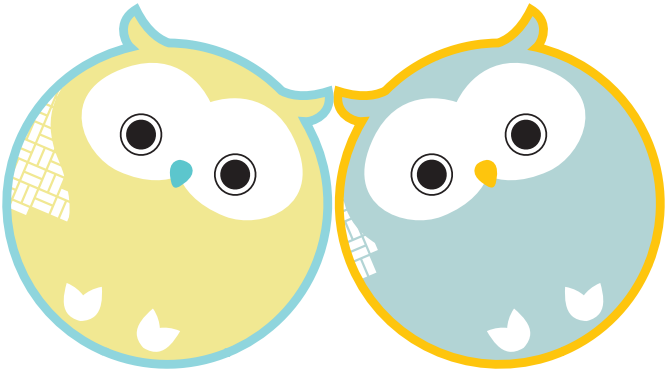
Fabry Disease Handbook

for Children



CONTENTS

■ Introduction

■ What is Fabry Disease?

- What Kind of Disease?
- Fabry Disease and Genetics
- Main Symptoms of Child Patients

■ Diagnosis of Fabry Disease

■ Treatment of Fabry Disease

- Symptomatic Therapy
- Enzyme Replacement Therapy

■ Precautions in Daily Living

■ Fabry Disease in Children

- Pediatrics
- Ophthalmology
- Neurology
- Otorhinolaryngology (ENT)
- Dermatology

■ When Your Child is Diagnosed with Fabry Disease

■ Requests to School Staff

■ Items to Stock in Preparation for Major Disasters

■ Our Experiences of Being Diagnosed with Fabry Disease

■ Activities of JFA

■ Afterword

Introduction

The Fabry Disease Handbook for Children, 1st Edition, was published two and a half years ago. We at JFA have received inputs, from patients, their families and healthcare professionals who used this Handbook, that they could improve understanding of the disease.

The recognition of Fabry disease is still very low. A child with the disease is frequently absent from kindergarten or nursery school, due to fever caused by decreased ability to sweat, severe pain in the limbs, and abdominal pain, and often cannot attend PE classes in primary and higher schools. Many children get mentally distressed, because their classmates tend to hold a prejudice to them for reasons as described above. We have prepared a revised edition of the Handbook, hoping to have more people understand the difficulties that face patients who develop Fabry disease in their early childhood, and ask for enhanced support.

Therapies other than enzyme replacement therapy are under development. It is expected that QOL of patients will improve, if the disease is broadly recognized by healthcare professionals, public health nurses, school teachers, etc., and if Fabry disease is diagnosed as early as possible, thereby enabling treatment to be started at an early stage.

We extend gratitude to all persons who cooperated in the preparation of this revised edition.

In the hope of elimination of Fabry disease from the earth

Editors

Booklet Production Project, Special Committee for Pediatric Chronic Diseases
General Incorporated Association Japan Fabry Disease Patients and Family Association (JFA)

What is Fabry Disease?

Yoshikatsu Eto

Emeritus Professor, The Jikei University School of Medicine
Director, Advanced Clinical Research Center & Institute for the Treatment of Genetic Disease, Institute of Neurological Disorders

◆ What Kind of Disease?

A patient with Fabry disease is not able to produce the enzyme alpha galactosidase, due to genetic reasons. This deficiency causes a type of lipid (GL-3) to build up in vascular endothelial cells, resulting in tissue disorders throughout the body, particularly in organs with many blood vessels (e.g. heart, kidney, and blood vessels of the brain). Large amounts of GL-3 and Lyso-GL-3 accumulate on peripheral nerves, autonomic ganglia, etc., causing severe pain in the limbs, hypohidrosis (decreased sweating ability) and other symptoms. Diverse clinical symptoms also result from accumulation in the heart, kidneys, blood vessels of the brain caused by the disease. It is possible to prevent the onset of these serious clinical symptoms through early diagnosis and treatment.

◆ Fabry Disease and Genetics

Fabry disease is inherited in an X-linked manner. The enzyme deficiency is localized on the X chromosome. When born from fathers with Fabry disease, all male children are normal, while all female children have symptoms as carriers. When born from mothers with Fabry disease, both 50% of male and female children have symptoms. Mutation is involved in approx. 5% of cases, which means that Fabry disease may occur without any other patients among relatives.

◆ Main Symptoms of Child Patients

A wide variety of clinical symptoms are observed with Fabry disease. Clinical symptoms develop earlier in male children than in female children, and

symptoms are severer. On average, symptoms of Fabry disease are observed at around six years old in male children, and at around eight in female children. From around the age of four to five years at earliest, male children have severe pain in the limbs, analgesia, anhidrosis, frequent diarrhea, abdominal pain and other symptoms. In adolescence, angiokeratoma and corneal opacity are also observed. Pain in the limbs starts earlier in some female children at three to four years of age, while many female children have no symptoms during childhood. In around adolescence, many male and female children have spoke-like corneal opacity. The height of children with Fabry disease tends to be shorter than the average. In rare cases during childhood, a valvular disease and arrhythmia are observed. Child patients also have hearing problems due to infection of the middle ear. Proteinuria is also observed in some cases. As children age and become adults, they have strong renal symptoms such as urine protein and kidney failure, as well as strong cardiac symptoms including chest pain, arrhythmia, a valvular disease, and heart failure. Symptoms are severer in male patients than in female patients. Neuropsychiatric symptoms include headache, cerebral infarction, intellectual disturbance, and psychosomatic diseases. Although otorhinolaryngologic (ENT) symptoms are rare during childhood, some children have hearing loss, vertigo, and ringing. Patients with Fabry disease have increasingly diverse symptoms as they become adults, including cough and other respiratory symptoms, and lower back pain caused by osteomalacia.

◆ Diagnosis of Fabry Disease

Characteristic clinical symptoms give a lead to diagnosis, particularly severe pain in the extremities, anhidrosis and angiokeratoma of skin in childhood. Verification of spoke-like corneal opacity is effective for the diagnosis of Fabry disease. For confirmation, deficiency of the enzyme alpha galactosidase should be verified using serum, white blood cells, dried blood spots, urine, etc. Diagnosis is confirmed when the accumulation of GL-3 in urine or blood is verified. Histopathologic examination is also important, because myelin-like accumulated mattes are observed by electron microscopy, as pathologic findings

in kidney and skin biopsy. Some female patients have no clinical symptoms, and it is also difficult to verify enzyme activity and accumulated matters in blood or urine. Therefore, final diagnosis is based on family history and genetic diagnosis in many cases.

Treatment of Fabry Disease

● Symptomatic Therapy

Pain

Pain caused by Fabry disease imposes a considerable burden on patients. Patients feel pain with burning sensation in their limbs from their infancy. Pain becomes particularly stronger during adolescence. Some female patients also start to feel pain in their limbs at the age of four to five years. Tegretol, gabapentin, and other drugs are effective.

Gastrointestinal symptoms

Abdominal pain, stomachache, diarrhea, etc. are observed. Administration of an antiflatulent is effective. Also take care of diet.

Cardiologic symptoms

Although cardiovascular symptoms are rare during childhood, some children feel chest pain. Also check for arrhythmia by electrocardiography. Cardiomegaly and a valvular disease occur during childhood in rare cases. It is important to take an echocardiogram. In adulthood, symptomatic therapies are performed for cardiomegaly, heart failure and arrhythmia. A pacemaker is effective for bradyarrhythmia. For myocardiac protection, administration of ACE inhibitor or ARB is recommended. It is important to prevent high blood pressure and hyperlipidemia. While renal disorder is rare during childhood, proteinuria is observed in some cases.

Some patients develop kidney failure in their teens. Proteinuria is

observed in many male patients in their 20s. Some female patients also have proteinuria. ARB and ACE inhibitor are said to be effective to protect kidneys. Low-protein and low-salt diet is required. For kidney failure, peritoneal dialysis, blood dialysis, and even kidney transplantation may be performed.

Symptomatic therapy for cerebral infarction: A child may suffer cerebral infarction, though rarely. Take a head MRI at least once a year. For an adult patient, aspirin or an anti-platelet drug may be administered as an anti-coagulant therapy to prevent cerebral infarction.

Others

In rare cases with child patients, vertigo and hearing loss are observed. Merislon is sometimes used for vertigo, and steroids for sudden deafness.

● Enzyme Replacement Therapy

For enzyme replacement therapy, two alpha galactosidase A enzyme preparations have been developed through genetic engineering methods to date: Agalsidase alfa (Replagal) and Agalsidase beta (Fabrazyme).

As for when to start enzyme treatment, it is desirable to start immediately following diagnosis for male children. This is mostly at the time of entry into primary school. The earlier treatment is started, the better tissue disorders can be prevented. In the case of female children, enzyme treatment should be started at around 20 years old, if they have pain or other symptoms.

A dose is 0.2 mg per 1 kg of body weight for Replagal, and 1 mg of intravenous administration once every two weeks for Fabrazyme. Possible adverse reactions include urticaria, chill, nausea, nasal discharge, mild blood pressure decrease, and unpleasant sensation in the airway. These are usually alleviated by the administration of an antihistamine or steroid. In many cases, adverse reactions are observed three to five months after administration, and alleviate later.

Effects of enzyme replacement therapy

1. Effects on pain: Pain tends to be relieved. Decreased sweating tends to be improved.
2. Effects on kidneys: The accumulation of GL-3 is removed, particularly in vascular endothelial cells in kidneys. Accumulation in podocytes is removed and renal function is maintained at a normal level, if treatment is started in childhood.
3. Effects on cardiac function: If enzyme replacement therapy is started at an early stage, myocardial hypertrophy and left ventricular mass are reduced. Improvement is also observed in left ventricular function.
4. Effects on cranial nerve system: Few symptoms are observed during childhood, except headache, etc. Early treatment prevents severer neurologic manifestations. Early treatment may prevent cerebral infarction and other cerebrovascular symptoms.
5. Otorhinolaryngologic symptoms: Few symptoms are observed during childhood, except vertigo, ringing, etc. Improvement through enzyme treatment is not clear.
6. Ophthalmologic symptoms: Both male and female children of school age often have corneal opacity, which sometimes gets alleviated through enzyme treatment. Care must be taken that loss of sight may be caused by retinal artery occlusion as children get older.
7. Skin symptoms: In particular, angiokeratoma is sometimes observed during school age. Enzyme replacement therapy seems to have little effect. However, enzyme treatment has effect on decreased or absent sweating, and QOL is improved through sweating.
8. Effects on gastrointestinal symptoms: It has been reported that diarrhea, etc. are improved through enzyme replacement therapy. Diarrhea and abdominal pain tend to be improved. In any case, various symptoms caused by Fabry disease may be prevented by starting enzyme replacement therapy at an early stage.

Precautions in Daily Living

Diet

Because lipid gets accumulated on vascular walls, it is preferable to minimize the intake of food that richly contains neutral fat (e.g. fatty meat, fried food). To prevent the accumulation of lipid peroxides, eat food that richly contains vitamins (e.g. vitamin C, B1, B2) (e.g. vegetables, fruits). It is also undesirable to eat too much rice. Avoid taking excessive calories. Many male patients have diarrhea. Refrain from eating indigestible food (e.g. beans, lardy meat, burdock and other hard vegetables). Adults have a lower level of lactase, and therefore tend to cause diarrhea by drinking milk. Take care not to consume too much hot food, spices or salt. Try to get used to lightly-flavored food.

Response to various symptoms (tips on relieving distress and observing your child)

Pain is the most difficult for a child to endure. Children feel more intense pain in summer due to heat. They also get sick, because they have decreased sweating ability.

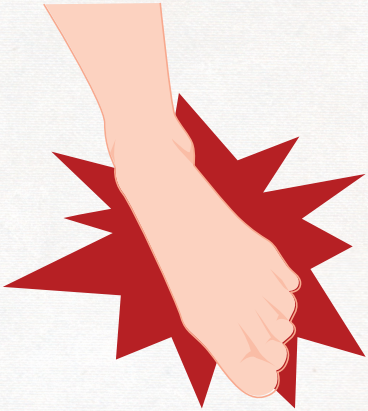
Have them stay in shades or air-conditioned rooms as far as possible, because they cannot sweat in hot rooms or under the blazing sun. Have them drink as much water as possible. A fever causes severe pain in their limbs.

When pain is excessively severe, use an antipyretic. Cool down burning sites on the limbs with towels, etc. Pain develops on various sites of the body. While extremities are the most common sites, pain may also be felt in the stomach, lower jaw, back, and other parts of the body. While the administration of Tegretol is the most effective, it is also helpful to apply Loxonin tape, etc. Some people experience side effects of Tegretol. The side effects include rash, urticaria,

weariness, drowsiness, liver dysfunction, and blood disorder. Avoid the excessive taking of Tegretol, Loxonin, etc.

Response to other diseases (e.g. influenza, appendicitis)

Patients with Fabry disease need to take care of infectious diarrhea and other diseases in summer. While diarrhea frequently occurs as a symptom of Fabry disease, viruses of summer cold (e.g. ECHO viruses, Coxsackie viruses, Adenoviruses) cause diarrhea as a cold symptom. Care must also be taken of bacterial diarrhea caused by food poisoning bacteria (e.g. Campylobacter, pathogenic E. coli). Children frequently have abdominal pain. Sometimes, assumed common abdominal pain of Fabry disease actually turns out to be appendicitis. Ileus and other serious diseases are also possible. Consult a doctor in the case of severe abdominal pain. In winter, influenza and other diseases often cause fever. Fever enhances intense pain. However, it should be avoided to use excessive antipyretics during influenza, because it increases the risk of influenza-associated encephalopathy. Pursue early diagnosis, and use influenza-specific medicines.



Fabry Disease in Children

Pediatrics

Masahisa Kobayashi

Lecturer, Pediatric Research Course, The Jikei University School of Medicine
Ward Director, NICU

Fever and pain in the extremities are the most frequent symptoms in patients with Fabry disease. Almost all male patients with classical Fabry disease experience both fever and pain in the extremities before and during school age. Fever is caused by decreased ability to sweat. In particular, patients do not like exercising on hot days, because heat tends to build up on hot summer days. They tend to prefer exercising in winter. Pain in the extremities is the hardest symptom for patients. Due to the absence of objective scales, their symptoms are sometimes confused with rheumatic diseases, gout, psychosomatic diseases, or malingering, adding to the suffering of patients. Many patients complain about attacks of "burning pain," which are said to be exacerbated by temperature changes, fever, physical exercise, fatigue, stress, and other causes. Patients become depressed due to this pain, and sometimes even commit suicide in severest cases. For fever, ambient temperature (room temperature) needs to be adjusted by air conditioning or other means, because patients are incapable of thermoregulation due to decreased sweating ability. For pain in the extremities, carbamazepine, gabapentin and other antiepileptic drugs are considered to be effective. To minimize exacerbation factors such as elevation of body temperature and changes in ambient temperature, it is recommended to use air conditioning, prevent bathroom temperature from rising too high, and use adequate protection against the cold in winter in order to avoid sudden contact with the cold outside air.

Diarrhea and abdominal pain are also relatively frequent symptoms that are reportedly observed in more than half of male and female patients. Abdominal pain tends to start in younger ages, at around ten years old. Compared to abdominal pain, diarrhea tends to start later, at 20 years of age or later. The frequency of diarrhea rapidly rises after 30 years old. These gastrointestinal symptoms often follow meals. This often causes patients to eat less, resulting in the loss of appetite and weight. For these gastrointestinal symptoms, symptomatic therapies are performed including the internal administration of antiemetic drugs, gastrointestinal analgesics and antispasmodics, antiflatulents, etc. However, the treatment effects of these drugs are unknown, and no clearly effective therapies are available at present.

Ophthalmology

Satoshi Goto

Lecturer, Ophthalmologic Course, The Jikei University School of Medicine
Visiting Lecturer, Omori Medical Center, Toho University
Part-time Lecturer, Ophthalmology, Tokyo Women's Medical University
Part-time Lecturer, Ophthalmology, Juntendo University Urayasu Hospital

Ophthalmologic effects of Fabry disease are relatively insignificant. Vision may be impaired in the case of cerebral infarction or vascular disorders in a nerve membrane in the eye called "retina." However, vision impairment is very rarely caused by corneal verticillata that is well known for Fabry disease, or by Fabry cataract.

It has been reported that corneal opacity caused by Fabry disease

develops by the age of four in male children, and by ten in female children.

There are no particular precautions in daily living. If a child suddenly loses vision, cerebral infarction or retinal vascular disorders are possible. Consult an ophthalmologist near you. It is rare that visual impairment develops in both eyes. Cover one eye at a time to confirm low vision. Fabry disease is not associated if low vision has been caused by hitting an eye on something.

Corneal verticillata occurs on a relatively superficial layer, and therefore is not considered to affect endothelial cells at the back of the cornea. Detailed long-term ophthalmologic course of patients with Fabry disease has yet to be identified. If child patients get older and want to put on contact lenses, my personal opinion is that they may, on condition of careful follow-up observation. Of course they need to carefully handle contact lenses, just as normal children do. When there is unpleasant sensation in the eye, glasses should be used instead of contact lenses. It should also be avoided to go to sleep before taking off lenses. There are different opinions concerning when treatment should be started. It is recommendable to seek regular prescription and follow-up observation through consultation with an ophthalmologist.

Neurology

Masaru Kawano

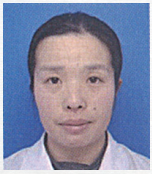
Head of Neurology, Fuji City General Hospital

Patients with Fabry disease complain about headache from their childhood relatively frequently. However, the frequency and characteristics of their headache have yet to be clarified. It often occurs that headache of patients

with Fabry disease is misdiagnosed as truancy or a psychosomatic disease. There are various causes for children's headache. There is no type of headache specific to Fabry disease. In most cases, it seems to be tension headache that only requires follow-up observation. However, there are rare cases where children in their adolescence have a cerebrovascular accident (e.g. cerebral infarction, white matter lesion). In other cases, it is important to effectively ask questions to your child when s/her complains about pain, in order to avoid missing a migraine, meningitis, etc. Did pain start suddenly? Did it grow gradually? Do you have a fever or runny nose? How long does pain continue? Where does your body hurt? All over your body? Around the temples? Did you see sparkling dots or hear large noise before pain started? Do you feel nauseated during pain? Can you shake your head from side to side? Can you nod? Is there a problem in moving your arms and legs?

In the case of a migraine, it is commonly observed that 1) it starts suddenly, 2) without a fever, 3) continuing for about an hour, 4) around the temples, 5) preceded by signs, and 6) often involving nausea. In the case of meningitis, 1) headache grows gradually, 2) with a high fever, 3) hurting continuously, 4) all over the head, 5) with no preceding signs, 6) involving nausea, and 7) making it impossible to nod due to severe pain. If 8) there is a problem in moving the limbs, a lesion may have occurred in the brain. In any of the cases above, consult a specialized doctor at an early stage.

Otorhinolaryngology (ENT)



Yuka Sakurai
Otorhinolaryngology, Jikei University Hospital

Otorhinolaryngologic symptoms of Fabry disease include hearing

loss, ringing, and vertigo. Hearing loss typically starts at around 30 years old, while ringing is reported from a relatively younger age. It must be noted that infants very rarely complain that they have a ringing in their ears. Suspect that your child may have ringing when s/he expresses "I hear a strange sound," "My ears screech," etc. Ringing usually develops together with hearing loss, but is sometimes perceived without it. First, it is required to confirm whether or not the child has hearing loss. It is recommended to take a hearing test in a department of otorhinolaryngology (ENT).

Although hearing loss starts past 30 years old in most cases, a possibility of hearing loss during childhood cannot be denied. It is characteristic to hearing loss caused by Fabry disease that it proceeds gradually, with repeated sudden and rapid deterioration. Children complain about hearing loss in a variety of expressions. Suspect hearing loss when your child complains, "I cannot hear," "My ears are plugged up," "I hear sounds strangely," "I hear a strange sound in my ears (in which case suspect ringing)," "My ears feel strange," etc. In addition, even if the child him/herself complains about nothing, hearing loss is also possible when the child does not turn around when s/he is called to, asks again many times, pronunciation is incorrect, or volumes up TV excessively. If any such symptom concerns you, it is recommended to take a hearing test in a department of ENT. Vertigo may also occur during childhood. There are various possible causes for vertigo, including an inner ear problem, cerebrovascular accident, and autonomic symptom. Vertigo is suspected when a child staggers, cannot walk straightly, or tumbles frequently.

When hearing loss deteriorates rapidly, hearing ability may be improved by receiving treatment similar to that of sudden deafness. In some cases, hearing is not be recovered even through treatment. Treatment of vertigo varies by its cause. There is no specific medicine for ringing. Unless daily living is substantially disturbed, only follow-up observation is performed. If a patient is extremely distressed by ringing, a symptomatic therapy may be performed (e.g.

administration of a tranquilizer).

Dermatology

Arifumi Ota

Head of Department of Dermatology, The Jikei University Katsusika Medical Center
Associate Professor, Dermatologic Course, The Jikei University School of Medicine

Fabry disease was first reported by a German physician, Johannes Fabry, in 1898. Small hemangiomas (dilated blood vessels to be exact) that involve hyperkeratosis in the cornified layer diffusively develop in the trunk. This symptom is therefore called "angiokeratoma corporis diffusum." This angiokeratoma is characteristically distributed in a swimming-suit shape, across the lower abdomen, thighs, external genitals, and buttocks, but it sometimes also occurs in the limbs. The size of petechia ranges from small red dots to 5-mm red spots. The redness may be thickened or thinned depending on blood flow. Angiokeratoma usually starts in the teens, and the number and size of dots/spots gradually increase. The number exceeds several hundreds of thousands at largest, but may be fewer than 30 at smallest. Many patients develop no hemangioma at all. Patients suffer decreased sweating ability from their childhood, and sometimes have a heatstroke. These skin symptoms are caused because globotriaosylceramide builds up in lysosomes in vascular endothelial cells and dermic cells in the skin, just as in kidneys, causing dilation of capillaries and secondary hyperkeratosis on the same site. Because sweat glands are also impaired by intralysosomal accumulation, patients suffer hypohidrosis or anhidrosis (decreased or absent sweating). On the other hand, patients with hyperhidrosis (excessive perspiration) have also been reported.

Fabry disease cannot be diagnosed based on skin rash only. It is

not possible either to distinguish it from other lysosomal storage diseases that manifest diffuse angiokeratoma in the trunk. While findings by electron microscopy are also important, it is required to measure enzyme activity (alpha galactosidase A activity) using plasma or white blood cells.

(Reference) Kanzaki, Tamotsu. Updated Compendium of Dermatology 10: Endocrine and Metabolic Disorders (Carbohydrate Metabolism and Fabry Disease). Tokyo, Nakayama Shoten, 2003. pp.74-77.

When Your Child is Diagnosed with Fabry Disease

It is very natural that you get taken aback at a disease name that you have never heard of, but keep your calm and accept the fact. Understand that this is a genetic disease, and check if anyone in your family or among relatives has similar symptoms. If there is someone who has similar symptoms, it is necessary to notify the person of the possibility of Fabry disease, but this is by no means an easy task. Reaction varies by person, from accepting at once to horrified rejection. To your child who has been diagnosed with Fabry disease, tell that the disease has been identified and there are available therapies in a positive manner, after suffering from various symptoms without knowing the disease name or how to treat it. If the child has siblings, they may also be patients. Girls usually have milder symptoms. The Japan Fabry Disease Patients and Family Association (JFA) also provides various information. Do not get scared or depressed based on incorrect knowledge.

■ Tips on daily living

At home

Symptoms vary by child. Take care to minimize your child's distress. Children who have decreased sweating ability feel pain when it is hot. Use air conditioners and keep it cool for your child. They also tend to have diarrhea. Avoid food that contains many additives, and make a point of well-balanced meals.

At school

Temperature in a classroom is not always appropriate for your child. Consult school staff for a well-ventilated seat, uniform arrangements, stocking dedicated cold packs in the school infirmary in summer, and other considerations.

In particular, commuting and PE classes in summer should be tough for a child with Fabry disease. It is also necessary that the child, his/her guardians, and school staff should adequately discuss procedure to be taken in response to an episode of pain in the limbs, etc., as well as administration of medicines. It is not possible to deposit Tegretol or other analgesics with a schoolteacher and have it provided to a child in the case of a pain attack, due to violation of the Medical Practitioners Act. If your child has not yet gotten familiar with taking Tegretol, etc., ask a school nurse to observe him/her while taking it in order to prevent an accident. Your child is ultimately required to manage his/her health conditions by him/herself. It is important to teach your child how to handle medicines and manage their health from an early stage, under the direction of a doctor.

In higher school years, your child may find that s/he cannot do the same activities as his/her classmates, or feel irritated or anxious because s/he cannot do what they want to do, during field trips, school excursions, athletic meets, hiking, studies, etc. It distresses a child both mentally and physically, more than anticipated, to have a disease while acting in groups. It is important to respect your child's feelings, and prepare an environment that helps his/her learning, including participation in school events within a reasonable range. School is an important place for children where they spend more than half of the day. Your child may still have some distress from time to time. Make necessary arrangements so that your child can report his/her condition and feelings to school staff or guardians without hesitation, and that adequate support is efficiently provided.

■ Learning

Some children need to frequently leave early or be absent from school, due to hospital visits and poor condition. Even home learning is difficult depending on their condition, causing a serious delay in learning. Frequent absence gives rise to concerns and stress that they cannot go to school, cannot play with their friends, lag behind in studies, and so on. Delay in studies affects the selection of career path in the future. Therefore, it is necessary to devise how to recover the

delay at school or at home. The amended Act for Special Support for Children with Pediatric Chronic Diseases searches for solutions to this problem. Look up and utilize support from the relevant public organizations.

■ Care during adolescence

It is difficult to accept our own disease even in adulthood. Even healthy children become hard to please during adolescence, and often disobey their parents and rebel against society. Especially children with a genetic disease such as Fabry disease are faced with many concerns about their health, higher schools, employment, marriage, giving birth and other future events, as well as problems that are difficult to resolve. Guide your child so that they can consult many people for ideas and resources when they hit the wall, and help them develop capabilities to examine and resolve problems. Also consider leveraging public services.

Requests to School Staff

Fabry disease is a genetic disease. It is difficult to identify children with Fabry disease by appearance, because they look just like normal children. However, they get tired extremely easily, and report episodes and sickness depending on the weather or physical condition of the day. In almost all cases, they report sickness suddenly, which often causes other children to misunderstand that a child with Fabry disease is trying to play truant or neglect classes, because s/he looked just fine until a little while ago. Sometimes classmates actually say so to the child. When such experience is repeated, prejudice or bullying may result. A child with the disease often makes efforts to do the same activities as others, but fails. A child gets caught in a dilemma through such experience, resulting in reluctance to make friends, stressful school life, and hardships that mentally hurt the child.

Children with Fabry disease are making best possible efforts to accept their physical condition and the situation in which they are placed, and to do whatever they could do in that situation. School staffs are requested to take reasonable considerations to respect a child's will and intention in school events and activities. Please focus on the personality of a child, rather than his/her disease, by acquiring the correct understanding of Fabry disease, instead of getting scared of it. It is sincerely requested to motivate a child to learn, and to develop his/her good points and strengths leveraging teachers' skills and experience. A child with a disease tends to fail in developing self-esteem. For a child to have a delight and fulfilling school life, understanding by teachers and friends is indispensable.

Guardians of a child send him/her out to school every day, filled with concerns about their child's possible sudden sickness. This does not mean that they want their child to be overprotected. They hope that their child can safely stay and learn at school, in harmonization and cooperation with other children. While some special considerations may become necessary from time to time, it is requested that school staff should treat a child with Fabry disease in the same manner as other children as far as possible. To this end, all teachers and related persons at school are sincerely requested to understand and support a child with Fabry disease.

Items to Stock in Preparation for Major Disasters

■ Stock of medicines and medications

At the time of earthquake or other disasters, medicines will become difficult to obtain, because prescription sheets are not available due to the collapse of hospital buildings or interruption of transportation network, or because pharmacies are closed down due to the evacuation of staff. Through consultation with the doctor in charge, keep a relatively large stock of prescription medicines that are critical or indispensable. Also select a dispensing pharmacy near your home, and maintain communication on a regular basis, so that information may be provided concerning a nearby hospital where necessary medicines could be prescribed. Also be sure to keep records of medicines in a medicine notebook. This expedites information exchange.

■ Necessities for thermoregulation

At the time of disaster, life in a shelter is likely. Thermoregulation is the most difficult among other problems. A child may become ill due to failure in thermoregulation. It will be helpful to prepare a blanket, heat packs, a raincoat and rain gear, and towels with high water retention for cooling down the body. ("Shammy towels" for swimmers are excellent for this purpose. When tightly squeezed and dried, they do not generate damp smell.)

■ Evidence that you have an intractable disease

In a shelter, you need to spend many days together with a large number of people. You may have to explain that you have an intractable disease, in order to ask for cooperation and considerations from other people. At the time of disaster, information management systems of municipalities will also get confused and non-functional. Carry a note that indicates information of your medical card, prescribed medicines, contact information of your hospital, etc. A child patient may find difficulty in effectively communicating or reporting that s/he needs help from adults. To prepare for such cases, it will be helpful to have a child carry a "help card" that indicates minimum necessary information and the need for support. A note or card of a size that can be put into a wallet is easy to carry with you or your child all the time.

■ Contact means among family members

If a disaster occurs during the day, it is expected that family members find shelters in different locations. On a regular basis, discuss and confirm contact means among the family members. It is said that carrying a photo that shows the faces of all members is useful when you need to look for family members who evacuated separately. Saving such a photo in a mobile phone may not be useful due to dead battery. It is strongly recommended to carry a printed photo with you.

■ Others

You may feel reluctant to buy a gasoline can, because it is of no use in your daily living. However, an automobile is a critical means of transportation for a person with a disease. At the time of disaster, most afflicted people suffer extreme difficulties both mentally and physically, and need to cooperate with each other to endure an extended period of time. You may find it difficult to

disclose that you have an intractable disease, and ask for support or cooperation. You may not want to have your disease known to other people. However, it is extremely demanding to, for example, queue up for rationing of water or goods. You may also be asked to participate in restoration work. If your disease is not shared with other people, you may be faced with such physically demanding situation. It is also said to be acceptable to consult private volunteers and welfare volunteers about these problems. Take into account the risk of getting ill during life in a shelter, and think in advance what you should do when you or your family are faced with difficulties.

Our Experiences of Being Diagnosed with Fabry Disease

Experience essays were contributed by patients in various age groups. Contributors report what they felt and experienced in diverse backgrounds, and their essays are summarized under different themes. Their stories and feelings may differ from yours or your child's, but hopefully may be of any help for you. (March 2015)

Symptoms in childhood and what I feel now

◆ **Female, 20s**

I guess obvious symptoms of Fabry disease started at around nine years old, when I was in the fourth grade of primary school. I had practiced ballet from three years old. In the fourth grade of primary school, I felt severe pains in my hands and feet after dancing in summer. I did not feel that I could no sweat well, but my face flushed, and my body temperature did not go down until cooled with ice, after dancing in summer. Pain in my hands and feet occurred not only after ballet and other heavy exercises, but also when I had a fever. Pain was caused merely by touching futon. I barely went to the bathroom on my hands and knees, so that my soles would not touch the floor. My mother thought something was wrong, and we together visited many hospitals, but all doctors said that it was my imagination, or that they had no idea. No cause was identified in those days. The extent of pain was not so severe as to affect my daily life during primary school. When I became a junior high school student, terrible pain started after walking outside for about ten minutes in summer, making it difficult for me simply to walk. My hands and feet were always hot even in winter. I could no longer participate in PE class in any season of throughout the year. It

had not yet been identified that I had Fabry disease. I had a medical certificate issued for another disease, and had to observe PE class. Because the cause was not very clear, classmates who disliked PE were often sarcastic to me, assuming that I was playing truant. It was spring of sophomore that the possibility of Fabry disease was pointed out. I visited an ophthalmologist to use contact lenses, who issued me a referral letter to a university hospital, saying that I had something in the cornea. The ophthalmologist at the university hospital whom I consulted said that I had characteristic opacity in the cornea, which was only observed in persons with Fabry disease, or persons with the history of taking medicines for heart disease. Later, when I was a senior, I contacted by myself a pediatrician at a university hospital that had specialists in inborn errors of metabolism.

Genetic testing was conducted immediately after I consulted the doctor, and I was confirmed to have Fabry disease. At present, I am receiving enzyme replacement therapy. I was physically weak by nature, and was often admitted into and discharged from hospitals for other diseases until I entered primary school. Therefore, I did not find the symptoms of Fabry disease extremely difficult in those days. After I entered junior high school, pain in my hands and feet escalated, affecting my daily life and finally forcing me to quit ballet, which I loved so much. I was extremely sad to have to give up what I loved so much, without knowing reasons. When I was diagnosed with Fabry disease, I was more relieved for finally knowing the cause for what had been continuously wrong with me, than becoming concerned about the disease.

◆ **Male, 40s**

After the onset of Fabry disease was identified, my parents told me that they had taken me to a local hospital during my infancy, because I frequently had a fever and did not sweat. At that time, the doctor could not identify the disease, and recommended my parents to keep the unknown disease from the child. As a result, I had not recognized that I had a disease. Due

to hypohidrosis, I could not control my body temperature, and my face flushed. Classmates and teachers often asked me if I was okay, which made me feel as if I was specially treated. Thanks to this sense of superiority, I never had mental distress. (At least, I did not feel any. LOL. My mother always told me that I could not control my body temperature due to absent sweating, and that therefore I should report to teacher when I became ill, and rest in shade after pouring water over my head. I was also feeble by nature, and did not feel anything special about it. During my infancy, severe pain occurred in my hands and feet when I had a cold, and I sometimes even got cramps. I had also assumed that cramps occurred to everybody, and thought that cold was a difficult disease. Because I could not sweat, I thought that I should study hard, so that I could work in an air-conditioned room in the future.

◆ **Male, 30s**

Symptoms that I had were 1) Pain in hands and feet, physical burden caused by anhidrosis, and hemangioma during primary school; 2) diarrhea (probably I had kidney failure) and weariness in addition to 1) from junior high school; 3) cardiomegaly and declined renal function in addition to 1) since 25 years old; and 4) chronic kidney failure, peritoneal dialysis, and kidney transplantation in addition to 1) after 35 years old.

I also have pain in my hands and feet as primary symptoms, but I am living a social life without a problem through disease control with medications. Mentally, I think I am calmly living with this disease without worrying too much, owing to increased patience, control with medications, and information provided by the doctor and JFA.

◆ **Female, 30s**

In my own infancy, I could not report pain or need of water, due to an education policy that emphasized patience. Therefore I could

not ask for help, but only had to endure to the limit. After an outline of Fabry disease was known, considerations are taken so that I can rest or drink water immediately when I have pain.

I suppose that anybody sometimes attribute mental difficulties to the disease. Recalling my adolescence, I often said that I could not or did not want to do something, due to various reasons. I believe that this reaction is characteristic to adolescence, whether or not a person has a disease, and can only observed. It may help to focus on an individual child or an individual person, rather than focusing on the disease itself.

◆ **Female, 40s**

Since my infancy, I often had a fever, and suffered abdominal pain and severe pain in my hands and feet. My two brothers, who were older than me by ten years or more, as well as my mother, were also suffered from pain in their feet. The doctor in charge of my brothers suspected my Fabry disease in a lower grade of primary school. Therefore, I recognized my disease, and took care to control pain from getting severer during outings and school life. When I was small, I thought it was not fair that I had to suffer from such excruciating pain. I was sometimes enraged by my useless body. As I grew up, going through bitter feelings and experiences, my way of thinking gradually changed positively, that it would work out somehow, and I should definitely live without regret, doing what I want to do, because my disease would not cure and life is short.

◆ **Female, 60s**

In our case, the disease was caused by mutation. My 37-year-old son is a patient. When he was in the first grade of primary school, he was a goal keeper in a local football team. There were several cases where, during mid-summer games, his face flushed, had a fever, and went home in

the middle of the game. He often had a slight fever and his absence increased, forcing him to quit football.

I believe he must have been disappointed, because my son liked doing exercises. He started to complain about pain in his feet in the third to fourth grade. Our family doctor (pediatrician) said that it was growing pains, and asked questions suspecting truancy. I consulted with other mothers who had boys, but we remained in uncertainty without knowing a clear cause. In the second term of the first grade in junior high school, we visited a university hospital that was established nearby, submitting a referral letter from the family doctor. After almost one month, my son was confirmed to have Fabry disease. Subsequently, he started to take analgesics. He did not speak a lot during his adolescence in high school. Although his attitude was sometimes disobedient to the doctor in charge, the doctor always responded to my son in the same manner without changes, for which I am still grateful. Fabry disease is a rare disease, and there were no therapies back in 25 years ago, nor were seminars or JFA. I did not have adequate knowledge or understanding of the disease, either, and could not explain the disease in detail to school teachers. I suppose teachers were also at a loss how they should treat my son. We knew of any other patients, and could merely depend on the doctor in charge. We always lived with worries about the disease.

◆ Male, 20s

I did not sweat since I was a kindergartener. When it was hot, heat accumulated in my body, and my hands and feet ached. (Looking back,) I also often had diarrhea, which suggests that I had gastrointestinal disorders to some extent. Until I was diagnosed with Fabry disease in the second grade of high school, I merely assumed that it was my natural constitution. Because classrooms in primary and junior high schools were not equipped with air conditioners, I stayed in school infirmary during almost all classes. Although I am receiving enzyme replacement therapy at present, only very subtle improvement has been seen in perspiration.

◆ **Male, 10s**

Since around the fourth grade, numbness starts in the evening, and develops into tingling pain in my hands and feet. I sometimes feel nauseated when I wake up in the morning. I feel refreshed after vomiting, and nausea does not last. I also have abdominal pain on some days, but do not need to be absent for that reason. I started to receive infusion therapy when I was in kindergarten. Because my mother has persistently told me to take care of my health by myself, I rarely left pain until it became very severe, except when I had a bad cold or influenza. I take medicines in advance when I perceive something strange.

◆ **Female, 40s**

In our case, my son was diagnosed with Fabry disease at first. My elder brother had also suffered from the same symptoms for many years. My brother visited various hospitals since his childhood, and was tested in university hospitals, but the disease name was not identified. My son gradually developed symptoms similar to those of my brother, and was examined in large hospitals, but his disease name was not identified, either. When my son was finally diagnosed with this disease, after my repeated requests, I was more relieved that there were therapies, than any other feelings.

◆ **Female, 70s**

I guess symptoms of Fabry disease started when I was in the fifth grade of primary school. It was shortly after World War II, and my family was poor. It was difficult to visit a large hospital in those days. I had severe pain in my hands and feet, and its cause was never identified. Only aspirin was prescribed when I had pain, and all I could do was endure while cooling my hands and feet and other parts of the body with ice. Pain gradually eased down after I started working and became older than 40 years of age.

Feelings to family

◆ **Female, 30s**

My 11-year-old son was present when definitive diagnosis was issued. The explanation of test results meant definitive diagnosis. Partly due to lack of my considerations, my son suddenly came to know his disease without adequate prior information or emotional preparation. When the disease is known after a child becomes a certain years of age, I suppose care must also be taken of notification of the disease in its true sense (acceptance by the child). To this end, parents are seeking information from various sources, and sharing it, as their daily efforts to facilitate notification of the disease in its true sense (acceptance by their child). Presumably many persons feel the most difficult until definitive diagnosis is issued. Therefore, support during that period would be extremely important. Based on the regret from diagnosis of my son, I asked a genetic counselor to accompany my daughter's genetic testing, and participate in explanation. When I ask her about what she felt at that time, she says that she could feel nothing would change even if she had Fabry disease. Reaction would vary by the type of a child, but these arrangements seem to have worked positively for my daughter.

◆ **Female, 20s**

I looked for a specialist by myself, and applied for genetic testing and certification of a specified disease without consulting my parents. My Fabry disease was probably inherited from my father. However, my father and mother were divorced shortly after I was born, and I have never met my father.

When I was small, I always complained about severe pain in my hands and feet whenever I had a fever. My mother watched me and said that my father also complained about pain in his hands and feet when he had a fever. This was one of the causes that I strongly suspected Fabry disease. Even after it was verified that I had Fabry disease, my mother seems to be refusing to accept the disease itself, saying "I cannot understand difficult things." I do not want to worry

my mother as far as possible. If she cannot understand the disease, she does not have to. I would like to resolve all issues concerning the disease and make decision by myself, as far as possible.

◆ **Male, 20s**

I always had relationships with hospitals including hospitalization, and my mother always accompanied me. Therefore, I had no particular problem with diagnosis or treatment. My mother and I were both rather pleased at diagnosis, because it meant that there were therapies.

◆ Male, 40s

It was when I was 26 years old that I was diagnosed with Fabry disease. I took a health check before purchasing a life insurance policy. Because urinary protein was identified in the check, I was recommended to take kidney biopsy, which led to my definitive diagnosis. At that time, I came to know the cause for symptoms in my body, including absent sweating. Urinary protein had started in my early 20s. I sometimes accused my parents, because I thought that some measures could have taken if I knew that I had Fabry disease. Subsequently, the administration of Fabrazyme was started, and proceeded to dialysis. At present, I am thankful to my parents, who frequently visited lectures concerning Fabry disease, made many researches, and donated a kidney to me through transplantation.

◆ **Female, 60s**

My son was 12 years old when his diagnosis was confirmed. I had always suspected that something was strange about his health. When it was verified that he had a disease, I was partly convinced at the fact, and was partly shocked by the disease name that I had never heard of. I immediately

contacted a son of my cousin in Hiroshima, who was a pharmacist, and asked him to research about the disease. A professor at Hiroshima University knew about the disease, but had never examined a patient with the disease. My son himself showed no particular changes in his feelings after knowing about the disease, probably because he could live a normal life depending on his condition. My husband and I, as well as our son's grandfather, tend to be preoccupied by our son's disease. This may have caused our daughter, older by two years, to feel lonely.

◆ **Female, 70s**

In my case, my father was dead in war when I was small, and my mother told me that he had symptoms similar to mine. Although I did not know about Fabry disease at that time, I vaguely suspected heredity, and sometimes had a grudge against the late father. About ten years ago, my daughter and grandchild were confirmed as having Fabry disease, and subsequently it was also verified that I and both of my two sons also inherited the disease. Unlike my old days, we were told that there were therapies. We were immediately certified for the disease, treatment was started. I still regret that my children and grandchild also inherited the disease. I simply wish that the day would come when this disease could be completely cured.

◆ **Female, 40s**

My father had died by the time of my definitive diagnosis. I was relieved that he died without knowing that Fabry disease was inherited from my mother to me and my child. My mother was repeatedly admitted to and discharged from hospitals since I was small, and often suffered from unknown headache. Therefore, I knew the difficulty of having an unknown disease without therapies. Because of this experience, I was rather relieved when my child was diagnosed with Fabry disease, and it was told that there were therapies.

◆ Male, 10s

I think it cannot be helped, because I have a disease. There is no use thinking about it, so I just accept it. I sometimes get mad when pain is too severe, but I get along well with my parents.

◆ Male, 30s

I had no special feelings about my parents when I was confirmed to have Fabry disease. Because my parents and I visited so many hospitals until definitive diagnosis was issued, we were relieved that the disease was identified. I sometimes blamed my parents and grandmother in my adolescence. However, now that I have found a job, got married, and had a child, I have no idea of blaming them. Rather, I am extremely grateful that they frequently accompanied me to hospitals, made explanation to school teachers, apologized, and donated a kidney to me for transplantation.

◆ Female, 40s

I did not blame my parents for the inheritance of the disease, but may have taken it out on them when I was being attacked by pain. My mother, as well as both of my two brothers, who were much older than me, all had the same symptoms, at a far severer level. Whenever I suffered from attacks, my mother apologized to me, saying, "This is my fault, I'm sorry." This rather irritated me, and I thought that it was useless she apologized many times, because she could do nothing.

When I decided to live apart from my parents to go to a higher school, my mother cried and said, "I want you to stay by my side. You have a disease, and it is impossible that you live by yourself." I hated this, feeling that she was being possessive because of my disease, and I did not speak to her for about one month. I argued with my parents many times, and now I am grateful for their worries about me. I believe that my persistence must have developed through these arguments.

LOL. This disease was also inherited to their grandchild. I always talk to my parents living far from us by phone, and relieve them that we are doing fine. When my son was five years old, both he and me were confirmed as having Fabry disease. He was not old enough to understand everything, but I gradually told him many things, including future risks, after he started to receive treatment. We frequently talk about our disease in our daily life. He relieves me, saying, "This is not anyone's fault. You do not have to worry, because pain can be controlled by medicines." However, he still hates IV drips, because it is painful when an injection needle is inserted. Treatment needs to be continued over a long period of time. I hope that a needle that causes less pain or a painless therapy should be developed, so that physical and mental sufferings of patients could be improved to some extent.

Care in daily living

◆ **Female, 40s**

Unlike normal children, I could not play outside in hot season. Therefore, I made efforts in activities that could help me and develop my confidence in my future.

◆ **Male, 40s**

In my case, anhidrosis is the most difficult symptom, and therefore I avoid hot places as far as possible. Whenever I feel my body temperature rise, I cool down my body with water, and take a rest. I also notify my disease to people around me, asking, "Please help me when my face is flushed, because I cannot sweat."

◆ **Male, 10s**

During PE class in summer, I wash my head under a water tap, and sometimes put wet Shammy towels around my neck or under my

arms. I take medicines when I feel a sign of pain start.

◆ **Female, 20s**

I suppose symptoms vary by patient. In my case, even after I became older, pain starts in my hands and feet when it becomes a little warm. In particular, taking a bath causes extreme pain. Therefore, I avoid soaking in hot water throughout the year, and use shower set to lower temperature. During hot season, I need to cool down my whole body with cold water after exercises. Otherwise, a high fever starts, or my body cannot move at all due to severe muscle pain, on the following day. Therefore, I make it a rule to cool down the back of my neck, arms, hands and feet with cold water, after arriving at school and coming home during summer.

◆ **Male, 30s**

In summer, I stay in a somewhat air-conditioned environment, where a certain level of tension is maintained. I have experience that I could endure pain better and my mind was calmer, while I was at the hospital waiting for examination. When I have pain, I take a medicine (Tegretol, etc.), and measure how long it takes until it takes effect. This enables me to feel calm and avoid panicking, even when I have pain. When I go out in summer season, I always carry a plastic bottle containing mineral water, and pour it in small amounts to continuously wet and cool down the parts of my body where arteries run (e.g. left and right sides of the neck, groins, under the arms). I think this had some effect, because my body was slightly deprived of the heat of vaporization, thereby lowering my body temperature. Because diarrhea became frequent due to renal impairment that started later, I identified the locations of lavatories in commutation routes, etc.

◆ **Female, 40s**

I make all possible efforts, including preventing a cold, taking influenza vaccination every year, taking a cold medicine or painkiller whenever I have a suspicious sign, always carrying a towel to cool down my body (which could also be used for warming my body), never forgetting to drink water, taking nutrients (e.g. amino acid, citric acid, supplement) when I feel tired, choosing shoes that release heat and impose less burden (I sometimes have a fever due to external stimulation caused by sandals that have small inner bumps, for example), and avoid pushing myself too hard. I never forget to do exercises that I can do, in order to develop my physical strength.

◆ **Female, 30s**

To prevent pain from starting, I always keep our home cool. When my son was in a lower grade of primary school, he became ill outside and I carried him on my back to a remote parking lot. It was a terrible experience, because my own hands and feet also started to ache on the way. Based on the lesson learned from this experience, I make it a rule to check up a nearest possible parking place before we go out.

◆ **Male, 20s**

It is an iron rule to avoid hot places whenever possible. I always carried antipyretics and analgesics in preparation for a sudden fever. I make proactive efforts to explain my disease and its symptoms to earn understanding from people around me, so that I will least annoy them when I get ill.

◆ **Female, 60s**

My child often had a slight fever when seasons changed. Now I know that his normal temperature was relatively high due to inability

to control body temperature, but I merely thought that he had a cold due to lack of knowledge in those days. I could immediately tell that he was not fine, when he woke up and I saw his face. I simply took care so that he would not push himself too much. When he said he was fine, I trusted him. The best efforts I could do were to take care so that he would not accumulate fatigue in winter in order to avoid catching a cold, so that he would not go outside under the blazing sun in summer, and so that he would take medicines punctually.

Requests to school staff

◆ **Female, 40s**

I think my child was often absent from school. He had not been diagnosed yet, and he could receive completely the same education as healthy children. I heard that his homeroom teacher told a lie for him once at entry examination to junior high school. When staff of the junior high school that my son took examination for contacted primary school and asked, "This child seems to have been often absent. Does he have any problem?" The then homeroom teacher answered, "That is because all classroom members were absent more frequently than normal years, due to cold and other reasons. This child has no particular problem." My son may have not passed the exam without this lie of the homeroom teacher. Still today, application guides and other entrance documents sometimes indicate a requirement "healthy child." I hope that children with Fabry disease will be accepted as well.

◆ **Female, 60s**

First of all, I hope that people would know about this disease. When we are ill or have pain or numbness in our hands and feet, we also get mentally hurt by other people's assumption that we are merely playing truant. I also think that it is important that parents make efforts to explain to school staff and earn their understanding.

◆ **Female, 60s**

When my son's disease was identified in the first grade of junior high school, we notified so to a homeroom teacher, and the same teacher took care of him over the three years as a homeroom teacher. This relieved us and we are thankful to him. Because high school education was no longer compulsory, my son had difficulty in attendance requirements. He was forced to be absent or leave early often, and nearly had to repeat the same year due to lack of credits. When this happened, we immediately visited our doctor in charge, and had a medical certificate issued that explained his disease in detail, stating that it was not obvious by appearance, but was an intractable disease. We brought this medical certificate and gave explanation to the principal. The principal was a physician himself, and understood the disease. Thanks to his decision that repeating the same year would do no good to my son, he could barely graduate from high school. I suppose we should not give up in face of difficulties, but take action by ourselves to have our disease understood by people around us.

◆ **Male, 20s**

During high school, I made arrangements to receive IV drips for enzyme replacement on different days of the week, in order to earn a required number of school days. Because I was recorded as absent on a roll book, IV drips may have also affected my school evaluation. At university, IV treatment during classes and exercises is authorized, and I am receiving treatment without a problem.

◆ Female, 30s

Teachers sometimes tell my child to refrain from doing certain activities, probably from good intentions. If we ask too much of teachers in such cases, they become afraid and regard my child as difficult to

treat. I hope that teachers would observe my child if he wants to do difficult activities, and is willing to make efforts.

◆ **Female, 40s**

It was when my child was in the first grade of high school that the disease was identified. Until then, I met a homeroom teacher whenever he proceeded to a higher grade or when teachers were exchanged, and explained symptoms as his "natural physical conditions," and asked for response. Because schools were located in remote places, we took him to and from school by car in summer, so that going to school would not cause his sufferings.

◆ **Female, 40s**

I merely observed or could not participate in almost all PE classes, athletic meets, and similar events. Because we lived in a hot region, even healthy students were worn out in PE class in summer, and there was no way that I could participate. I was also told by teachers to refrain from participating in other events, because it might push myself too much. I felt out of place in many cases. I also quarreled with other students who were sarcastic to me, saying, "I envy her for being allowed to observe all exercises!"

Only swimming classes were not difficult for me, because water adequately deprived me of body heat. Unfortunately, our school did not have many swimming classes, due to frequent water outage in our region. Therefore, I went to a swimming school to develop physical strength. When I became an adult, the intensity and frequency of pain in my hands and feet were eased, and I started to sweat in large amounts. Therefore, I boldly decided to become a swimming instructor, which required much physical strength. This decision killed several birds with one stone. Thanks to continuous physical movement at work, I no longer get badly ill as I used to. As for my son, he participates in all PE classes and school events, with cooperation from school staff. They also take

care to let him take a rest during classes/events. Just like me, he started to go to a gymnastics school to develop physical strength, and became good at mat exercises. He sometimes shows models in place of school teachers. Even students whom he does not know sometimes talk to him, saying, "Oh, you are the boy of back flip!" Both of us were fortunate to be able to leverage our strengths. Other children may be good at drawing, telling stories, playing musical instruments, and so on. I hope that school staff would effectively guide them to leverage their strengths in their school life, without specially treating them. Children with a disease may not be able to do the same activities as other students at school. They may be stressed or feel inferior for that reason. Even small strengths could help them have self-confidence, and communicate well with their friends. Both my son and I have told our schoolmates, friends and neighbors that we have an intractable disease. So far, no problem has been caused by others knowing about our disease. Instead, they always help us out and take care of us when we suffer. We are extremely grateful for their frequent assistance.

◆ **Male, 10s**

To be honest, I sometimes want to use a school elevator, because stairs are difficult for me, particularly when going up. I also hope that shoes and gym wear designated by school to have high breathability. I also want to go to school by bicycle, because my feet sometimes ache from walking to school. I sometimes find difficulty when all beds in school infirmary have been preoccupied. I cannot ask other students to give away beds for me, LOL. I am also worried about going to school by train after I become a high school student in the next spring. Keeping standing for a long time should be difficult for me. Of course I know that all of these wishes are impossible.

◆ **Female, 20s**

In my case, Fabry disease was not identified until after I became a university student. Therefore, I do not think of any requests to school staff.

◆ **Female, 70s**

Commutation to school is always difficult for us. Both my husband and I were working, so we could not immediately go and pick up our son or daughter when we frequently got a call from school. They therefore sometimes came home by themselves, enduring pain, after they became junior high school students. It was also difficult for us to carry our children in a building not equipped with an elevator, or to our home, after they bodies became larger. Fortunately, my mother and relatives lived nearby, and they helped me out including observation for a short while. Frequency of pain increases in adolescence, and it will be necessary that adequate talks should be had among family members and with school staff. Unlike in old days, when it was difficult to merely explain about the disease, various materials are available at present, so it will be effective to use such items.

◆ **Male, 30s**

I hope that teachers interview a student with a special disease in advance, as to what they can do, what they cannot do, and what help is needed when doing what activities, and that collected information should be effectively shared among all teachers. If care for a student with a disease depends on reports from the student, s/he may be forced to do certain activities due to hesitance or humility. The same is the case when information is not shared among teachers. A student feels ashamed or guilty to repeat the same reports, and tends to refrain from reporting his symptoms.

◆ Male, 40s

I have two daughters. Fortunately, both of them have no symptoms except skin dryness and cracks, despite the onset of Fabry disease. Therefore, they are sending normal primary school life. In my own student days, I did not feel much mental distress, owing to good understanding by my teachers. What I want from school staff is understanding of the disease.

Care in working life

◆ Female, 40s

I have experienced various jobs, including retail customer service, printing industry, office clerk, and sports instructor. I cannot write that I have an intractable disease in my c/v. After a certain period has passes since my employment, I disclose that I am receiving treatment for an intractable disease. This is always the case with me.

I once tried to open up from the beginning. However, when I shared the disease during a job interview, questions often focused on my physical strength, and no positive replies were received, though I do not know for sure whether it was because of my disease. This may be natural, because it was difficult to report absence frequently in any of those jobs. When I tell my colleagues, "I cannot tell this to management executives, but honestly I ...," they are surprised at first, but usually follow-up on me with understanding. I particularly endeavor to completely take care of my health. I also endeavor to maintain favorable interpersonal relationships, so that I could ask for cover-up when I become extremely ill. The most difficult problem is how to visit the hospital. It is often the case that I cannot take days off on other than specified days of the week. If I make an appointment for tests in addition to IV drips, scheduling sometimes becomes difficult, and I cannot rest at all on days off. I also take all qualifications required for each job. It is good to have qualifications that I can list on a c/v, and they are also effective in job interviews. They sometimes turn out helpful in different jobs. There must be many persons who have intractable diseases,

but can make efforts and have more excellent abilities than others. I hope that, in future society, more companies will correctly evaluate the abilities and motivation of applicants, rather than regarding their diseases as handicaps, and employ them for proactive utilization.

◆ **Male, 30s**

I have always worked indoors, so there was no occasion when I had to go out under the blazing sun. I can also apply for days off in advance at my workplace, so there have been few problems in making appointments for hospital visits.

◆ **Male, 40s**

I have endeavored to work in air-conditioned rooms since my childhood, and therefore I have had no particular difficulties throughout my career to date, which has ranged from a programmer to a visiting troubleshooter for PCs, and to a self-employed PC repair shop. I also worked part-time in a gas station for nearly seven years, but I avoided heat by taking evening or later shifts in summer. The key point would be to avoid hot hours and places, and to notify our weak points to people around us, so that they would understand and help us avoid heat.

◆ **Female, 70s**

Pain did not start suddenly or continuously, and it was difficult for me to explain to people around us, so I hid my pain, disguising if I was fine. Only medicines could control my pain, so the doses gradually increased. In my case, pain was less likely during standing work, rather than sitting work. Probably due to aging, symptoms changed as I became older. The basic precaution is not to push myself too much.

◆ **Female, 20s**

I am still a student, and cannot describe difficulties while working. However, right now I am faced with difficulties in career selection and job finding. I have done sound research at university. So far, I have been engaged in research activities, aiming to join the faculty of university in the future. However, my hearing is declining recently, probably due to the progression of Fabry disease. The largest problem at present is whether I can continue with sound research, or I have to find another way. Problems are also arising in my daily life, such as I cannot hear conversation, or I cannot notice phone calls. I went to several interviews for job finding, but sometimes I could not hear what interviewers were saying. Younger patients could make various efforts, such as finding an employment while they are relatively healthy and the progression of symptoms are not yet obvious, or to take effective qualifications.

◆ **Female, 60s**

I was confirmed to have Fabry disease after I started working. Subsequently, I changed my employment style to temp staff. Hospital visits are very difficult, because there are still very few hospitals that can examine us on Saturdays.

◆ **Female, 60s**

It took my son a few more years than other students to enter and graduate from university. He learned English in a faculty of foreign studies, and wanted to find employment in a hotel, but had to give up due to physical reasons. He took a qualification as a caregiver immediately after that. He was also qualified as a care manager while working at a special nursing home for the elderly. At present, he is working as a consultant. His workplace is quite demanding. He gets sometimes ill, and is working as if walking on a tightrope. He was hospitalized several times and caused trouble to the workplace, but has

continued with his job to present, owing to understanding from his colleagues. He has been taking immunosuppressive agents after kidney transplantation. Therefore, he takes extreme care to avoid cold and other infectious diseases.

◆ **Female, 40s**

I was physically weak, and had a fever during a two-week training camp before entry into the company. I was working as a secretary after entry into the company, and it was extremely demanding to work in line with my boss. Because it was the company motto that health management was one of our duties, I went straight home after work, without going for a drink with my friends, and went to bed at 10:00 every night. The best efforts I can make is to preserve and maintain my stamina.

◆ **Female, 30s**

In my case, I entered a dormitory as an apprentice for hairdresser. A "dormitory" meant an apartment house that the beauty parlor rented, where I lived together with my seniors. There were no employment rules, and I had lessons until late at night. Meal hours were not fixed, and standing work was extremely demanding. I was hospitalized for one month and a half for an unknown fever, but vigor during youth gave me power to go through such difficulties. However, when sickness is repeated, colleagues start to say, "Are you sick yet again?" I go to work somehow, because I do not want them to say so, mentally hits the limit, and the time comes when I have to give up. I wish that the time would come when working hours could be arranged without hesitation. I also think that support for job changing would be necessary. At present, we need to receive infusion therapy once every two weeks, which would be extremely demanding for career-oriented persons. If I would start enzyme treatment, even regularly working might be fairly difficult without ideas and efforts.

◆ Male, 20s

The largest concern is whether I could work adequately. I am worried what I should do when I cannot move due to a sudden fever or pain. To alleviate such worries to some extent, understanding from managers and colleagues would be necessary. While some symptoms are difficult for other people to understand, we will need to earn their understanding little by little.

Messages to children who will start treatment and their families

◆ Male, 30s

It is recommendable to collect information concerning the disease from doctors and JFA. It will be extremely helpful not only to collect medical information, but also to meet patients in person, and listen to actual care that individual patients are taking.

◆ Female, 40s

I suppose that it is extremely demanding to have Fabry disease. However, it is not a bad luck to be diagnosed with Fabry disease. It means that there are therapies. You can meet doctors and fellow patients who will share difficulties that you have suffered from. I myself met a lifetime friend in an infusion room. I also came to know a doctor who relaxes my heart after hardening once every two weeks.

◆ Female, 60s

Today, we can collect information on the Internet. We also have JFA, so we can participate in seminars and other events to understand the disease, and be positively affected through meeting and talking with fellow patients and their families. Warm relationships are also developed through long-term exchange. I have two granddaughters, who are all carriers, but medicine is

advancing day by day. I believe that curative treatment will be established five or ten years later, and new drugs will also be developed. I have many expectations for doctors and pharmaceutical companies.

◆ **Female, 20s**

I am still a student, and have to make many decisions concerning employment, marriage, giving birth, and so on. I am studying about Fabry disease little by little, because I think that any knowledge about the disease would help me make decision concerning treatment and career path. Mental support in life with a disease probably differs from patient to patient, such as family, friends, job, and so on. I hope that every patient would find a mental support that helps them.

◆ **Female, 30s**

There is no disappointment. The day will definitely come when you feel that you were lucky to be born in today's world. You are not alone, either. Many people are spending their lives to develop future treatment for us. If you feel negatively, we at JFA are beside you. This is no one's fault. You do need to blame yourself, either. Thank you for being born. I sincerely hope that this message reaches you.

◆ **Male, 40s**

Honestly I feel sorry to my wife and children, but I hope that they recognize the actuality and live brightly.

◆ **Female, 40s**

I have taken care so that my child could meet many people, live positively, and always live with smiles, without getting depressed by his disease. There is no use regretting the disease. I always want to accept the disease and live positively. Accept your disease, and learn about your disease. Fabry disease is a very rare disease that many doctors do not know about. Collect information from the Internet and other sources as to what kind of disease it is. The Japan Fabry Disease family and Family Association (JFA) also provides various information. You should not get scared or depressed at incorrect knowledge.

◆ **Male, 20s**

The requirement for periodic infusion may annoy you at first. However, you may think of spending that time on something useful. For example, you can read books, do other hobbies, study, or make up for lack of sleep. We can rarely perceive the effect of IV drips, but it motivates us a little to think that infusion is functioning inside our body. Do not become pessimistic due to your disease. It unexpectedly delights us to think of benefits brought about by the disease! For example, we can have discounts... We live only once, whether or not we have a disease. There is no reason to enjoy it!

◆ **Female, 60s**

I hope that patients will endeavor to continue receiving treatment. I also request researchers to establish easier therapies at an early stage.

◆ **Female, 70s**

Unlike in old days, Fabry disease can be diagnosed effectively. I hope that patients can think about what they should do after knowing about their disease, rather than suffering from an unknown disease. At the same time, taking into consideration the influence caused by the disease on the entire body, it is recommended that treatment should be started before organs begin to deteriorate. Let us endeavor together.

◆ **Male, 10s**

I started infusion therapy at five years old. Honestly, I sometimes do not want to go to the hospital, because time to play with my friends decrease, and I also hate injection. However, I endeavor to continue hospital visits, hoping that the disease would cure some time. I know that all of you are suffering, but I hope that you also endeavor to continue with treatment.

◆ **Female, 40s**

Conditions are not the same among patients. They have different environments, standpoints, and feelings. Parents may feel sorry to their family. Patients sometimes hit the wall and troubled by anxiety for their child's future, their own future, and so on, more than healthy people do. My policy is to make best possible efforts I can do, and enjoy living. However, I have also wondered, got troubled, stopped, and proceeded again, in various events of my life.

I suffered the most when I knew that the disease was inherited by my child. At that time, I fortunately encountered an encouraging friend at the hospital where we received treatment. Luckily (or naturally), the friend also had Fabry disease, had a child of the same age as mine, and was of mostly the same age as me. Encounter with her encouraged me to positively receive treatment, and protect my child to the extent possible. Because both of us and both of our

children have Fabry disease, we can talk frankly. Whenever we meet, we talk a lot about ourselves, exchanging stupid jokes, consulting with each other about child care, our treatment, and ask questions such as "Recently, I have had symptoms like this. Have you?" Our children are also good friends. We often say that they could support each other in the future, after their parents are gone. Both families are members of JFA, and we have opportunities to talk with other patients. It surprises us to know that symptoms vary substantially among patients, even we have the same disease. We can also learn a lot from other patients. I think it is extremely important that patients with the same disease have opportunities to exchange. It feels sometimes difficult to receive continuous treatment without knowing when it may end. Spitting out accumulated mental stress from time to time is indispensable to maintain our mental health and continue with child care and treatment. You are not alone, either. JFA and other organizations provide support for you. Let us have a hope for the future, and join hands to continue treatment.

Activities of JFA

The former Japan Fabry Disease Patients and Family Association was established in September 2002.

The association was incorporated as the Japan Fabry Disease Patients and Family Association (JFA) in June 2014. JFA started full-scale activities as a nationwide organization. We continue with activities to help patients resolve their concerns and live vigorous lives.

< Activities in Japan >

Because patients and their families are scattered across Japan, we hold seminars and symposiums in different regions, in order to help patients collect latest medical information, and receive fair and impartial medical service at optimal healthcare settings. We operated a website, and issue periodic JFA news and topics.

- Nationwide seminars and symposiums are held in seven key areas (two districts and five blocks).
  - Hokkaido District (Sapporo Satellite Seminar), Sapporo
  - Tohoku Block (Sendai Open Seminar), Sendai
  - Kanto-Koshinetsusei Block (Tokyo Symposium, regular plenary session, and regular exchange meeting), Tokyo, jointly held
  - Chubu-Hokuriku Block (Nagoya Open Seminar), Nagoya
  - Kinki-Chusikoku Block (Osaka Open Seminar), Osaka
  - Kyushu Block (Fukuoka Open Seminar), Fukuoka
  - Okinawa District (Naha Satellite Seminar), Naha
- The Special Committee for Pediatric Chronic Diseases of JFA tackles issues of child patients.
- We also endeavor for early identification, diagnosis, and treatment of the disease, as well as for newborn screening.
- We also emphasize awareness improvement, consultation service, and information services, so that QOL of patients and their families can be

improved.

- To deepen understanding and knowledge about the disease, we hold open seminars broadly inviting physicians, nurses, healthcare professionals, administrative officers, pharmaceutical companies, supportive organizations, and the general public.
- We aim at establishing reliable systems to support all patients after onset of the disease, and help them receive fair and impartial medical service, so that all patients can live with dignity and peace of mind in all regions in a symbiotic society.

< International activities >

International exchange is extremely important in the present and future. Patients with Fabry disease also live in different parts of the world. Because it is a rare disease, we are aiming at its curative treatment through cooperation with fellow patients overseas. In May 2015, we held an international symposium in the auditorium of The Jikei University School of Medicine, with 47 participants from overseas. In concurrence, the 4th FIN Expert Meeting was held.

- Europe: JFA joined the Fabry International Network (FIN) in December 2013.
- USA: JFA has participated in the WORLD Symposium, FSIG Expert Fabry Conference in San Diego, since February 2014.
- Asia: JFA has participated in Young Leaders Seminars in Singapore since September 2013.

* Participants in overseas events are selected from members to represent JFA. Vigorous application is invited through JFA news and other media.

Invitation to Membership

The Japan Fabry Disease Patients and Family Association (JFA) invites patients and their families as its members. Periodic information magazines seminars are available. Share your feelings with us, instead of getting troubled alone.

Regular membership fee: 3,000 yen per patient and their family
Supporting membership fee: 3,000 yen per individual who supports the purpose of JFA and warmly observes patients and their families; 10,000 yen per association or corporation

[Contact] Japan Fabry Disease Patients and Family Association (JFA)
TEL: +81 80 5720 2085; FAX: +81 3 4400 5954; URL: http://www.fabrynet.jp

Afterword

Fabry disease is a rare disease, and is designated as an intractable disease by the Japanese government. Patients are scattered across Japan. It is a genetic lysosomal storage disease with inborn errors of metabolism.

Most physicians and healthcare professionals say that they have never examined a patient and do not have particular knowledge. Therefore, they treat patients assuming other diseases, resulting in no improvement in symptoms and visits to different hospitals, until they are finally diagnosed with Fabry disease after many years. The situation remains the same to date.

Children with Fabry disease look just fine by appearance. Therefore, they are often misunderstood when they complain about symptoms of the disease. They cannot even move when they have a high fever, or pain in their limbs. All they can do is enduring. They are also forced to endure mental distress, even during childhood.

Children and their guardians have explained about the disease to schoolteachers and people around them. We hope that all people proactively learn about the disease, share information concerning the disease, and provide support to children.

We wish that care should be taken so that children with an intractable disease could send their daily life and school life with more fun.
This Handbook was prepared to play such a role. Thank you for reading.

Hisao Harada, President
General Incorporated Association Japan Fabry Disease
Patientt and Family Association (JFA)

Fabry Disease Handbook for Children

March 2015: Published 1st Edition
December 2017: Published 2nd Edition

Supervised by:

Yoshikatsu Eto

Emeritus Professor, The Jikei University School of Medicine Director, Advanced Clinical Research Center & Institute for the Treatment of Genetic Disease, Institute of Neurological Disorders

Published by:

General Incorporated Association Japan Fabry Disease Patients and Family Association (JFA)

Edited by:

Special Committee for Pediatric Chronic Diseases, JFA

Cover design: Shakenabe

[Contact]

General Incorporated Association Japan Fabry Disease Patients and Family Association (JFA)

KitaMedia Associate K.K., 4-12-16-707 Hongo, Bunkyo-ku, Tokyo 113-0033

TEL: +81 80 5720 2085; FAX: +81 3 4400 5954

URL: http://www.fabrynet.jp

Nothing is better than your help.

www.fabrynet.jp