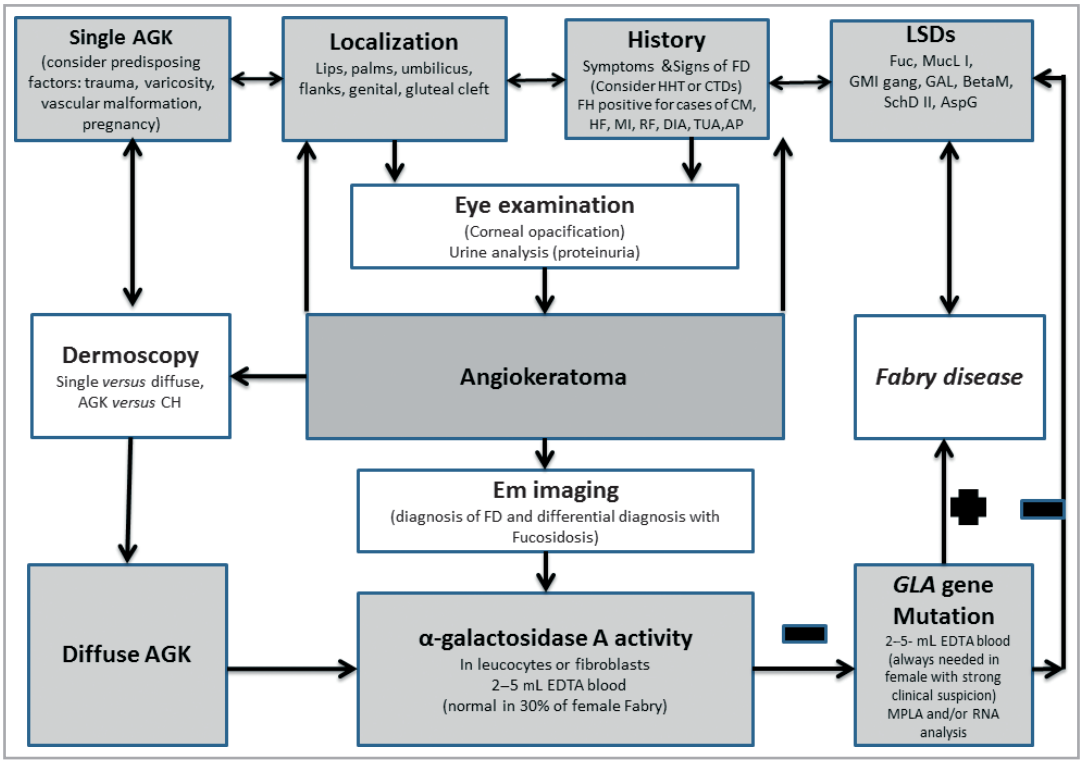

Fig 7. The algorithm proposed to manage patients with angiokeratomas as potential Fabry patients. AGK, angiokeratoma; FD, Fabry disease; CH, cherry haemangioma; EM, electron microscopy; HHT, hereditary haemorrhagic telangiectasia; CTDs, connective tissue diseases; FH, family history; CM, cardiomyopathy; HF, heart failure; MI, myocardial infarction; RF, renal failure; DIA, dialysis; TIA, transient ischaemic attack; AP, apoplexy; Fuc, fucosidosis; MucL I, mucolipidosis I (sialidosis); GM I gang, GM I gangliosidosis; GAL, galactosialidosis; BetaM, β-mannosidosis; SchD II, Schindler disease type II (Kanzaki disease); AspG, aspartylglucosaminuria; MLPA, multiplex ligation-dependent probe amplification.

terized by mutations in the *ENG* gene located on chromosome 9q33–q34.1, that encodes endoglin (ENG or CD105), a membrane glycoprotein primarily associated with human vascular endothelium. Mutations in *ACVRL1* gene, located on 12q11–q14 encoding activin receptor-like kinase, lead to HHT type 2 (OMIM 600376).[57] Both proteins modulate transforming growth factor-β superfamily signalling in vascular endothelial cells.[58] Recurrent epistaxis, presence of multi-organ arteriovenous malformations and associated haemorrhages are the main clinical manifestations. The typical skin vascular lesions are also highly suggestive, namely cutaneous and mucosal red papules and spider naevi, the latter usually visible in the same areas as AGK in Fabry disease. Therefore, HHT should always be considered as an important differential diagnosis of FD.[59]

Angiokeratoma: the algorithm

Assessment of the skin to ascertain whether AGK are present, and if so, to assess their number and distribution, are the first steps in the diagnostic algorithm (Fig. 7). Dermoscopy and skin histology support the diagnosis of AGK. Dermoscopy may also be a useful tool to detect multiple lesions when these are not visible to the naked eye. In the presence of isolated or localized AGK, a detailed evaluation of the history of the lesion and of predisposing conditions should be performed. Symptoms, signs and family history suggestive of FD will help to determine the need for further investigations (Table 1). Sudden and/or premature deaths from cardiac or renal disease in parents or other relatives should always be considered highly suspicious and investigated – irrespective of the number and site of AGK. In both sexes, a negative family history does not exclude the diagnosis: *de novo* mutations have been reported.[60]

Electron microscopy (EM) imaging may help to distinguish between the AGK of FD from other LSDs, in particular fucosidosis, where lysosomes appear empty. Nonetheless, typical zebra bodies are not always present in the skin in females with Fabry disease and negative EM does not exclude the diagnosis in this group. Low-cost procedures such as urine analysis searching for proteinuria and eye examination to exclude cornea verticillata should be performed.

Deficient α-galactosidase-A activity in plasma and leukocytes or fibroblasts is commonly used to diagnose males. Mutational analysis is required to define the type of mutation better and it is always mandatory in females in whom about 30% of patients can have normal levels of the enzyme.[61,62] In females, when the standard sequence analysis fails to reveal a mutation but the clinical suspicion remains strong, the presence of deep intronic mutations or large deletions should be excluded by multiplex ligation-dependent probe amplification (MLPA) and/or RNA analysis. In the presence of widespread angiokeratomas, the next diagnostic steps should be measurement of α-galactosidase and mutation analysis. If the diagnosis of FD is ruled out, symptoms and signs of other, rarer metabolic causes of AGK should be looked for.

Table 1 List of the main symptoms and signs recorded in Fabry disease. The list can be useful when considering patients potentially affected by this disorder

Organs and systems	Symptoms and signs
Central NS	Fever, headache
	Previous signs or events of TIA and/or stroke, especially in young individuals
	MRI (pulvinar sign and/or megadolicobasilar anomaly)
Peripheral NS	Pain (especially acral pain, hands and feet)
	Hypohidrosis
	Hyperhidrosis (less frequently)
	No symptoms referred
Eye	Corneal opacification (cornea verticillata) on slit-lamp examination
	Tortuous retinal vessels
Ear	Hearing impairment (sensorineural hearing loss)
	Tinnitus, vertigo
Heart	Arrythmia, hypertension, ECG alterations
	Echocardiographic features (concentric LVH)
	Myocardial infarction, heart failure
LVS	Severe lymphoedema of legs
GIS	Diarrhoea/constipation, nausea, vomiting
	Bloating, abdominal pain
Kidney	No symptoms usually referred
	Microalbuminuria, proteinuria, renal failure

NC, nervous system; TIA, transient ischemic attack; MRI, magnetic resonance imaging; LVH, left ventricular hypertrophy; LVS, lympho-vascular system; GIS, gastrointestinal system.

Discussion

The differential diagnosis of the underlying disease in AGK includes, besides FD, several other conditions. Because isolated lesions can be present in healthy subjects and diffuse lesions in other metabolic disorders, the detection of AGK does not necessarily imply the diagnosis of Fabry disease. Furthermore, diffuse AGK have been described without any association with metabolic diseases (although it cannot be ruled out whether on these occasions one had failed to detect mutations of Fabry or other LSD). Even if the main problem is to differentiate AGK from other similar vascular lesions, the proposed algorithm can lead physicians towards FD starting from the skin examination. The most useful procedures such as EM imaging and dermoscopy are not available in all dermatological centres. In these cases, one should assess the level of suspicion of a metabolic disorder on the basis of the clinical features and the personal and family history. Common low-cost procedures such as such urine analysis and eye examination searching for proteinuria and cornea verticillata, respectively, can then be performed. The algorithm can potentially change the current approach to a patient with suspected Fabry disease by speeding up the diagnostic process. Nevertheless, some patients may be reluctant to be tested for a genetic disease, because of the potential impact on quality of life deriving from a positive

result, with all subsequent implications for other family members.[63] It remains to be ascertained whether the use of an algorithm may reduce the number of genetic consultations – this raises the issue of the risk of alarming patients when this could be avoided.[64,65]

In classical FD, AGK usually appear during late infancy and adolescence. These young patients, concerned about their genital AGK, may seek their doctors' advice after an internet Google search and a self-diagnosis – which may be correct or not – of FD. As, to date, FD is commonly misdiagnosed by physicians, this algorithm can help clinicians to handle these patient's requests promptly and correctly, starting from the skin examination with the appropriate use of available medical resources.[66,67] Several studies have shown that effective treatments are currently available for Fabry disease and that the greatest benefits occur when these treatments are started at an early stage.[68,69] Although it should be underlined that a third of males with FD and up to two-thirds of females do not have AGK,[28] the use of the algorithm for AGK may help physicians to formulate an early diagnosis of Fabry disease, allowing the best management of these patients and a timely onset of an effective treatment.[70,71]

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