Corneal Lattice Dystrophy, a Concealed Ophthalmic Problem in Thailand†

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Abstract

One single family of corneal lattice dystrophy was examined and interviewed to elucidate the variety of clinical manifestations, factors associated with visual impairment, and the impact on the patient's quality of life.

Forty-three out of 88 family members (48.9%) were affected. The inheritance pattern was autosomal dominant. Corneal haze grading from 1 to 4 was 5.3 per cent, 26.3 per cent, 43.4 per cent, and 25 per cent respectively. Surface irregularity grading from 1 to 4 was 18.4 per cent, 39.5 per cent, 32.9 per cent, and 9.2 per cent respectively. Forty-five per cent of the patients had VA $\leq$ 20/200. Corneal haziness, irregularity, corneal erosion and disease duration were significantly related to visual impairment ($p < 0.05$). This disturbed the patient's activities such as reading (79.1%), working (62.8%) and daily life (69.8%).

Corneal lattice dystrophy within the same family may present with different manifestations depending on the severity and duration of the disease and might be misdiagnosed. Inadequate knowledge among patients was susceptible to the high prevalence of the disease leading to impaired quality of life.

Key word : Corneal Lattice Dystrophy, Corneal Dystrophy, Genetics Inheritance, Quality of Life, Public Health Ophthalmology

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Lattice dystrophy is the most common corneal stromal dystrophy that is inherited either in an autosomal dominant or autosomal recessive. Abnormal deposition of amyloid in the corneal subepithelium and stroma causes refractile lines which subsequently lead to recurrent corneal erosion, stromal haze, corneal scarring and impaired vision(1). As poor vision becomes a burden to daily activity, phototherapeutic keratectomy and keratoplasty are required. However, recurrence usually occurs(2-4) and the visual prognosis is eventually guarded.

Each type of corneal dystrophy was formerly believed to be clearly distinct clinicopathologically. However, several studies revealed that some corneal dystrophies such as granular, lattice and Thiel-Behnke dystrophy are closely related(5). Another example is Avellino dystrophy which contains both granular and lattice dystrophy. It is known that these types of dystrophy result from a mutation of the same gene(6-8).

To the best of our knowledge, there are no reports of the clinical variations of lattice dystrophy among the same family members and the impact of this disease on their lives. The purposes of this study were; to study the clinical variations of lattice dystrophy in a large affected family; to show the correlation between several factors and impaired vision; to evaluate the patients' attitude and knowledge, and to elucidate the importance of lattice dystrophy in public health terms in Thailand.

MATERIAL AND METHOD

Patients

The study was performed at Siriraj Hospital, Bangkok and in the Kamtalay Sor district, Nakhon Ratchasima province, a rural area in the north-east of Thailand (patients' village) from June 1999 to March 2002. One large family with several affected members was selected as the study model. Eighty-eight family members underwent eye examination with slit-lamp

Table 1. Grading of corneal stromal haze and corneal surface irregularity.

Corneal stromal haze	
Grading	Haziness
1	Stroma clear, fine lattice line
2	Subepithelial and mid stromal opacity localized at the center of cornea
3	Diffuse stromal opacity, cannot refract
4	Dense total corneal scar, cannot identify a lattice line
Corneal irregularity	
Grading	Irregularity
1	Smooth surface
2	Slightly irregular surface due to the lattice line
3	More irregularity, easy to detect by slit lamp
4	Markedly elevated line, no area of smooth surface

Table 2. Demographic and visual acuity of the patients.

Total cases/eyes	43/86
Sex (M/F) (cases)	17/26
Mean age (min-max) (years)	41.2 ± 14.8 (23-72)
Mean age onset (min-max) (years)	28.6 ± 8.1 (20-50)
Mean duration of disease (min-max) (years)	12.6 ± 11 (1-52)
History of erosion (cases)	83.7% (36/43)
Visual acuity	
20/20-20/40	5
20/50-20/100	17
20/125-20/160	12
20/200-Fc 3'	24
< Fc 3'	25

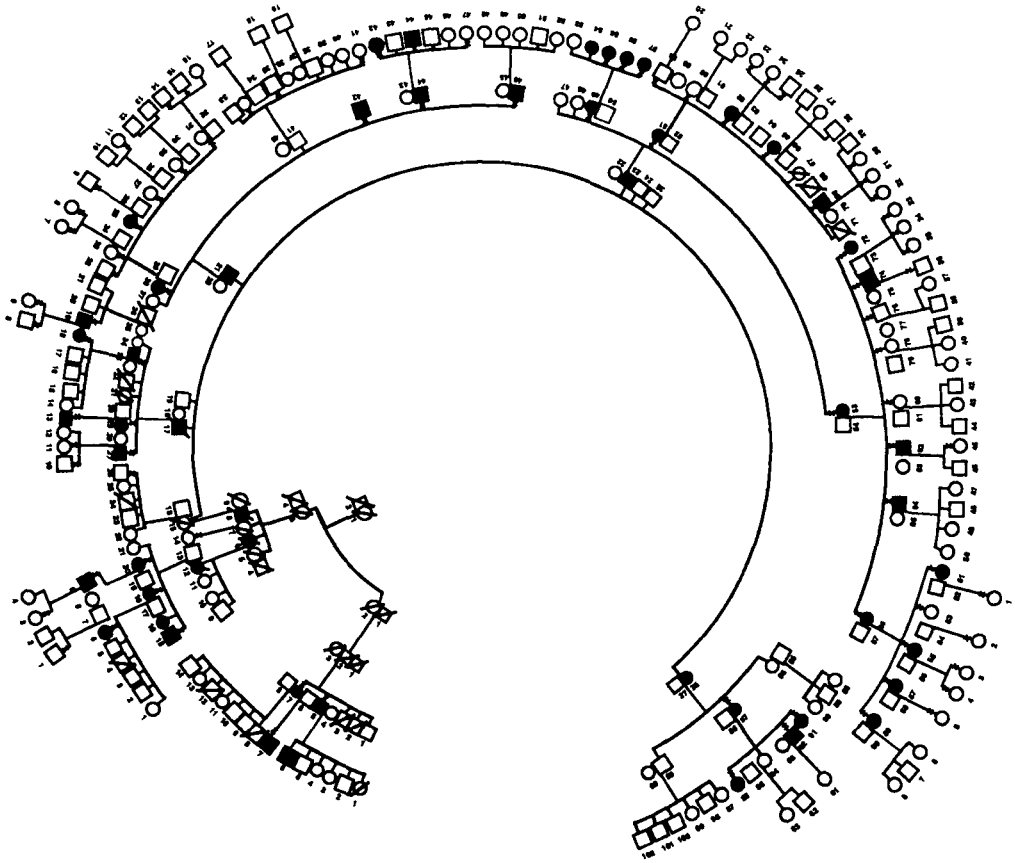

Fig. 1. Pedigree demonstrating 8 generations including 216 individuals from this family. Forty three patients had corneal lattice dystrophy confirmed by slit lamp examination. Solid circles and squares indicate affected patients; open circles and squares indicate unaffected patients. A slash (/) through a symbol indicates a patient who is dead. A times sign (x) above the symbols indicates a patient who was examined clinically by PP.

biomicroscopy. Patients with corneal dystrophy were identified.

Method

Affected patients underwent an interview, completed a questionnaire and had an eye examination. The information obtained consisted of a detailed history of eye disease, quality of life, treatment expense and the patient's knowledge of the disease. Quality of life was assessed and scored using the questionnaire and a visual analog scaling method. Family history, pedigree and family tree were studied and drawn. Eye examination including corrected visual acuity, slit-lamp biomicroscopy, retinoscopy and indirect ophthalmoscopy was performed. Eyes with any abnormality other than corneal lattice, which interfered with vision, were excluded from the study. Corneal surface irregularity and stromal haze were graded by a single investigator (PP) according to the criteria shown in Table 1. Corneal buttons from patients who underwent penetrating keratoplasty (12 eyes) were submitted for routine histopathologic study.

Statistical analysis

The data were analyzed based on SPSS version 9.0 with the assistance of the statistics unit

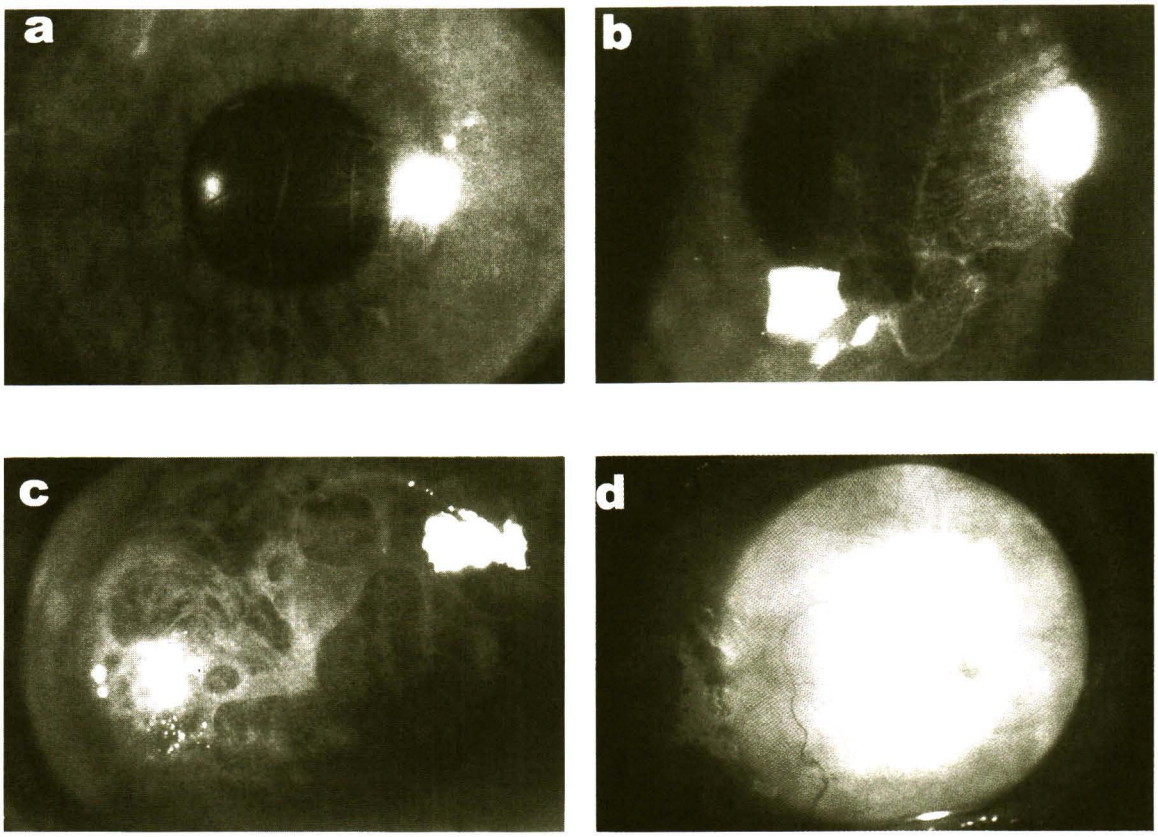

Fig. 2. Demonstrates the clinical manifestations of each grade of corneal stromal haze. 2a) Grade 1 : Stroma clear, fine lattice line. 2b) Grade 2 : Subepithelial and mid stromal opacity localized at the center of the cornea. 2c) Grade 3 : Diffuse stromal opacity, cannot refract. 2d) Grade 4 : Dense total corneal scar, cannot identify a lattice line.

of the Department of Ophthalmology, Siriraj Hospital. Correlation between visual acuity, duration and severity of the disease were analyzed by Pearson Chi-Square and Spearman method. The correlation between quality of life and visual acuity were analyzed by the Spearman method.

RESULTS

There were 216 members (8 generations) in the family. Eighty-eight joined the study, 102 could not be contacted and 26 had died before the beginning of the study. Forty-three out of 88 members (48.9%) had corneal lattice dystrophy. Seventeen were males and 26 were females. All cases were affected bilaterally. Three eyes with no light perception as a result of previous trauma were excluded from the study, leaving a total of 83 eyes to be analyzed.

The pedigree is as shown in Fig. 1. The pattern of inheritance is clearly autosomal dominant. The mean age of the patients was 41.2 ± 14.8 (range 23-72) and the age of onset of symptoms was 28.6 ± 8.1 years old (range 20 to 50). The average age at which vision become significantly impaired was 37.6 ± 13.3 (range from 24 to 70) years old. Thirty-six of 43 patients (83.7%) had a history of recurrent corneal erosion during the course of the disease (Table 2). The mean duration of the disease was 12.6 ± 11 years (range from 1-52).

No patients showed signs of systemic involvement. Corneal manifestations in each patient

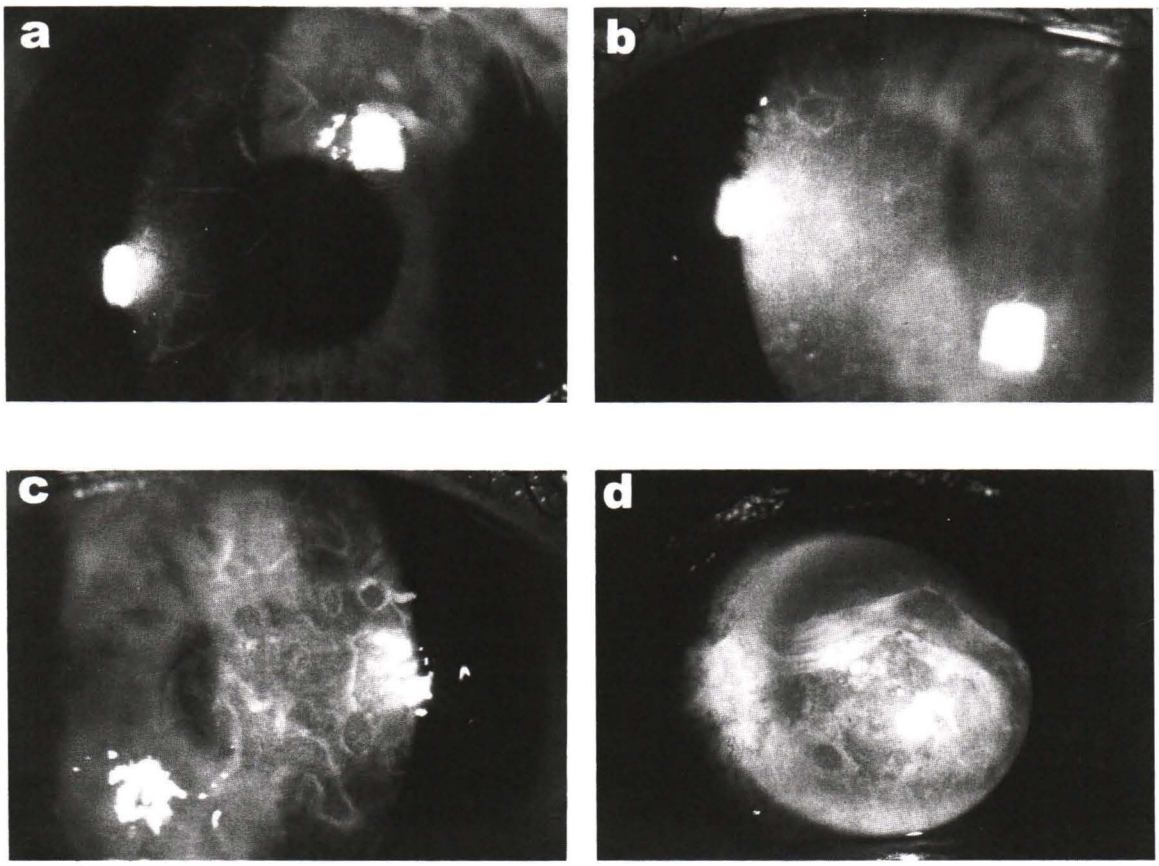

Fig. 3. Demonstrates the clinical manifestations of each grade of corneal surface irregularity. 3a) Grade 1 : Smooth surface. 3b) Grade 2 : Slightly irregular surface due to the lattice line. 3c) Grade 3 : More irregularity, easily to detect by slit lamp. 3d) Grade 4 : Markedly elevated line, no area of smooth surface.

varied from mild to severe. Mild cases usually showed the characteristic findings of typical lattice type I, which includes intrastromal refractile lines from the central cornea to the periphery sparing the limbus. The corneal surface was usually smooth and the stroma clear with a normal retinoscopic reflex (Fig. 2a, 3a). In severe cases, the refractile lines were usually obscured by diffuse stromal opacity, making it difficult to distinguish lattice from corneal leukoma of other causes (Fig. 2d). The corneal surface eventually becomes irregular due to elevated thick lattice lines (Fig. 3d) causing pain and discomfort.

Of the 83 eyes in this study, 7 eyes underwent penetrating keratoplasty before entering the study, leaving 76 eyes to be evaluated and graded according to the criteria in Table 1. The results of the grading are shown in Fig. 4. More than half of the patients (53.5%, 23 of 43 patients) had a visual acuity equal to or less than 20/200 (Table 2).

Factors significantly related to decreased visual acuity were corneal haziness ($p = 0.001$, Pearson Chi-Square), surface irregularity ($p = 0.011$), duration of the disease ($p = 0.001$) and a history of recurrent corneal erosion ($p = 0.011$). The duration of the disease was also significantly correlated with severity (surface irregularity and corneal haze, $p = 0.018$ and 0.003 respectively, Spearman). Quality of life as evaluated by questionnaires was significantly affected by the degree of visual impairment ($p = 0.001$, Spearman). The mean quality of life score was 5.02 ± 2.4 (range

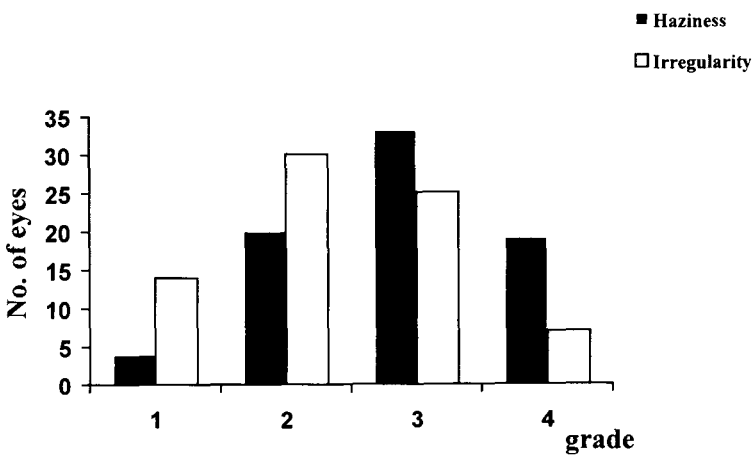

Fig. 4. Graph demonstrating the number of eyes in each grade of corneal stromal haze and corneal surface irregularity. Solid bars indicate the number of eyes with corneal haziness and strip bars indicate the number of eyes with surface irregularity.

from 0-8). The disease disturbed the patients' quality of life by interfering with their daily activity (eating, cooking, bathing, dressing, crossing the road, recognizing faces) in 69.8 per cent, making them unable to read (a newspaper, small labels) in 79.1 per cent and prevented them from working (agriculture, driver, laborer) in 62.8 per cent.

Fig. 5 (b-d) illustrates the pathological sections of a corneal specimen obtained from one patient during keratoplasty. Amyloid is clearly demonstrated by hematoxylin and eosin staining (H&E) as pale axórphous material throughout the entire stroma (Fig. 5b). The section stained positive with Congo red and shows a characteristic apple green birefringence appearance under polarized light as seen in Fig. 5c and 5d respectively. Periodic acid-Schiff (PAS) and Masson trichrome staining give a negative result. Descemet's membrane is unremarkable and endothelial cells are attenuated.

At the end of the study, 38 eyes underwent phototherapeutic keratectomy (PTK), 12 received penetrating keratoplasty (PKP) and 26 remain on the waiting list for a donor cornea. Two eyes required a second PTK and PKP due to recurrence. The average expense for non-surgical cases, including the medications and transportation to the hospital was 1,160 ± 591.9 baht/year. For patients who underwent PTK and PKP, the average expenses were 18,367 ± 7,262.9 baht/year and 32,786 ± 10,445.3 baht/year respectively. The average income of the patients was 35,571 ± 27,390.9 baht/year (range 12,000-84,000 baht). Compared with the patients' income, the expense of treatment ranged from 4.2 to 337.25 per cent of their income.

At the beginning of the study, 81.4 per cent of the patients (35 out of 43) were unaware of this disease, 58.1 per cent (25 of 43) did not understand the genetic inheritance of the disease, 76.7 per cent (33 of 43) did not recognize the importance of birth control in preventing this disease and 48.8 per cent (21 of 43) had no knowledge regarding the prognosis of the disease.

DISCUSSION

Corneal lattice dystrophy was first described by Biber in 1890[9], and Haab[10] and Dimmer in 1899[11]. It was later classified as lattice dystrophy type I. The inheritance pattern is as an autosomal dominant trait. The corneal change usually manifests during the first decade of life, with recurrent episodes of corneal erosion. It is recognized clinically by characteristic refractile lines in the stroma that result from accumulation of amyloid substance. In 1972, Meretoja [12] reported a case of corneal lattice dystrophy with systemic manifestations which was later classified as lattice dystrophy type II by Klintworth[13]. Lattice dystrophy type III was reported in 1987 by Hida[14] who described thick lattice lines which extended from limbus to limbus. This type III corneal lattice dystrophy usually occurs between the age of 60 to 80.

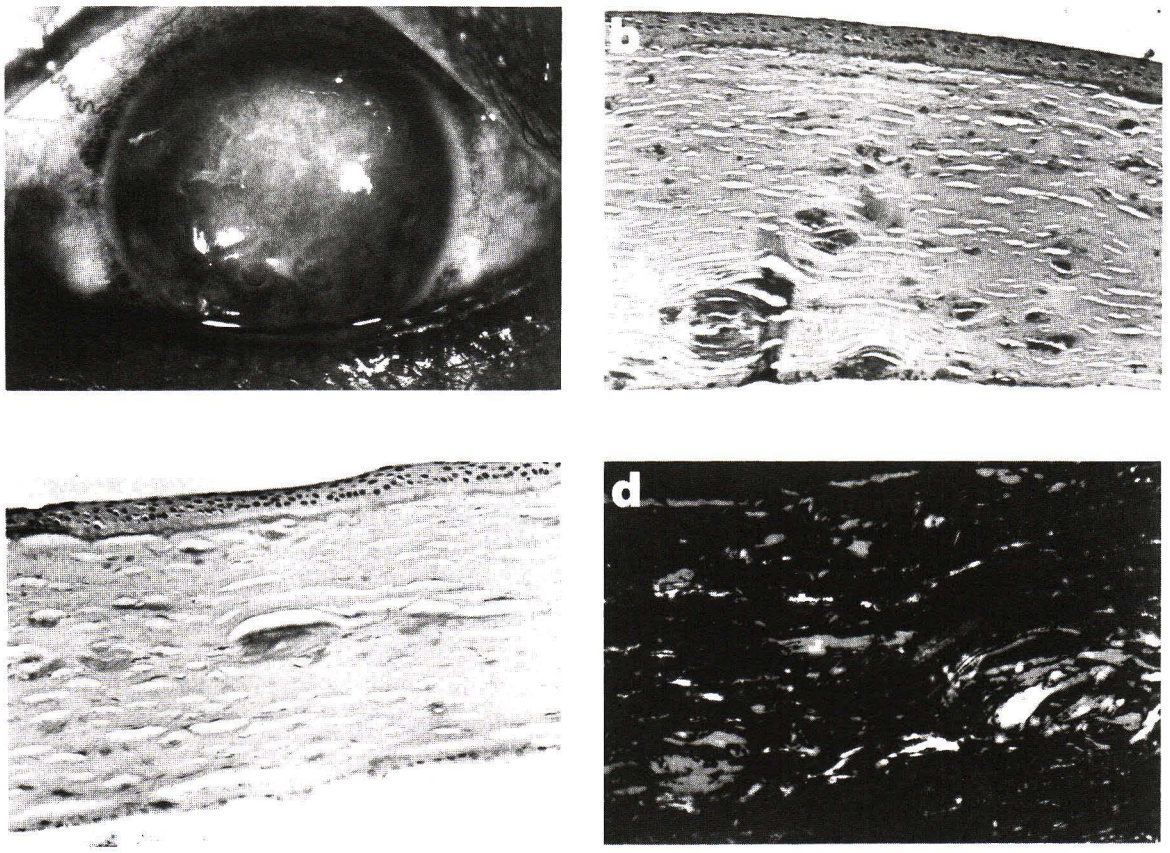

Fig. 5. Clinical manifestation and corneal histopathology of patients. 5a) clinical manifestation showing corneal stomal haze grade 3 and surface irregularity grade 3. 5b) H&E staining demonstrating hyaline amorphous material. 5c) congo red staining positive. 5d) showing apple green birefringence under polarized light.

The inherited pattern is autosomal recessive in type III and autosomal dominant in type IIIA which was first reported by Stock[15]. Recurrent corneal erosion is unlikely.

In the present study, there was no sex preponderance and the mode of inheritance strongly represents an autosomal dominant pattern. The authors also found a later age of onset for these patients (second decade of life) compared with previous reports[5,6, 16,17]. However, it may occur at different ages of onset as described by Stansbury, Hesse, Bucklers and Ramsey[18-21]. Most of the patients in the present study have had recurrent corneal erosion.

However, it is worth noting that the corneal manifestations of the patients in this family vary widely. They ranged from classic fine lines with a clear limbal region (Fig. 2a) as described in type I, to thick ropy lines or an elevated surface due to thick abnormal lattice lines which radiated from limbus to limbus in moderate cases (Fig. 2c, 3c, 3d) as described in type IIIA. The surface irregularity was due to amyloid deposition in the epithelium, or basement membrane as proved by histopathologic section[22] and confocal microscopy[23].

In severe cases, the opacities eventually become confluent, forming a dense central corneal leukoma which makes lattice lines unidentifiable (Fig. 2d). In some cases, the clinical manifestations were mixed between those of lattice and Reis-Bucklers corneal dystrophy. These findings are supported by

the fact that these diseases are caused by mutations of the same gene, the beta transforming growth factor-induced gene (Big-h3 gene) on chromosome 5 (5q31) (5,6). Factors influencing the phenotypic expression of the disease, causing a difference in corneal manifestations, might be the duration of the disease or the difference in genetic mutation between members of the same family or both. In the present study, the authors found a correlation between the duration of the disease and the severity of the disease of the cornea. A genetic study of these family members is on going to improve our understanding.

Since variation in the clinical manifestation of lattice dystrophy exist especially at the late stage, ophthalmologists may overlook or underdiagnose this condition. A thorough review of the past history and family history, and examination of family members would be very helpful in making a correct diagnosis.

The present study shows that the vision impairment is significantly correlated with corneal surface irregularity, corneal haze, duration of the disease and history of recurrent corneal erosion. The more the erosions occurred, the denser the corneal scar became. This finding is consistent with that of Bron(6).

As the disease progresses, the impaired vision gradually becomes a burden to the patients' work and family life. Although PTK and PKP(1,24, 25) can be performed in severe cases, the disease usually recurs(2-4). Besides, the severe shortage of corneal donors in Thailand puts these patients on a long waiting list for PKP, making the situation difficult for them. Furthermore, all of the patients had to pay for treatment, which was a considerable amount of money compared with their average income. This makes corneal lattice dystrophy a very important genetic disease in Thailand. There needs to be greater public awareness of the disease and the treatment available.

The present study clearly demonstrates how a couple with corneal lattice dystrophy, an uncommon genetic disease, can convey this disease to their offspring and rapidly increase the gene pool of this disease. Lack of knowledge regarding the disease and ignorance of family planning accelerated the number of affected members, creating a severe bio-psycho-social problem to the patients, their families and the society at large. This may also reflect the inadequacy of health education and the health systems in rural areas of Thailand.

In summary, corneal lattice dystrophy deserves more attention both from the clinical medicine and public health point of view. Without a proper strategy to approach this disease, it may no longer be an uncommon genetic disease in the near future.

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ผลกระทบของกระจกตาเสื่อมชนิดแลตติสต่อปัญหาสาธารณสุขของไทย†

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ได้ทำการศึกษาในเรื่อง ลักษณะแสดงออกทางคลินิก, ปัจจัยที่มีผลต่อระดับสายตารวมถึงผลกระทบของโรคต่อการดำรงชีวิตประจำวันของผู้ป่วย ในผู้ป่วย corneal lattice dystrophy 1 ตระกูลในประเทศไทย

จากสมาชิกครอบครัวจำนวน 88 รายได้รับการตรวจตาและตอบแบบสอบถาม พบว่าเป็นโรค corneal lattice dystrophy จำนวน 43 ราย คิดเป็น 48.9% โดยมีลักษณะการถ่ายทอดทางพันธุกรรมแบบ autosomal dominant โดยมีลักษณะทางคลินิกที่แตกต่างกัน ได้แบ่งระดับความขุ่นและความขรุขระของกระจกตาเป็น 4 ระดับ จากความรุนแรงน้อยไปมาก โดยผู้ป่วยที่มีความขุ่นของกระจกตามีจำนวน 5.3%, 26.3%, 43.4% และ 25% และผู้ป่วยที่มีความขรุขระของกระจกตามีจำนวน 18.4%, 39.5%, 32.9% และ 9.2% ตามลำดับ

ผู้ป่วย 45% มีระดับสายตาต่ำกว่า 20/200 โดยปัจจัยที่มีผลทำให้ระดับสายตาเลือนลางคือ ความขุ่นของกระจกตา, ความขรุขระของพื้นผิวกระจกตา, การหลุดลอกซ้ำของพื้นผิวกระจกตา และระยะเวลาของการเป็นโรค ($p < 0.05$) การเป็นโรคนี้มีผลกระทบต่อการดำรงชีวิตทางด้านการอ่านหนังสือ (79.1%) การทำงาน (62.8%) และการทำกิจกรรมประจำวัน (69.8%)

จากการศึกษาครั้งนี้พบว่า corneal lattice dystrophy ในตระกูลเดียวกันสามารถมีลักษณะแสดงออกทางคลินิกที่แตกต่างกันขึ้นกับระยะเวลาการเป็นโรคและความรุนแรงของโรค ซึ่งอาจทำให้จักษุแพทย์วินิจฉัยโรคผิดพลาด การที่ผู้ป่วยขาดความรู้และความเข้าใจต่อโรคทำให้โรคมีการแพร่กระจายและส่งผลกระทบต่อปัญหาทางสาธารณสุขของประเทศไทย

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