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JAPANESE DERMATOLOGICAL ASSOCIATION GUIDELINE

Xeroderma pigmentosum clinical practice guidelines

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ABSTRACT

Xeroderma pigmentosum (XP) is a genetic photosensitive disorder in which patients are highly susceptibe to skin cancers on the sun-exposed body sites. In Japan, more than half of patients (30% worldwide) with XP show complications of idiopathic progressive, intractable neurological symptoms with poor prognoses. Therefore, this disease does not merely present with dermatological symptoms, such as photosensitivity, pigmentary change and skin cancers, but is "an intractable neurological and dermatological disease". For this reason, in March 2007, the Japanese Ministry of Health, Labor and Welfare added XP to the neurocutaneous syndromes that are subject to government research initiatives for overcoming intractable diseases. XP is one of the extremely serious photosensitive disorders in which patients easily develop multiple skin cancers if they are not completely protected from ultraviolet radiation. XP patients thus need to be strictly shielded from sunlight throughout their lives, and they often experience idiopathic neurodegenerative complications that markedly reduce the quality of life for both the patients and their families. Hospitals in Japan often see cases of XP as severely photosensitive in children, and as advanced pigmentary disorders of the sun-exposed area with multiple skin cancers in adults (aged in their 20–40s), making XP an important disease to differentiate in everyday clinical practice. It was thus decided that there was a strong need for clinical practice guidelines dedicated to XP. This process led to the creation of new clinical practice guidelines for XP.

Key words: **DNA repair, neurological symptoms, photoaging, skin cancers, xeroderma pigmentosum.**

BACKGROUND FOR CREATING THE GUIDELINES

Xeroderma pigmentosum (XP) is a genetic photosensitive disorder in which patients show a high susceptibility to skin cancers on the sun-exposed body sites. It was first recorded at the end of the 19th century by a dermatologist, Moritz Kaposi, who described a severe photosensitivity disorder that was accompanied by pigment change.[1,2] In 1968, the American radiobiologist, James E. Cleaver, reported for the first time that XP is a genetic disease in humans, in which genetic abnormalities occur in the DNA repair process. He discovered that XP cells unable to repair DNA damage caused by ultraviolet radiation (UV).[3] In Japan, more than half of patients (30% worldwide) with XP show complications of idiopathic progressive, intractable neurological symptoms with poor prognoses. Therefore, this disease does not merely present with dermatological symptoms, such as photosensitivity, pigment change and skin cancers, but is "an intractable neurological and dermatological disease". For this reason, in March 2007, the Japanese Ministry of Health, Labor and Welfare added XP to the neurocutaneous syndromes that are subject to government research initiatives for overcoming intractable diseases.

Neurocutaneous syndromes comprise four diseases: neurofibromatosis type 1, neurofibromatosis type 2, tuberous sclerosis and XP. However, the clinical image varies depending on each disease, and the clinical practice guidelines have been developed separately.[4] The three diseases, except for XP, have strong elements of phacomatosis. Meanwhile, XP is one of the extremely serious photosensitive disorders in which patients

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easily develop multiple skin cancers if they are not completely protected from UV. XP patients thus need to be strictly shielded from sunlight throughout their lives, and they often experience idiopathic neurodegenerative complications that markedly reduce the quality of life (QOL) for both the patients and their families. Hospitals in Japan often see cases of XP as severely photosensitive in children, and as advanced pigment disorders of the sun-exposed area with multiple skin cancers in adults (aged in their 20–40s), making XP an important disease to differentiate in everyday clinical practice.

Clinical practice guidelines for XP are mentioned in Japan Dermatological Association-approved guidelines on genetic diagnosis of skin diseases, but the items on XP are not extensive or comprehensive.[5] It was thus decided that there was a strong need for clinical practice guidelines dedicated to XP, and not just as a part of guidelines for neurocutaneous syndromes or genetic skin diseases. This process led to the creation of new clinical practice guidelines for XP.

POSITION OF THESE GUIDELINES

This committee consists of members of the team of "Establishment of practice guidelines based on scientific evidence by the clinical department cross-sectional examination on neurocutaneous syndrome" supported by the grant on "Research on Measures for the Intractable Diseases Project" from the Japanese Ministry of Health, Labor and Welfare, the cooperative researchers, and the committee members who were entrusted by the Japanese Dermatological Association. These guidelines were developed after this committee and the discussion in writing had been held in June 2014. These guidelines aim to show a standard of fundamental and standard medical care of xeroderma pigmentosum in Japan at present.

Escape clause

In these guidelines, the views of the committee members who developed these guidelines were intensively compiled based on the available data at the time of preparing the report, which might be forced to change conclusions or recommendations in this report depending on the results of future studies. In addition, it is accepted that it might even be desirable to deviate these guidelines for some specific patients and under some specific conditions. Consequently, physicians who provided treatment cannot escape their liability arising from negligence only by their reason that they complied with these guidelines, and deviation from these guidelines cannot be necessarily considered as fault.

DEFINITION AND CONCEPTS

XP is a hereditary photosensitive disease governed by autosomal recessive inheritance. In XP patients, their skin is extremely vulnerable to UV because of a congenital defect of repair ability for UV-induced DNA damage. If these patients do not take appropriate protection from sunlight, they will develop serious photosensitivity, progressive development of freckle-like pigment disorder and skin cancers that have the tendency of develop frequently and multifocaly regardless of young age. In Japan, the majority of XP patients have progressive neurodegenerative symptoms of unknown cause, of which severity will impact their prognosis.

XP is classified into eight subtypes (group A–G genetic complementation groups and a variant type [V]) of which each responsible gene has been identified. Each form has various clinical features (Table 1). It has been noticed that there is an association between the gene mutation and the phenotype, even in the same responsible gene[6,7] In Japan, genetic complementation group A (XP-A), of which patients develop serious XP with neurological symptoms, accounts for more than half of XP patients, followed by XP variant type (XP-V), of which patients develop only cutaneous symptoms.

EPIDEMIOLOGY

In Japan, XP occurs as rarely as one in 22 000 people. However, it is difficult to consider this incidence of XP as an extremely rare disease as compared with the incidence in Western countries (one in 1 million people). XP-A, in which both cutaneous symptoms and neurological symptoms are the most severe, accounts for 55% of XP patients in Japan, followed by XP-V, in which patients develop only cutaneous symptoms (25%), XP-D (8%), XP-F (7%) and XP-C (4%). Patients with XP-E are rare, and there is no case report of patients with XP-B. In Japanese patients with XP-A, the founder mutation, IVS3-1G>C, is detected, and about 80% of them show homozygous mutation of IVS-1G>C in *XPA* gene. The frequency of being a carrier of XP-A is one in 100 Japanese people.[8] Unlike the cases in Western countries, many of the Japanese patients with XP-D have no neurological symptoms.[9]

PATHOGENESIS AND CLINICAL CONDITIONS

XP occurs because the repair system (nucleotide excision repair [NER] and translesion synthesis) for UV-induced DNA damage (cyclobutane-type pyrimidine dimer, 6-4 photoproduct) does not act properly as a result of genetic abnormality. These responsible genes are *XPA*, *XPB* (*ERCC3*), *XPC*, *XPD* (*ERCC2*), *XPE* (*DDB2*), *XPF* (*ERCC4*), *XPG* (*ERCC5*) and *XPV* (*POLH*). All of them are NER-related factors (DNA damage recognition, DNA strand-opening around the lesion, excision of the DNA lesion by endonucleases, synthesis of a new complementary DNA strand and ligation), except XPV protein, which exerts translesion DNA polymerase in the translesion synthesis system. If pathological mutation occurs in either of these genes, XP will occur.

Symptoms

XP is classified into the following types: XP cutaneous disease in which patients develop only cutaneous symptoms; XP neurological disease in which patients develop cutaneous symptoms with neurological symptoms; and XP/CS complex in which patients develop cutaneous symptoms with Cockayne syndrome (Table 2). Of Japanese XP patients, XP cutaneous disease accounts for 45% (including 90% of XP-D, XP-E, most

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Table 1. Genes responsible for xeroderma pigmentosum, and its clinical and cytological characteristics

		Clinical manifestation				
		Skin symptoms			Cytological characteristics	
	Responsible gene	Photosensitivity	Skin cancer (mean age onset of BCC [years])	Neurological symptoms	UDS (%)	Lethal sensitivity to UV, D_0 (J/m^2)
A	*XPA* 9q34.1 (31 kD)	+++	9.7	+++	<5	0.4
B	*XPB/ERCC3* 2q21 (89 kD)	++	+	– to ++	3–7	
C	*XPC* 3q25 (106 kD)	++†	14.0	–	10–20	1.0
D	*XPD/ERCC2* 19q13.2 (87 kD)	++	38.0	– to ++	20–50	0.77
E	*DDB2* 11q12-p11.2 (48 kD)	+†	38.3	–	40–60	2.2–2.4
F	*XPF* 16p13.13 (126 kD)	+	43.7	– (+)	10–20	1.7–2.2
G	*ERCC5* 13q33 (133 kD)	++	32	– to ++	<5	0.6
V	*POLH* 6p21.1-6p12 (83 kD)	+†	41.5	–	75–100	2.4–4.5

†No exaggerated sunburn occurs. BCC, basal cell carcinoma; D_0, ultraviolet radiation dose that gives 37% cell viability after exposure to ultraviolet radiation; UDS, unscheduled DNA synthesis; - (+), most of XPF case do not have neurological symptoms.

XP-F, and XP-C patients and 75% of XP-G and XP-V patients), and XP neurological disease accounts for 55% (including XP-A, some XP-D and some XP-G patients). In Japan, XP with Cockayne syndrome (XP/CS complex) is extremely rare, and has been found in just three patients (two patients with *XPD* mutation and one patient with *XPG* mutation). XP-F, which was thought to be XP cutaneous disease conventionally, has been recently found in several reports on patients with neurological symptoms, and thereby can be classified into XP neurological disease.

Clinical classification of XP judging from cutaneous symptoms

Exaggerated sunburn reaction type (XP-A, XP-B, XP-D, XP-F and XP-G): severe and abnormal sunburn reaction occurs at the sun-exposed area upon a minimum sun exposure (e.g. face, nape, ear auricle, dorsum of hand, and upper and lower limbs). Unlike normal sunburn, this exaggerated sunburn reaction is often associated with strong redness, swelling, blister and erosion, and is exacerbated for 3–4 days after exposure, and persists for at least 1 week. After having repeated severe sunburn-like reactions, freckle-like small pigmented maculae are found at the sun-exposed area. Small pigmented freckles increase whenever a sunburn-like reaction is repeated. In comparison with normal freckles, the size of small pigmented maculae are various, and their color tone is heterogeneous. Small pigmented maculae can be found not only on the face, but also on the nape, the dorsum of the hand and the upper chest.[10] Sun-exposed areas of the skin tend to be xerotic easily and multiple malignant skin tumors (actinic keratosis, basal cell carcinoma, malignant melanoma, squamous cell carcinoma etc.) will be found on the face and other sun-exposed areas of the skin at a young age. If such patients do not carry out strict protection from sunlight, skin malignant tumors can occur 30–50 years earlier than in healthy people, and the frequency is considered as 1000-fold or more as much as healthy generation.

Abnormal pigment change type (XP-C, XP-E, and XP-V): XP cutaneous disease.

Freckle-like dyschromatosis gradually progresses without producing abnormally exaggerated sunburn. This pigmented maculae varies in size from small to large, its color tone is heterogeneous and its border is indistinct. It is progressive, and such patients present with photoaging skin that is unsuitable for their age at the sun-exposed skin sites, including the face. Multiple skin malignant tumors occur on the skin of sun-exposed body sites at a younger age.[11]

Table 2. Clinical type and frequency of xeroderma pigmentosum in Japan

XP cutaneous disease: 45%
XP-V, XP-D, XP-E, XP-F, XP-C, XP-G
XP neurological disease: 55%
XP-A, XP-D, XP-G, XP-F (exceptional)
XP-B: rare worldwide; no case reported in Japan
XP/CS complex: extremely rare (3 cases)
XP-B/CS, XP-D/CS, XP-G/CS: rare worldwide

XP, xeroderma pigmentosum; XP-A, xeroderma pigmentosum group A; XP-B, xeroderma pigmentosum group B; XP/CS, xeroderma pigmentosum/Cockayne syndrome complex; XP-D, xeroderma pigmentosum group D; XP-D/CS, xeroderma pigmentosum group D/Cockayne syndrome complex; XP-E, xeroderma pigmentosum group E; XP-F, xeroderma pigmentosum group F; XP-G, xeroderma pigmentosum group G; XP-G/CS, xeroderma pimentosum group G/Cockayne syndrome complex; XP-V, xeroderma pigmentosum variant type.

Neurological symptoms of XP

In Japan, progressive central and peripheral neurodegeneration occurs in approximately 100% of XP-A patients, and approximately 10% of XP-D patients. For typical development in children with XP-A in which the most severe symptoms are found, the head is held up at an average of 3.5 months-of-age, roll over is achieved at an average of 6 months-of-age, sitting position is achieved at an average of 7 months-of-age, pulling up to standing is achieved at an average of 12 months-of-age and walking is achieved at an average of 15 months-of-age. Although children with XP-A show slight delay in their development, they can acquire

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approximately age-appropriate functions. The peak of physical performance is achieved at approximately 6 years-of-age, gait disturbance occurs at approximately 12 years-of-age, and wheelchairs are required at approximately 15 years-of-age.[12] Deformity in the foot, such as contracture in the pes equinovarus and pes cavus deformity, can be found at approximately the timing of entrance to elementary school (6 years-of-age).[13] In some cases, it can be complicated with callosity, skin ulcer, contact dermatitis and tinea pedis as a result of foot deformity and the use of prostheses. Regarding auditory function, hearing loss occurs at the first half of school age, and wearing of hearing aid devices is required in the second half of school age. At approximately 15 years-of-age, auditory function is almost non-existent. Regarding speech function, the peak is achieved at 5–6 years-of-age. The language that they once acquired is maintained despite the progressive deafness during the elementary school period. However, they show dysarthria with decline of intellectual ability and advanced deafness, and their speech function disappears at approximately 15 years-of-age. Involuntary movement, such as tremor and myoclonus, can also be found in older children. Deep tendon reflexes in the extremities gradually disappear. Progressive sensory-dominant axonol neuropathy is found by peripheral nerve conduction studies. Brain computed tomography and magnetic resonance imaging show atrophy of all the cerebrum, brainstem, and cerebellum with ventricular dilatation. Before and after entrance to junior high school, choking and dysphagia occur. In some cases, tracheotomy might be required because of vocal cord paralysis and larynx dystonia at approximately 20 years-of-age.[14,15] Afterwards, at age approximately 30 years, they commonly die of aspiration, infection and traumatic injury. There is a rare report that symptoms of photosensitivity were not very severe in an XP-A patient, and neurological symptoms developed in middle age or later.[16] XP-D patients in Western countries frequently develop neurological symptoms. Meanwhile, XP-D patients in Japan commonly do not develop neurological symptoms, and the symptoms are mild, if any, and they can do normal work. Rarely, some XP-F patients show neurological symptoms.

Eye manifestation of XP

In XP patients, the eye tissue exposed to UV is also involved. Therefore, they have lesions in the anterior ocular segment, such as conjunctival xerosis and corneal drying, conjunctivitis, keratitis, evagination, corneal ulcer, and decrease of lacrimation. As most ultraviolet B (UVB) does not reach the retina, no morbid change as a result of direct exposure to UV occurs, while abnormalities in the optic nerve as a neurological symptom of XP can occur.

A summary of eye manifestation of 87 XP patients in the USA reported conjunctivitis (51%), corneal neovascularization (pannus; 44%), corneal drying (38%), corneal cicatrization (26%), ectropion (25%), blepharitis (23%), pigmentation of the conjunctiva (20%), cataract (14%), visual field disturbance (13%), optic neuropathy (5%) and malignant tumor (10%).[17–19]

TESTS FOR DIAGNOSIS OF XP

Figure 1 shows a flow chart for diagnosis of XP.

Photosensitivity test

Exaggerated sunburn reaction type (XP-A, XP-B, XP-D, XP-F and XP-G): decreased minimum erythema dose; delay of peak in erythema reaction.

Abnormal pigment change type without sunburn (XP-C, XP-E and XP-V): normal minimum erythema dose; no delay of erythema reaction.

DNA repair test using cultured fibroblasts

1. Measurement of unscheduled DNA synthesis after irradiation with UV

It decreases to <50% of normal cells, except XP-V. Unscheduled DNA synthesis is more than 70% in XP-V patients.[10]

2. Test of lethal sensitivity to UV (colony formation assay)

XP cells, except XP-V, are hypersensitive to UV. The sensitivity of XP-V cells to UV is slightly hypersensitive or a normal level. However, its UV sensitivity is increased in the presence of caffeine.

3. Genetic complementation test

The genetic complementation group of XP is determined based on the restoration of DNA repair ability after co-transfection with the reporter gene and cDNA of each XP complementation group using plasmid or virus vector.[18]

4. Western blot analysis of gene product of responsible gene of XP

Patients with XP of NER-deficient types are diagnosable by a genetic complementation test. In XP-V, which does not present defects in NER, it is useful in a diagnosis to examine the presence of DNA polymerase eta (POLH) protein as the responsible gene product.[20]

Genetic analysis using peripheral blood- or patient-derived cultured cells

In genetic analysis of XP-A, which accounts for the majority of XP patients in Japan, 78% are homozygotes of G to C substitution in the 3′ splice acceptor site of intron 3 of the *XPA* gene (IVS3-1G>C), 16% harbor a heterozygous mutation of IVS-1G>C, 2% are homozygotes of the nonsense mutation of Exon 6 (R228X) and 9% harbor R228X heterozygously.[10]

These genetic mutations (IVS3-1G>C, R228X) are regarded as founder mutations of the *XPA* gene in Japanese patients, and can be identified easily by polymerase chain reaction followed by restriction fragment length polymorphism analysis (*Alw*NI, *Hph*I). Based on this strong founder effect, gene mutation can be easily and quickly identified in most XP-A Japanese patients, and it is used for genetic tests in medical practice. For patients with XP-A who are undiagnosable with

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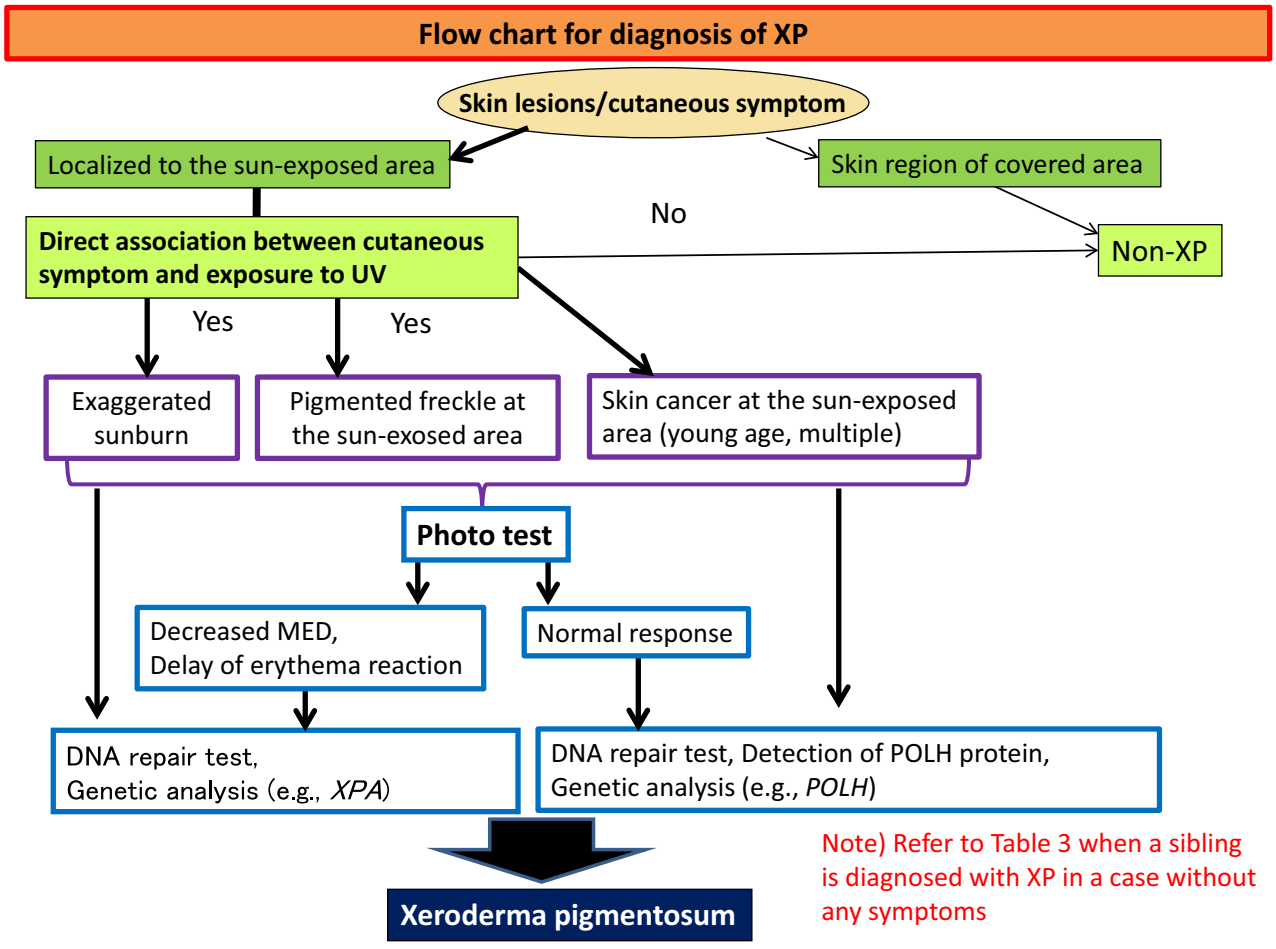


Figure 1. Flow chart for diagnosis of xeroderma pigmentosum (XP).

this method or possible other complementation groups of XP, mutation identification is tried by DNA direct sequencing. It is known that there are four types of mutations that frequently occur in Japanese patients with XP-V. Approximately 90% of the patients with XP-V harbor one of those mutations. In direct base sequence determination, it is efficient to start examination with these mutations.[20,21] These genetic screens are important in clinical settings, because XP-A and XP-V account for approximately 80% of XP in Japan.

DIAGNOSTIC CRITERIA AND SEVERITY CLASSIFICATION FOR XP

Figure 1 shows a flow chart for the clinical practice for XP, and Table 3 shows guidelines for definitive diagnosis of XP that have been newly developed. Table 4 shows a classification of the severity of XP with various parameters as an indicator. Patients whose definitive diagnosis of XP is established carry out strict protection from UV, and receive regular examinations at departments of dermatology and ophthalmology.

After definitive diagnosis of XP, if patients showed "4" of "A. symptoms "in Table 3, alternatively, when they showed the XP neurological symptom-related gene mutation even if they showed no "4" symptoms, setting up a team with pediatric neurologists, neurologists, otolaryngologists, orthopedists and rehabilitation specialist staff, as well as dermatologists and ophthalmologists, is crucial to following up such patients as a patient with strictly XP neurological disease (Fig. 2).

DIFFERENTIAL DIAGNOSIS OF XP

Freckles

There is no serious symptom of photosensitivity. A differentiation from mild XP can be achieved by ruling out XP through various DNA repair tests. Eruption is limited to the face, and does not spread through the nape, the dorsum of hand and the upper chest.

Dyschromatosis symmetrica hereditaria

There are some patients who require a differentiation from XP, as mild symptoms and freckle-like pigmentation on the sun-exposed area, such as the face and the dorsum of the hands, are often found. The point of differentiation from XP is as follows: patients show dyschromatosis in not only the dorsum of the hands, but

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Table 3. New diagnostic criteria for xeroderma pigmentosum (guidelines for definite diagnosis)

Medical fee aid for definite and probable

A. Symptoms
1. Symptoms of chronic photosensitivity (characteristic pigmented freckle localized to the sun-exposed skin that is more prominent for the patient's age, which may be associated with skin atrophy, telangiectasia etc.)
2. Symptoms of acute photosensitivity (excessive sunburn reaction after minimum sun exposure) (see note)
3. Skin cancer on sun-exposed areas in patients aged 50 years or younger (basal cell carcinoma, squamous cell carcinoma, malignant melanoma, etc.)
4. Progressive neurodegenerative symptoms of unknown origin (e.g. hearing loss and gait disturbance)

Note: The following characteristics due to excessive sunburn after sun exposure:
Patients experience sunburn caused by UV of which level is much less than the level that healthy subjects experience sunburn, and develop excessive inflammatory edema and blistering that are not found in healthy subjects; a peak of development of sunburn is delayed, the peak is achieved at around the fourth day, and it takes about 10 days until it disappears.

B. Examination findings
1. Peripheral neuropathy (decline of deep tendon reflex; sensory-dominant axonopathy found by a peripheral nerve conduction study.
2. Abnormal findings of post-UV DNA repair ability (hypersensitive to UV in terms of colony formation; deceased level of unscheduled DNA synthesis after exposure to UV.
3. Lethal hypersensitive to UV in patient's cells, or enhanced susceptibility in the presence of caffeine.
4. Hearing loss (abnormal wave I and II of auditory brainstem response; decrease of the hearing level on the audiogram)

C. Differential diagnosis. Differentiate the following diseases: porphyria, dyschromatosis symmetrica hereditaria

D. Genetic analysis
1. Gene mutations in either *XPA*, *XPB*, *XPC*, *XPD*, *XPE*, *XPF*, *XPG* and *XPV*

Categories of diagnosis
Definite XP:
1. A patient develops the abovementioned symptoms (A) or is suspected to have XP because the patient's family developed these symptoms, and pathological mutation is identified in XP-related gene by genetic analysis.
2. A patient develops either of the abovementioned symptoms (A-1, 2 or 3) and meets the abovementioned criteria (B-2), and the DNA repair ability is restored by introducing known XP responsible gene in genetic complementation test while pathological mutation of XP responsible gene is undetermined or no genetic analysis is carried out.

Probable XP
1. A patient develops only the abovementioned symptom (A-4) and meets the abovementioned criteria (B-2), and the DNA repair ability is restored by introducing known XP responsible gene in genetic complementation test while pathological mutation of XP responsible gene is undetermined or no genetic analysis is performed.
2. A patient meets all the abovementioned symptoms (A-1,2 and 3).

Possible XP
1. A patient develops only the abovementioned symptom (A-4) and meets the abovementioned criteria (B-2), and the DNA repair capacity is not restored by introducing known XP responsible gene in genetic complementation test or no genetic analysis is carried out.
2. A patient meets the abovementioned symptoms (A-1 and 2).
3. A patient meets either of the abovementioned symptoms (A-1 or 2), and it is denied that the patient has a disease with symptoms the same as XP.
4. A patient develops either of the abovementioned symptoms (A-1, 2, 3 or 4) and the patient's sibling has a diagnosis of XP.

UV, ultraviolet radiation; XP, xeroderma pigmentosum.

also the dorsum of the feet, and they have co-localizing intermingled pigmentation and spot of depigmentation.[22] The differentiation is possible by taking a family history (autosomal dominant inheritance). Pigmented freckle is often found in the elbow and the patella, even if there is no eruption at the extensor of the forearm and the lower leg, as well as the dorsum of the hands and dorsum of the feet, and is different from pigmented freckles of XP limited to the sun exposed area. The final diagnosis is possible based on gene (*ADAR1*) analysis of this disease.

Erythropoietic protoporphyria

This is an autosomal dominant inherited disease that occurs as a result of the loss of function of ferrochelatase, which is one of the enzymes of the heme biosynthesis process. A small scar is left following after an acute reaction such as edema or erythema, and blisters occur on the skin after sun exposure. A high level of free erythrocyte protoporphyrin, or red fluorescent material in red blood cells under fluorescence microscope is observed. A definite diagnosis can be made by analysis of the *FECH* gene as a gene responsible for this disease. Its pigmented freckle is not outstanding.

Impetigo contagiosa, staphylococcal scalded skin syndrome

The onset of eruption is unrelated to sunlight. Patients respond to systemic administration with antibiotics.

TREATMENT AND PATIENT CARE

As this is an inherited disease, a radical cure cannot be expected. The basics of patient care are complete defense from UV and symptomatic treatments for complications. The

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Table 4. Assessment and classification of the severity of xeroderma pigmentosum

Classification of the severity
Medical fee aid for patients with stage 2 or higher[†]
Indicator to assess the severity of XP
Cutaneous symptom (D) score
☐ Exaggerated sunburn: 0, No; 3, Yes
☐ Freckle-like eruption: 0, No; 1, mild (only from the bridge to the buccal region); 2, moderate (expansion to the entire face); 3 severe (expansion to the neck and shoulders)
☐ Skin cancer: 0, No; 2, Yes (single); 3, Yes (multiple)
Extracutaneous symptoms (N) score
☐ Hearing ability: 0, Normal; 1, decline (no hearing aid device is required); 3, decline (a hearing aid device is required).
☐ Movement: 0, no disturbance; 2, gait disorder; 3, wheelchair; 4, bedridden
☐ Intellectual function: 0, normal; 2, disturbance; 3, difficulties in daily life
☐ Swallowing and respiratory function: 0, normal; 2, sometimes choking; 3, aphagia and dyspnea; 4, tracheostomy and gastrostomy
Severity of cutaneous symptoms
☐ D1: D score of 0-2: early cutaneous XP
☐ D2: D score of 3-5: pre-severe cutaneous XP
☐ D3: D score of 6 or more: severe cutaneous XP
Severity of extracutaneous symptoms
☐ N(0):no neurological symptoms
☐ N1: N score of 0; early neurological XP
☐ N2: score of 1-4; progressing neurological XP
☐ N3: N score of 5 or more; advanced neurological XP
Classification of XP depending on the severity
☐ Stage 1: D1 + N (0)
☐ Stage 2: D2 + N (0), D1 + N1
☐ Stage 3: D3 + N(0), D1 + N2, D2 + N1
☐ Stage 4: any D+N3, D3 + any N

[†]Aid for medical expenses is indicated for patients who require continuing expensive medical care though these patients are not included in a certain group by the severity classification for xeroderma pigmentosum (XP).

prognosis of patients depends on the following issues: how early a definite diagnosis of XP is made to initiate protection from sunlight; can strict protection from sunlight be carried out thoroughly; how can early skin cancer be detected and treated on the skin after sun exposure; control of the neurological symptoms; and how appropriate treatment is provided to prevent progress (Fig. 2).

Protection from UV

XP patients have to carry out strict and complete protection from UV, especially from UVB to UVA2 in order to prevent progression of dyschromatosis on the sun exposed area and prevention of development of skin cancer. Specific protections are as follows:

1. Apply a sun-screen formulation with a high sun protection factor and high protection grade of UV-A (PA) to the skin before going out. Wear clothes with long sleeves, trousers, protective clothing from UV and glasses for UV protection.
2. Apply a film offering UV protection to windows, and use a sunshade curtain to protect from light when the windows are opened.
3. When the patient is school age, apply a film for UV protection to the windows in the school, and be careful to avoid direct exposure to UV during outdoor activities and attending school.

Complete protection from UV can prevent from progress of freckle-like pigment change and development of malignant skin tumor in the future.

Measures for skin cancer

Encourage patients to visit a dermatologist every 3–6 months to judge whether the protection from sunlight is successful based on history taking and findings of the skin (the presence or absence of development of sunburn and the presence or absence of progress of dyschromatosis). Furthermore, check the skin of sun-exposed body sites carefully for early detection and treatment of malignant skin tumors.

Treatment of skin cancer

For skin cancer in XP patients, early case detection and early excision are principles. However, in Western countries, there are reports on the usefulness of topical application of a liposome lotion containing prokaryotic DNA repair enzyme (bacteriophage T4 endonuclease V) and oral administration of 13-cis-retinoic acid in XP patients who cannot undergo radical operation because of poor general condition and the number of tumors, aiming at a suppressive effect on skin cancer development. It has been also reported that imiquimod is useful for actinic keratosis and basal cell carcinoma, and interferon-α is useful for melanoma.[23–26]

As there is also a report that delayed awakening from anesthesia occurs in XP patients, it is desirable to carry out treatment early before general anesthesia is required.

Measures for eye manifestation

For the purpose of education for eye protection from sunlight, prevention of cataracts and early detection of intraocular tumors, it is useful that ophthalmologists check the eye manifestation of XP patients every 3–6 months.

Measures for extracutaneous symptoms, such as neurological symptoms

There is no useful evidence-based therapy, as the pathogenesis for neurodegeneration of XP is still unknown. However, rehabilitation can be carried out to deal with motor impairment and intellectual disability associated with neurodegeneration. In many children with neurological symptoms, their development tends to be delayed for their age, and their peak of development is achieved at approximately 5–6 years-of-age, before school age. Therefore, it is desirable to bring the peak of development to be higher by early rehabilitation. Encouraging educational activities, whole-body exercise, massage, and

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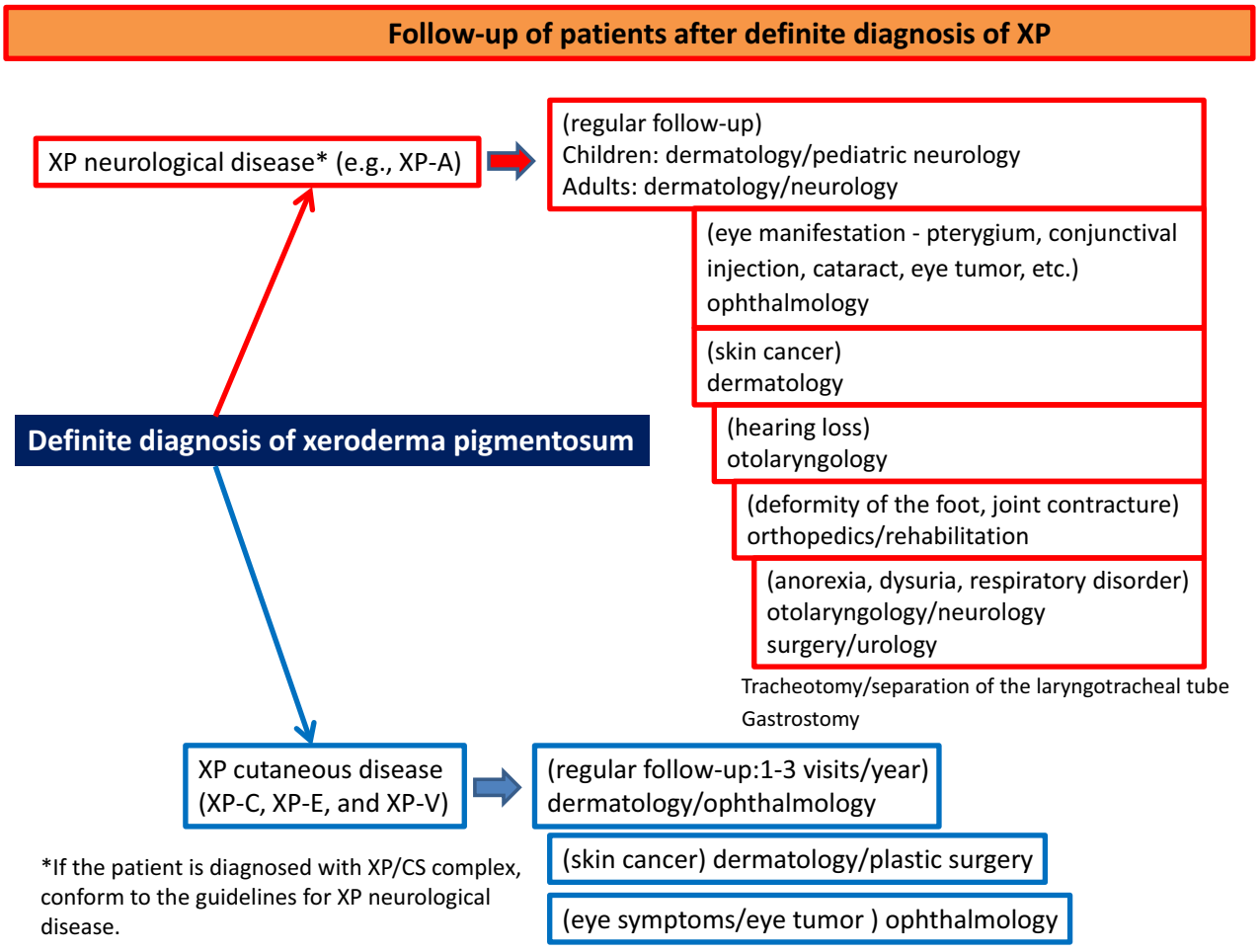


Figure 2. Follow-up of patients after definite diagnosis of xeroderma pigmentosum (XP). CS, Cockayne Syndrome; UV, ultraviolet radiation; XP-A, xeroderma pigmentosum group A; XP-B, xeroderma pigmentosum group B; XP-D, xeroderma pigmentosum group D; XP-E, xeroderma pigmentosum group E; XP-F, xeroderma pigmentosum group F; XP-G, xeroderma pigmentosum group G; XP-V, xeroderma pigmentosum variant type.

parent–child swimming from infancy and childhood. It is important to allow such children to have a great deal of experience by stimulating their five senses (e.g. listen to music, watch a picture book and draw) and promoting communication with others. Although hearing loss often occurs before and after starting school age, hearing tests should be carried out at regular intervals to start wearing a hearing aid device early in order to prepare an environment that allows patients to enjoy listening to music, watching TV and engaging in smooth conversation, which leads to maintenance of acquired language and enhancement of the patient's QOL. As loss of muscle strength and joint contracture come to be gradually remarkable after school age, encourage patients to visit a department of rehabilitation regularly for the purpose of delay of progression of motor impairment and suppression of contracture. In particular, practice stretching mainly in the lower limbs, and instruct the patients' parents on dorsiflexion exercise of the ankle using a tilt table. In consideration of making an arch support and ankle foot orthosis because the ankle is easy moved to the equinovarus position, aim at prolongation of the period that they can walk. During this period, activity in school life becomes important. Therefore, seek the cooperation of teachers in a support school, confirm their activities in daily school life and suggest an exercise instruction menu depending on each patient. Also, the amount of speech can decrease. In such a case, speech therapy can be added. Patients aged 15 years or older have difficulties in ambulation. A wheelchair and a supporting structure to maintain a sitting position are indicated for such patients. As joint contracture and deformity also advance, provide an appropriate wheelchair, prepare a supporting structure to maintain a sitting position, prescribe orthotics, and provide rehabilitation in order to maintain the patient's activity of daily living and reduce the burden on caregivers as much as possible. If muscle tonus of the upper and lower extremities is worsened and nursing seems to be hard, treatment with botulinum toxin might be coonsidered.[27]

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Orthopedic surgeries, such as tendon transfers, were carried out in the past. However, currently orthopedic surgery is seldom carried out for the following reasons: (i) as activity is decreased during hospitalization, neurological symptoms progress, which take a long time for the patient to recover from; and (ii) some patients cannot recover to the original level.

Dysphagia and respiratory disorder progress from the late teens. Choking and aspiration pneumonitis occur easily. In addition, sudden dyspnea as a result of larynx dystonia can occur, and emergency treatment might be required. If the frequency of respiratory disorder increases, separation of the laryngotracheal tube or tracheotomy might be required. A percutaneous endoscopic gastrostomy is often constructed for improvement of undernutrition caused by poor oral intake. When neurological symptoms progress, cystitis as a result of urinary retention and dysuria can frequently occur. Such a patient might have to visit a department of urology. Even if patients have difficulties in communication as a result of aphonia and advanced disturbance of motor dysfunction, their comprehension of language is commonly maintained. Therefore, make an effort to improve the patient's QOL through active communication using a hearing aid device, as well as the residual auditory and visual ability.

It has been reported that neurological symptoms of XP are caused by oxidative stress.[28] However, it will be an issue in the future to examine whether anti-oxidants are effective. In addition, it has been reported that a low dose of levodopa is effective for larynx dystonia, which is considered to be a cause of respiratory disorder in XP patients.[29]

It is required that not only parents of children, but also the teachers in charge of the child understand the aforementioned information. It is desirable to treat XP by not only dermatologists, but also a team consisting of pediatricians, neurologists, otolaryngologists, rehabilitators and ophthalmologists.

Genetic counseling/life consultation

As XP is a hereditary disease, genetic counseling is indicated for all XP patients. A genetic analysis is carried out easily and quickly by polymerase chain reaction-restriction fragment length polymorphism for XP-A patients whose founder effect is strong. In genetic analysis for other XP genetic complementation groups, a sequence of all exons is required. However, as a possibility that the XP gene mutation might be associated with the clinical severity has been mentioned, it is very useful from the viewpoint of not only diagnosis, but also estimation of the prognosis after definite diagnosis.

In Japan, carrier detection and prenatal diagnosis are limited to XP-A, in which the most severe symptoms are found, and easy and quick diagnosis is available, and requires severe review by the ethical committee of the institution where the test is carried out, and adequate informed consent for clients before the initiation of the test.

Prognosis of XP patients is extremely poor in Japan, where there are many XP-A patients. Onset and progression of cutaneous symptoms and neurological symptoms bring strict protection from sunlight and limitations of going out, which impairs the QOL of patients and their family remarkably. In addition, considering that there is no therapy and that this disease can be inherited (genes are inherited to the next generation), XP patients and their family have to bear considerable burden economically, physically, and mentally. Therefore, patients and their families are required to receive mental care provided by nurses, genetic counselors, and clinical psychologists. An exchange of information between patients and families through a society consisting of XP patients and their family is commonly beneficial.

PROGNOSIS

Patients with typical XP-A experience choking and dysphagia from approximately 15 years-of-age, and might require tracheotomy at approximately 20 years-of-age because of vocal cord paralysis and larynx dystonia.

They commonly die of aspiration, infection or trauma at approximately 30 years-of-age. Vital prognosis in patients with XP/CS is approximately 5 years, because it is complicated with renal failure. Recently, few cases of death have been attributed to skin malignant tumor, because diagnosis of XP is carried out early in the patients' lives. Consequently, if appropriate diagnosis of XP cutaneous disease is carried out early and appropriate protection from sunlight is carried out, the prognosis is good.

CONCLUSION

XP involves serious inherited photosensitivity that occurs as a result of a deficiency in the repair ability of UV-induced DNA damage. Clinically, photosensitivity occurs repeatedly with every instance of sun exposure, and photoaging including freckle-like dyschromatosis progresses; in addition, malignant tumors appear on the skin that is exposed to sunlight with a high frequency when patients do not carry out strict protection from UV. In the majority of Japanese patients, XP is complicated with abnormalities in the central and peripheral nervous systems, such as psychomotor retardations of which progression and severity greatly influence the prognosis. Diagnosis of XP is made with various DNA repair tests and genetic analyses. Definite diagnosis at an age that is as young as possible, sun protection education provided by professional staff, patient care, and early detection and early excision of malignant skin tumors greatly contribute to the improvement of QOL of patients and their families.

We hope that these XP clinical practice guidelines that we developed will be helpful in clinical practice.

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