Movement Disorders

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Hong-Fu Li, Yu Lin, Hao Yu, Yi Dong, and Hong-Lei Li

Abstract

Movement disorders are a large group of diseases caused by extrapyramidal damage. Generally, movement disorders are classified into two major categories: hyperkinetic movement disorders referring to excessive, repetitive, and involuntary movements and hypokinetic movement disorders referring to akinesia, hypokinesia, bradykinesia, and rigidity. Actually, movement disorders were very common in clinical practice, with age at onset from childhood to old age. Among them, inherited movement disorders accounted for a large proportion, such as early-onset Parkinson's disease (PD), Wilson's disease (WD), Huntington's disease (HD), dopa-responsive dystonia (DRD), neuroacanthocytosis (NA), paroxysmal kinesigenic dyskinesia (PKD), pantothenate kinase-associated neurodegeneration (PKAN), and so on. Some of these disorders (such as WD, HD, PKD, etc.) have only one causative gene, while some (such as PD, DRD, NA, etc.) have more than two culprit genes. In the inherited movement disorders, neuropathology plays a less role in the diagnosis. On the contrary, detecting the disease-causing mutation is crucial for diagnosis. For example, HTT mutation is important to differentiate HD from HD-like disorders. In this chapter, we presented several movement disorders caused by genetic mutations. Some of them had typical clinical manifestations, while some are difficult to diagnose at beginning.

Keywords

Movement disorders • Parkinson's disease • Wilson's disease • Huntington's disease • Dopa-responsive dystonia • Neuroacanthocytosis • Paroxysmal kinesigenic dyskinesia • Pantothenate kinase-associated neurodegeneration

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4.1 Parkinson's Disease (PD)

A 22-Year-Old Male Complained About 3 Years of Limb Tremors

Clinical Presentations

The patient was a 22-year-old man who suffered limb tremors for 3 years. His developmental milestone was unremarkable until the age of 19, when he experienced intermittent tremor in left leg. This condition was aggravated in anxiety or stress but was disappeared in calmness and sleep. He did not take any medicine because he was diagnosed with anxiety neurosis in local hospital. One year later, he noticed involuntary shaking in his left hand and the flexibility of left limbs was decreased. He could not button his coat agilely when he got dressed. Amantadine was prescribed for him but was not effective enough in controlling his tremor. Oral administration of levodopa was then conducted, which significantly relieved his symptoms at low dose. In the following 1 year, he found that it was difficult to turn around. There was no fluctuation of his symptoms in the morning and afternoon. His olfactory function was not impaired, and he did not complain about unsteady gait, dysarthria, or memory impairment. The urination and defecation disturbance was not present. His younger brother had similar symptoms to him. His parents were not internuptial, and neither of them exhibited similar symptoms (Fig. 4.1).

Examination of cranial nerves revealed a clear utterance but stiff facial expression. His left hand and leg exhibited involuntary tremor at a frequency of 3–5 Hz. The muscle strength was essentially normal. Increased muscle tension was present in his four limbs. Gear-like rigidity was apparent in his left extremities. Sensory examination was unremarkable. Knee reflex was brisk bilaterally. Babinski sign was negative. Finger–nose and heel–knee–shin test could not be completed accurately.

Laboratory examinations revealed normal blood cell counting, hepatic function, vitamin B12, ceruloplasmin, serum ferritin, and thyroid hormones. Brain MRI scanning and EEG were unremarkable.

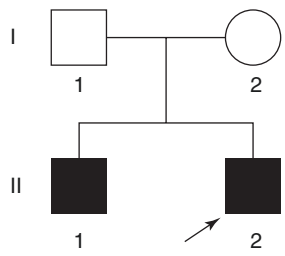

Fig. 4.1 The pedigree chart of this family. *Squares* represent males; *circles* represent females; the *black symbols* represent affected individuals; *arrows* represent the proband

Primary Diagnosis

This was a young man with predominant feature of limb tremor. The involuntary tremor, increased muscle tension, and gear-like rigidity revealed the impairment of extrapyramidal tract. Pyramidal signs and cerebellar signs were inconspicuous in the neurological examinations. Level diagnosis was thus located in extrapyramidal tract. The early onset, progressive course of disease, and positive family history implied that this patient may have suffered from hereditary disorder. Alternatively, metabolic disturbance and intoxication should be considered too. The differential diagnosis included Wilson's disease (WD), juvenile Parkinson's disease (PD), Parkinsonism syndrome, and dopa-responsive dystonia (DRD), neurodegeneration with brain iron accumulation (NBIA), and so on. Despite autosomal recessive inheritance, WD could be excluded because of normal ceruloplasmin, hepatic function, brain MRI, and absence of Kayser–Fleisher (K-F) ring. The favorable response to levodopa and normal MRI implied that Parkinsonism syndrome was less possible. No fluctuation of his symptoms in the morning and afternoon hinted that DRD should not be listed in priority. NBIA is less common in Chinese population. Therefore, PD was the paramount consideration. Genetic screenings of autosomal recessive PD should be conducted.

Additional Tests or Key Results

Targeted next-generation sequencing including 23 PD-related genes was performed in the proband. The detected mutations were further verified by Sanger sequencing. We found two

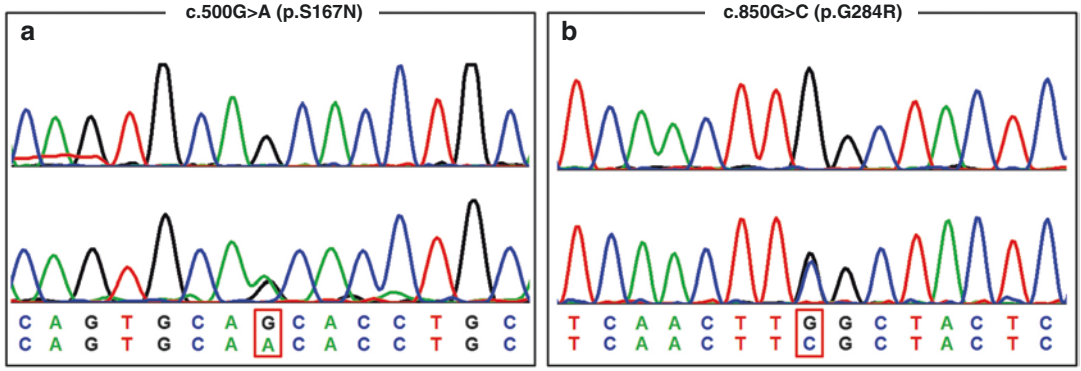

Fig. 4.2 Chromatogram of c.500G>A (**a**) and c.850G>C (**b**) mutation of *Parkin* gene. The *upper panel* depicts the normal sequence, while the *lower panel* represents heterozygous mutated sequence

compound heterozygous *Parkin* mutations, c.500G>A p.S167N and c.850G>C (p.G284R) in this patient (Fig. 4.2a, b). Further investigations revealed that his brother carried the same mutations and his father harbored p.S167N mutation and his mother carried p.G284R mutation.

Discussion

PD is the second commonest neurodegenerative disease after AD [1]. Most patients begin to exhibit symptoms after 50 years of age. However, about 10% of patients have young-onset or juvenile-onset Parkinsonism, which is generally defined as early-onset PD (EOPD) [2]. The clinical features of EOPD are not discriminative from classical PD except for the early onset [3]. Of note, the majority of EOPD cases had a positive family and harbored specific genetic mutation or variances.

The patient described here had an affected brother who had similar symptoms to him. This clearly indicated that hereditary factor should be firstly considered when we explore the etiology of his symptoms. He presented with asymmetric onset of tremor, slow progression, and favorable response to levodopa, which highly implied the diagnosis of PD. Combining the pattern of recessive inheritance, a cluster of autosomal recessive PD gene should be screened in this patient. Using targeted NGS followed by Sanger sequencing, we detected two heterozygous Parkin mutations in this patient. The co-segregation with the disease in this family further verified that this patient was a patient of EOPD.

Parkin-linked PD has variable clinical phenotypes. Generally, most cases exhibit early-onset Parkinsonism between 30s and 40s [4]. The disease usually progresses slowly, with a favorable response to low dose of levodopa. Nevertheless, patients carrying Parkin mutation are more common to develop motor fluctuation and levodopa-induced dyskinesias during treatment [5, 6]. Cognitive impairment or dementia is rare, but behavioral problems and psychiatric symptoms have been reported with variable frequency [7, 8].

Various drugs are effective in ameliorating the PD symptoms. However, selecting the optimal treatment for PD is highly individualized. Recommending drugs for early PD consists of carbidopa/levodopa, dopamine agonists, and MAO-B inhibitors [9]. Anticholinergics, such as benzhexol, are not widely used for EOPD due to the risk of cognitive damage, confusion, hallucinations, and so on.

4.2 Paroxysmal Kinesigenic Dyskinesia (PKD)

A 17-Year-Old Male Complained About Paroxysmal Attacks of Involuntary Movements for 6 Years

Clinical Presentations

A 17-year-old male complained about repeated transient attacks of involuntary movements for 6 years. He had an unremarkable birth and development milestone, with exception of febrile seizure from 8 months to 2 years old. At the age of 11, he developed sudden attacks of chorea which was first evident when he began to run in gym class. His arms extended and his hands flexed, followed by athetotic movement of his torso. He was aware of his attacks but could not control the episodes. The attacks usually lasted 20–40 s. A diagnosis of epilepsy was rendered in local hospital and valproate was prescribed for him. However, valproate did not show remarkable effect on relieving his attacks. In the following 3 years, he developed many such attacks which are usually triggered by sudden movement such as standing up, starting walking or running, and shifting position. The events usually lasted less than 1 min and occurred up 3–10 times daily. Consciousness never altered during or after attacks. He was then started on carbamazepine at dose of 100 mg twice daily, which resulted in complete resolution of his signs.

The neurological examination revealed negative signs of cranial nerves, normal muscle strength and tension, sensation, and deep tendon reflexes. The Babinski sign was bilaterally negative. Blood routine, blood smear, ferritin, and ceruloplasmin revealed no significant findings. EEG showed unremarkable findings. The brain MRI scanning was uninformative.

His father had similar attacks between 15 and 30 years old (Fig. 4.3). The involuntary movements usually occurred when initiating walking, running, or standing up. These episodes gradually disappeared after the age of 30. His mother and brother were asymptomatic. The physical examination was essentially normal in his father, mother, and brother.

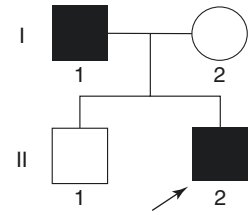

Fig. 4.3 The pedigree chart of the family. *Squares* indicate males; *circles* demonstrate females; the *black symbols* depict affected individuals; *arrows* indicate the proband

Primary Diagnosis

This case mainly presented with repeated and paroxysmal choreoathetosis. His neurological examinations, laboratory tests, EEG, and brain MRI are essentially uninformative. According to his symptoms, the localization most likely involves extrapyramidal system or cerebral cortex. A positive history with autosomal dominant inheritance suggests that heredity may be the main etiology of his attacks. His periodic, transitory, and repeated episodes highly resemble the seizure attacks or transient ischemic attack (TIA). However, the fully preserved consciousness during the attacks suggests that epilepsy is less likely. His symmetrical spells and exciting symptoms imply the little possibility of TIA. The paroxysmal choreoathetosis with undisturbed consciousness hints a diagnosis of paroxysmal dyskinesias (PDs), which include paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), and paroxysmal exercise-induced dyskinesia (PED). The patient described here had a trigger of sudden movement, consistent with the features of PKD. Screening of *PRRT2* gene was necessary.

Additional Tests or Key Results

Sequencing of *PRRT2* gene was performed in this patient. We found heterozygous c.649dupC (p.R217Pfs*8) mutation in *PRRT2* (Fig. 4.4). Further investigations revealed that this mutation was also identified in his affected father but not in his asymptomatic mother and brother.

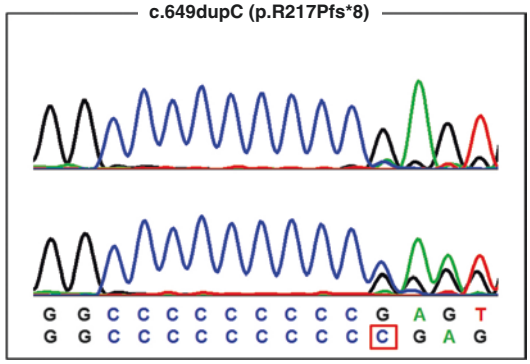

Fig. 4.4 Chromatogram of c.649dupC mutation in *PRRT2* gene. The *upper panel* depicts the normal sequence, while the *lower panel* indicates heterozygous mutated sequence

Discussion

PKD is a movement disorder with autosomal dominant inheritance and character of episodic involuntary movements which are usually triggered by sudden movement [10]. PKD attacks consist of chorea, athetosis, dystonia, and ballism, which are usually sudden, short, and relatively stereotyped. Consciousness is not altered during the attacks [11]. The frequency of episodes is variable among patients, ranging from 1 per month to 100 per day [12]. The symptoms usually commence in childhood or early adolescence and show a trend of remission with age in most cases. Stress and anxiety increase frequency of spells. It usually had favorable respond to antiepileptic drugs (AEDs), among which carbamazepine and phenytoin are priority drug. The causative gene of PKD is *PRRT2* which was located in 16p11.2 [13]. To date, more than 50 mutations within *PRRT2* have been reported, among which c.649dupC is a mutation hotspot worldwide [14].

This patient suffered from paroxysmal choreoathetosis which was usually triggered by sudden movement. The age at onset, precipitating factor, feature of attacks, and response to carbamazepine were all consistent with PKD. With the identification of *PRRT2* mutation, diagnosis of PKD is assured. PKD is the most common subtype of PDs. An important feature of PKD is the precipitating factor of sudden movement, which differentiates PKD from PNKD and PED. PNKD is usually triggered by substance like alcohol or coffee, menstruation, and strong emotion [15]. In contrast to PKD, PNKD attacks occur in lower frequency, last longer (10 min to 1 h), and respond poorly to AEDs [16]. The culprit gene of PNKD is *MR-1* [17]. PED is usually precipitated by prolonged exercise, and its attacks last several minutes (2–5 min on average) [18]. AEDs were usually not helpful for PED [19].

The good response to AEDs suggests that PKD may be an ion channel disease, although the underlying mechanisms remain largely unknown. Genotype–phenotype correlation of PKD revealed that patients carrying *PRRT2* mutations had earlier AAO and longer duration and tended to present with phenotype of dystonia and chorea [20, 21]. Among the AEDs, carbamazepine and phenytoin are the first selected drugs for patients with PKD. For the cases with *PRRT2* mutation, it was demonstrated that low-dose (50 mg/d) carbamazepine can completely resolve the attacks [20].

4.3 Dopa-Responsive Dystonia (DRD)

A 15-Year-Old Boy with Diurnal Fluctuation Abnormal Gait for 2 Years

Clinical Presentations

A 15-year-old boy came to our clinic with complaint of abnormal gait for 2 years. From the age of 13, he experienced a stiffness of right leg and gait disturbance. Two years later, he experienced stiffness and twisting in the trunk, the lower limbs, and right arm. All of the symptoms were improved in the morning, but aggravated toward the afternoon. He found it difficult to write and walk in the evening. The patient denied headaches, eyelid drooping, double vision, swallowing difficulty, or shortness of breath. His developmental history was unremarkable. He had no prior history of encephalitis, meningitis, febrile seizures, or head injury.

Neurologic examinations showed that cranial nerves were negative. His muscle strength was normal without muscle atrophy. The lower limbs muscular tension was increased. His lower limbs' deep tendon reflexes were exaggerated without ankle clonus. Hoffmann, Babinski, and Romberg signs were bilaterally negative. His deep and superficial sensation examinations were symmetric and normal. There were also no cerebellar impairment signs. The tiptoe gait was observed in the afternoon, but disappeared in the morning.

The blood routine examination was normal. Serum biochemistry analysis was normal (including lactic acid, uric acid, ceruloplasmin). The ophthalmic examinations excluded the presence of a Kayser–Fleisher (K–F) rings. The brain MRI disclosed unremarkable findings.

Interestingly, the patient's father, aged 40 years, developed similar symptoms at the age of 14 (Fig. 4.5a). The father manifested persistent posture tremor of upper extremities and torticollis around 20 years old. Whereas abnormal posture of his lower legs attenuated from his third decade. All the symptoms were mild after sleeping in the night, but aggravated in the afternoon and after exercise.

Primary Diagnosis

The patient showed muscle stiffness and twisting at the limbs and trunk; lower limbs' deep tendon reflexes were exaggerated without muscle weakness and Babinski signs. These symptoms were typically dystonia in which repetitive or sustained muscle contractions lead to twisting and repetitive movements or abnormal fixed postures. This disorder was presumed dysfunction of the basal ganglia.

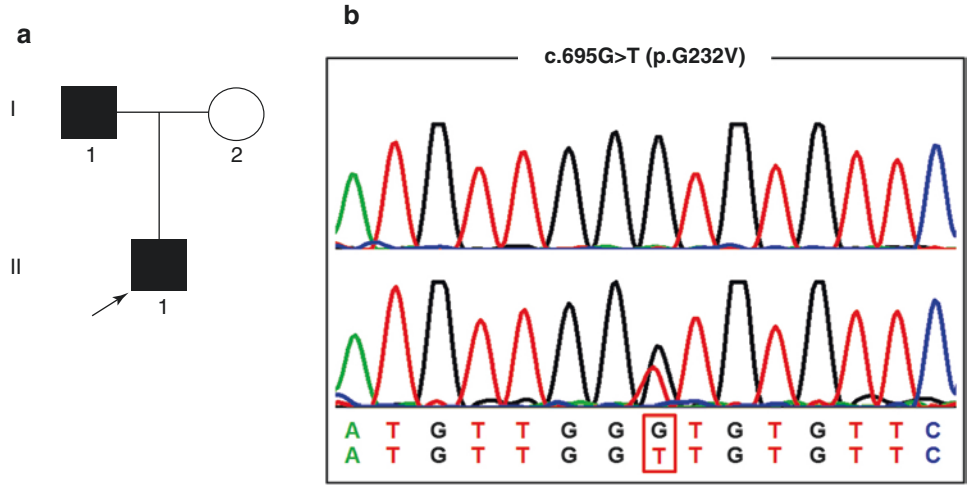

Fig. 4.5 Pedigree and mutation analysis of the patient. (**a**) The patient's pedigree chart. *Arrow* indicates the proband. (**b**) Chromatogram of p.G232V mutation within *GCH1* gene. The *upper panel* represents normal sequence of the control, whereas the *lower panel* is heterozygous mutated sequence of the patient

The disorder may be hereditary or caused by other factors such as birth related, infection, poisoning, or reaction to pharmaceutical drugs. The symptoms were childhood onset and positive family history, all of which implied that hereditary neurological disease should be considered first for this patient. The differential diagnosis includes dopa-responsive dystonia (DRD), Wilson's disease, juvenile-onset Parkinson's disease, and torsion dystonia. Wilson's disease was ruled out as the patient showed negative K–F ring and normal level of ceruloplasmin. Torsion dystonia was unlikely because the symptoms were diurnal fluctuation.

Subsequently, the trial of levodopa was propitious to differentiate dopa-responsive dystonia from other movement disorder. However, a positive response to levodopa does not differentiate DRD from juvenile-onset Parkinson's disease. Typically, patients with DRD will have a sustained benefit from low doses of levodopa without developing motor fluctuations and dyskinesia, in contrast to juvenile Parkinson's disease, in which these motor complications are a frequent occurrence. And most importantly, a gene test is necessary to confirm the diagnosis.

Additional Tests or Key Results

After treatment of 100 mg/day of levodopa for 3 days, the proband's symptoms were completely disappeared. He could walk and write normally in the evening. However, the father' posture tremor and torticollis were improved incompletely after administration of levodopa/benserazide (200 mg/day levodopa and 50 mg/day benserazide) for 10 days. The childhood onset of gait disturbance and dystonia mainly involved in lower limbs, noticeable diurnal fluctuation of those symptoms, a positive family history, and good response to levodopa strongly suggested the diagnosis of DRD. *GCH1* gene analysis by direct sequencing of PCR product amplified was performed. Both of the proband and his father carried a heterozygous mutation c.695G>T in exon 6 of the *GCH1* gene which would lead to a transition at codon 232 from a glycine to valine (Gly232Val) (Fig. 4.5b).

Discussion

DRD, also known as Segawa's disease, is a rare inherited disease with a prevalence of 1 per 2 million. This disorder is characterized by marked diurnal fluctuation, exquisite responsiveness to levodopa, and dystonia features. Clinical manifestations of DRD vary widely; patients with childhood onset may present with a posture dystonia, which typically starts in one leg. Some patients may show clubfoot and tiptoe walking due to the progression of dystonia. The symptoms can spread to other limbs in the early twenties, after which progression slows, and all symptoms reach a plateau at length. While adult-onset form may be action dystonia and parkinsonian feature, such signs may include torticollis, writing spasm, tremors, slowness of movement, stiffness, and balance difficulties. Approximately 25% of patients show abnormally exaggerated reflex responses in the legs [22, 23].

Both autosomal dominant and autosomal recessive forms of the DRD have been reported. The causative gene of autosomal dominant DRD is the *GCH1* gene located on 14q22.1-q22.2 [24]. Mutation in the gene *GCH1*, which encodes the enzyme GTP cyclohydrolase I, disrupts the production of tetrahydrobiopterin (BH4). BH4 is the cofactor for dopamine synthesis. About 50–87% of DRD cases are caused by *GCH1* mutations [25]. In the fewer autosomal recessive DRD, the mutations were reported in the genes for tyrosine hydroxylase and sepiapterin reductase. Tyrosine hydroxylase is the rate-limiting enzyme for dopamine synthesis. And sepiapterin reductase is also the cofactor for BH4 synthesis [26, 27].

In this DRD family, both of the patients have posture dystonia of lower legs in teens. However, the father exhibited posture tremor and torticollis several years later, which reflect that DRD patients have particular symptom in different age stage. The age-relative features are decided by dopa-relative pathway. It is the impairment of direct pathway and its descending output which mature early that lead to posture dystonia, while the involvement of subthalamic nucleus–internal segment and the globus pallidus–thalamus pathway that mature later causes tremor and torticollis, respectively [28]. However, these action dystonias were usually disabling and may be responsive to levodopa incompletely. These symptoms demanded further therapy, such as local injection of botulinum [29]. Therefore, early genetic diagnosis and therapy with small dose of levodopa for DRD patients in the age of adolescence may avoid developing into action dystonia later and bring patient long-term benefits.

4.4 Wilson's Disease (WD 1)

An 11-Year-Old Girl with Walking Difficulty and Slurred Speech

Clinical Presentations

An 11-year-old girl presented with walking difficulty for 10 months and slurred speech for 2 months. The girl was healthy at birth and grew up with normal developmental milestones. In the age of 10 years, the girl felt her legs were easier to get tired than usual after walking a long distance. At the same time, her parents noticed that her legs were gradually becoming misshapen with the emergence of knock-knees. Then the girl developed a knee pain while walking, which occurred more and more frequently and severely. The condition progressed so rapidly that the girl soon became unable to walk after 3 months. There were no symptoms of headache, tremors, or speech problems. Two months later, the girl underwent the orthopedic surgery for corrective therapy. However, 3 months after the surgery, she developed slurred speech, obvious drooling, slow swallowing, and writer's cramp. Her parents were worried about it and brought her to our clinic. There was no history of fever or loss of consciousness. She was not on any regular medications. Her parents and other family members did not have similar symptoms. Her parents said she had ever been hospitalized with liver dysfunction 5 years ago but had recovered and never recurred.

Neurological examinations revealed hypomimia and dysarthria. Her muscle force, tone, and reflexes were normal except an increased tone of upper limbs. Babinski sign was bilaterally negative. There were no signs of ataxia or sensory abnormalities. Routine blood count, liver and renal function, thyroid function, and serum electrolyte were normal. Notably, the abdominal ultrasonography showed a diffuse liver disease with nodules.

Primary Diagnosis

The history and examination revealed a bone deformity, liver disease, and neurological problems in childhood. The drooling, dysphagia, hypomimia, dysarthria, and increased tone in upper limbs suggested the impairments of extrapyramidal system. The differential diagnosis included Wilson's disease (WD), juvenile Parkinson's disease, early-onset primary dystonia, dopa-responsive dystonia (DRD), Niemann–Pick disease type C (NPC), drug effects or toxicity, central nervous system neoplasia, and hereditary ataxias. The multiple organ involvement implied the metabolic disorder like WD and NPC. However, the intact cerebellar function made the diagnosis of NPC highly unlikely. Brain imaging and biochemical tests were helpful to distinguish the WD with other non-metabolic diseases.

Additional Tests or Key Results

The serum ceruloplasmin was markedly decreased to level of 40 mg/L (reference, 200–400 mg/L), which highly suggested a diagnosis of WD. The serum copper was also lower (0.2 μg/mL) than normal (reference, 0.8–1.9 μg/mL). Her urinary copper of 24 h was elevated (484 μg, reference 0–100 μg). The ophthalmic examination confirmed the presence of Kayser–Fleisher (K–F) ring in her corneas (Fig. 4.6), which was sufficient to establish the diagnosis with the decreased ceruloplasmin. Consistently, magnetic resonance imaging (MRI) of the brain showed symmetrical T2-weighted hyperintense lesions in bilateral basal ganglia and thalami (Fig. 4.7). In addition, the *ATP7B* mutation analysis found compound heterozygous mutations, c.2621C>T (p.A874V) and c.2975C>T (p.P992L), which confirmed the diagnosis of WD (Fig. 4.8). The biallelic mutations were verified by the analysis of family members.

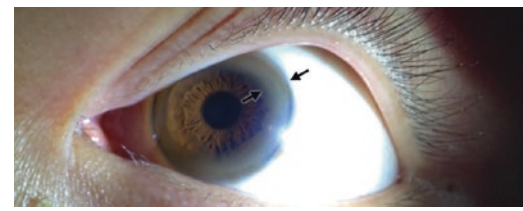

Fig. 4.6 The Kayser–Fleisher ring. Notice the green ring (*arrows*), which consists of copper deposits where the cornea meets the sclera

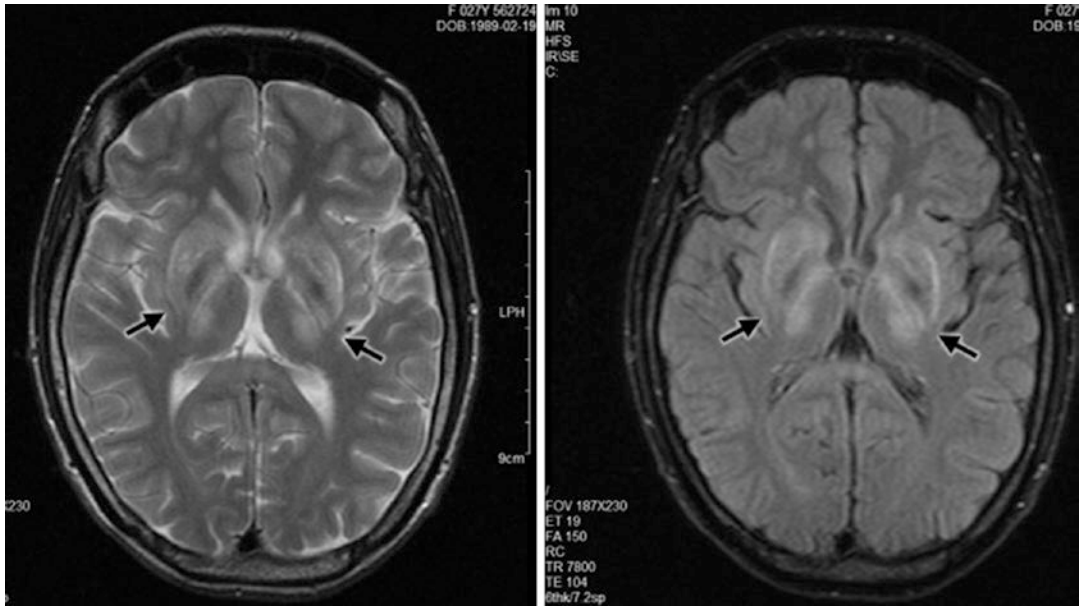

Fig. 4.7 Magnetic resonance imaging (MRI) of the brain in the patient. Axial MRI exhibits hyperintensity (*arrows*) in the bilateral lenticular nuclei and thalami on T2-weighted images (*left*) and T2-FLAIR (fluid-attenuated inversion recovery) images (*right*)

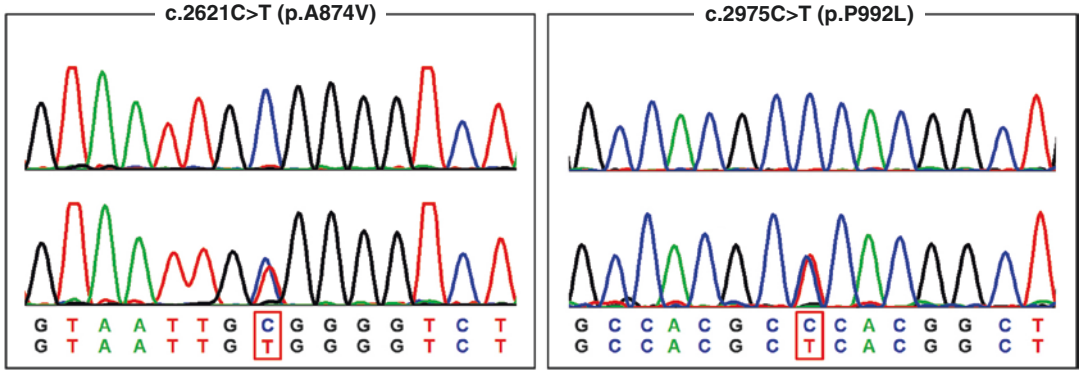

Fig. 4.8 Chromatogram of the *ATP7B* c.2621C>T (p.A874V) and c.2975C>T (p.P992L) mutations. The *upper panels* are normal sequences, whereas the *lower panels* represent mutated ones

Discussion

WD, also known as hepatolenticular degeneration, is an autosomal recessive disease (incidence 1/30,000) characterized by the color rings of corneas (K–F rings) and multisystem damage, including liver cirrhosis, extrapyramidal symptoms, psychiatric disorder, and musculoskeletal deformity. The disease is caused by mutations in ATP7B gene, which encodes a copper-transporting protein in the liver. A deficiency in the enzyme activity can lead to a toxic copper accumulation in multiple organs, which may be responsible for its wide variety of symptoms [30].

Despite a wide variety of clinical manifestations, WD typically presents with liver dysfunction or neurological disorders. Musculoskeletal abnormalities, including premature osteoarthri-

tis, skeletal deformity, and pathological bone fractures, can be occasionally found in WD patients with hepatic or neurologic types [31, 32], but very rare as chief complains [33]. These conditions often lack typical hepatic and neurological symptoms, and the diagnosis can be challenging [34]. Most patients are never considered WD until the neurological impairments emerge, as in our patient. However, some typical signs of WD were present in our patient, such as K–F rings or abnormal abdominal ultrasonography.

In addition, the serum ceruloplasmin is a very sensitive test in WD patients even without any apparent hepatic and neurological signs. Ceruloplasmin below 0.1 g/L is highly suggestive of WD, but lower levels can also occur with aceruloplasminemia, malabsorption, renal or enteric protein loss, liver disease, and heterozygotes for WD [35]. Therefore, if the patient has a low-serum ceruloplasmin without K–F rings, the diagnosis should be based on combination of the urinary copper excretion, liver biopsy, and genetic test. Urinary copper excretion above 100 μg/24 h is typical in patients with symptomatic WD, but less sensitive than ceruloplasmin and can be false positive with hepatic and renal disease. Liver biopsy is an invasive procedure and has been gradually substituted by genetic test. Genetic testing is confirmatory and convenient for screening family members.

The main treatment of WD is copper-chelating agents including D-penicillamine, trientine, dimercaptopropane sulfonate and dimercaptosuccinic acid, and zinc salts. Our patient took oral D-penicillamine (62.5 mg t.i.d.) combined with zinc gluconate (280 mg t.i.d.). After 1 year of follow-up, her symptoms of drooling, dysphagia, and writer's cramp relieved much.

In summary, when a child or adolescent presents with unexplained joint pain or bone dysplasia, the possibility of WD should be considered. Biochemical tests, abdominal ultrasound, slit-light examination, and brain MRI can help establish the diagnosis. Earlier diagnosis can initiate an earlier treatment and prevent the further damage.

4.5 Wilson's Disease (WD 2)

A 22-Year-Old Male Presented with Abnormal Behavior for 10 Months

Clinical Presentations

A Chinese male patient, aged 22, was referred to the Clinic of Neurology due to abrupt behavior change. According to his comrades, the affected individual was noted to soliloquize and have insomnia over the past 10 months. Sometimes he behaved weirdly in front of his comrades and became to be easily irritated with increased hostility toward comrades. There is no family history of any mental disorders. His birth, developmental milestones, and early childhood are normal.

On admission, complete physical examinations revealed practically normal somatic signs, including afebrile, eupneic breathing, normal heart rate, and normotensive without the occurrence of organomegaly. On mental state examination, he was easily irritable and provocative. He has poor control of aggressive personality, hypersensitivity, and soliloquy. Neurological examinations, including extrapyramidal system, all showed normal.

During the primary evaluation, his routine tests in the form of hemogram, renal function, and brain magnetic resonance imaging (MRI) did not display any abnormality. However, liver function (ALT, 46 U/L; normal range is 8–40 U/L) and ultrasound examination of the abdomen revealed moderate impairment.

Primary Diagnosis

Based on his clinical presentations, diagnosis of schizophrenia was initially made for him by psychiatrists from two different hospitals. Therefore, he began to take antipsychotic medications including risperidone and benzhexol. However, after receiving regular therapy, his distress did not improve significantly.

After 10 months, he was presented to a general practitioner who subsequently referred him to genetic clinic. We carefully reviewed his disease course and the related test results. Moderate liver function abnormalities were observed during the overall disease course, even before receiving medication treatment.

Additional Tests or Key Results

In addition, when we evaluated Kayser–Fleischer (K–F) rings using a slit lamp, noted K–F rings were found in his eyes. Therefore, other laboratory tests, including 24-h urinary copper excretion and ceruloplasmin level, were further carried out in the affected individual. Consequently, the low-serum ceruloplasmin level (0.03 g/L, reference value is 0.15–0.31 g/L) was observed, whereas urinary copper was normal. Therefore, this case was highly suggestive of Wilson's disease (WD) and screened for *ATP7B*, which is causative gene of WD patient. Genetic test demonstrated that the patient harbored two heterogeneous mutations, including p.R778L and p.V1106I (Fig. 4.9), thus confirming the diagnosis of WD.

Discussion

WD is an inherited disorder of copper metabolism due to ATP7B protein dysfunction, which mainly affects the liver and central nervous system. Clinical profile often includes hepatic, neurologic, or psychiatric disturbance or a combination of these [30]. Liver disease may be in the form of recurrent jaundice, elevated transaminase level, and chronic liver disease or cirrhosis, while neurological manifestations may include choreiform movements, rigidity, gait disturbance, tremors, dysarthria, etc.

The psychiatric findings are variable and can span a range of diagnostic entities. Depression, cognitive impairment, and personality changes are the most common findings in WD patients with psychiatric form [36]. Compared to these presentations, schizophreniform symptoms are less commonly observed in patients with WD. A clinical investigation from India revealed that only three cases presented with schizophreniform among 350 affected individuals [37]. Grover et al. reported that the overall prevalence of psychosis in patients with WD varies from 0 to 11.3% [38]. Although psychiatric disturbances are well known in WD, the exclusive psychiatric

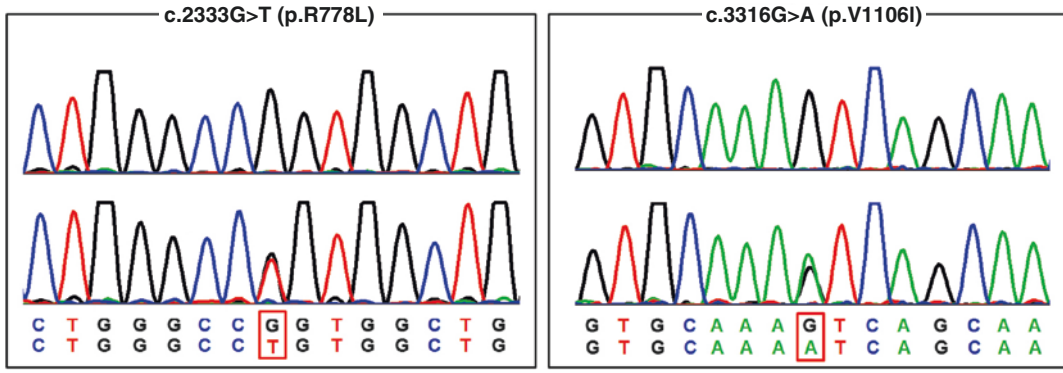

Fig. 4.9 Chromatogram of the *ATPTB* p.R778L and p.V1106I mutations. The *upper panel* represents normal sequence, while the *lower panel* being heterozygous mutated sequence

manifestation mimicking a schizophrenic psychosis without noted hepatic or neurological disorders is relatively rare.

In our case study, the affected individual initially presented with psychosis disturbances and was given the wrong treatment as a schizophrenic patient. Combined with other reports, early recognitions to WD patients only with psychiatric abnormalities are critical because timely initiation of chelation therapy can prevent a catastrophic outcome. We feel that WD diagnostic possibility should be suspected in patients experiencing with abrupt neuropsychiatric symptoms, especially accompanied by unknown liver function abnormalities and abdominal ultrasound for architectural alternation in liver.

4.6 Pantothenate Kinase-Associated Neurodegeneration (PKAN)

A 47-Year-Old Man Had Involuntary Movement for 1 Year

Clinical Presentations

A 47-year-old male came to our Department of Neurology because of involuntary movement for 1 year. He is a shopkeeper and denied any history of toxic exposure. Without any precipitating factor, he suffered from intermittent hypsokinesis of head last year. The attacks usually last 1–3 s and occurred 3–5 times per day. It was mainly involved in his head and occasionally in his neck. There were no convulsions, tremor of limbs, or consciousness alteration during the episodes. He was diagnosed with physiological tremor in local hospital and was prescribed arotinolol hydrochloride at dose of 5 mg thrice daily, which did not relieve his symptoms at all. Four months later, he found his symptoms were aggravated, as the frequency was increased to 5–10 times per day. When he sought his medical attentions in our hospital, he presented apparent dystonic posturing of head. His older brother and parents were all asymptomatic. He denied any family history of consanguinity or neurological disorders.

Cranial nerves examination revealed negative signs except for the involuntary movement of head. The muscle strength was 5/5 in four limbs, and muscle tension was essentially normal. There was no abnormality of somatosensory. Deep reflex was symmetrical and pathological sign was bilaterally negative. Ataxia was not observed. His recognition was not impaired, with MMSE score of 29/30. Complete blood count, T3 T4, ceruloplasmin, serum ferritin, albumin, and lipoproteins were in normal range. Brain MRI showed bilateral hyperintensity within surrounding hypointensity in the globus pallidus on T2 weighted (Fig. 4.10a) and T2-FLAIR (Fig. 4.10b). Susceptibility-weighted image (SWI) revealed low hypointensity in the globus pallidus (Fig. 4.10c).

Primary Diagnosis

This patient mainly presented repeated and intermittent hypsokinesis of head, which resembles the feature of dystonia. There was no sign of pyramidal tracts and cerebellum in physical examination. The level diagnosis was thus located in extrapyramidal tract. Adult onset, slow progression, and no relapsing-remitting episode excluded the infection, inflammation, vessel, and trauma as the etiologic diagnosis of disease. Metabolism, intoxication, degeneration, and heredity should be considered. Showed as in SWI

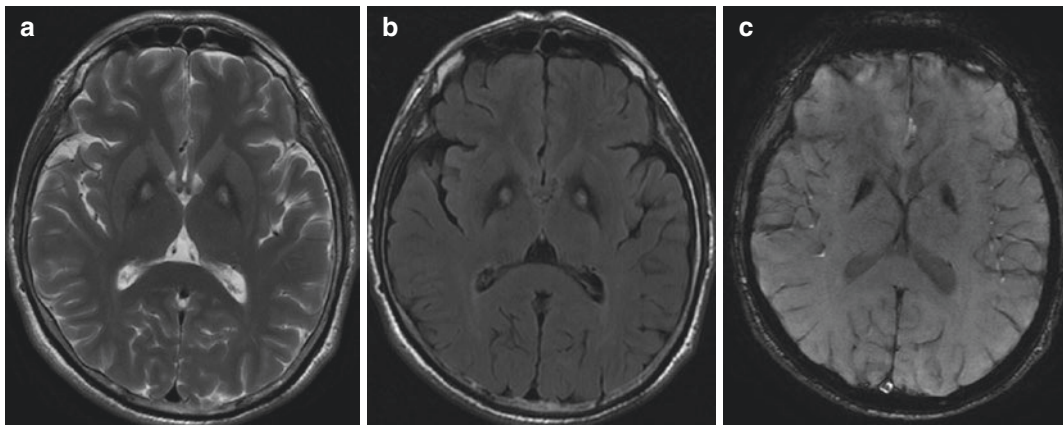

Fig. 4.10 Brain MRI of the patient revealed bilateral hyperintensity within surrounding hypointensity in the globus pallidus on T2 weighted (**a**) and T2-FLAIR (**b**). Susceptibility-weighted image (SWI) revealed low hypointensity in the globus pallidus (**c**)

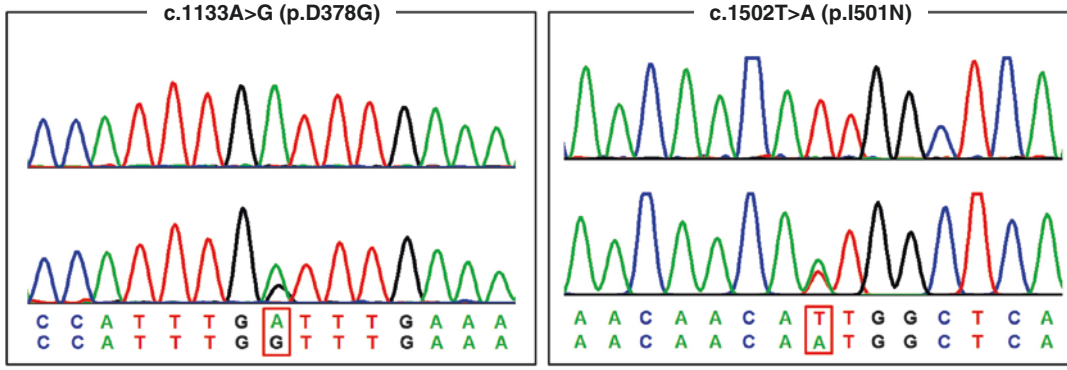

Fig. 4.11 Chromatogram of c.1133A>G (p.D378G) and c.1502 T>A (p.I501N) in *PANK2* gene. The *upper panel* indicates the normal sequence, and the *lower panel* shows heterozygous mutation

sequence, the low hypointensity in the globus pallidus implied the deposition of iron. Extrapyramidal symptoms and iron accumulation in globus pallidus implied that neurodegeneration with brain iron accumulation (NBIA) was the paramount consideration.

Additional Tests or Key Results

There are ten subtypes of NBIA and the majority is autosomal recessive inherited [39]. Among the NBIA groups, pantothenate kinase-associated neurodegeneration (PKAN) is the most common type, accounting for 30–50% NBIA cases. Therefore, genetic screening of *PANK2* gene should be first conducted. After sequencing of *PANK2* gene, we identified two heterozygous c.1133A>G (p.D378G) and c.1502 T>A (p.I501N) mutations in the proband (Fig. 4.11). Further investigation demonstrated that his father carried c.1502 T>A mutation and his mother carried c.1133A>G mutation.

Discussion

PKAN is a rare neurodegenerative disorder with autosomal recessive inheritance and iron accumulation in the globus pallidus [40]. Previously, this disorder was well-known as Hallervorden–Spatz syndrome and renamed in 2011. Clinically, PKAN is characterized by early onset of extrapyramidal symptoms and rapid progression [41]. Nevertheless, a fraction of cases with atypical PKAN had relatively late AAO and slower progression [42, 43]. Due to the recessive inheritance, family history is usually inconspicuous, resulting in the missed diagnosis of this disorder. "Eye-of-the-tiger" sign is a specific imaging feature in PKAN. It was shown as symmetrical hypointensity with a central region of hyperintensity in globus pallidus.

This patient presented with neck dystonia at age of 46. We did not consider hereditary diseases at first because of his onset of adulthood, 1-year disease course, and negative family history. However, his brain MRI revealed classic "eye-of-the-tiger" sign, which is a crucial clue for the diagnosis of PKAN. "Eye-of-the-tiger" sign is a specific imaging feature. It is mainly seen in PKAN and occasionally observed in neuroacanthocytosis and other conditions. In this case, we also performed peripheral blood smear but did not find increased number of acanthocytes (>5%). Neuroacanthocytosis was therefore excluded. He was detected to carry compound heterozygous PANK2 mutations, which co-segregated with the disease. He was finally diagnosed with PKAN.

Current treatment in PKAN is primarily symptomatic for relief of spasticity, dystonia, and other movement disorder. Commonly used drugs are benzodiazepines, anticholinergic, baclofen, neuroleptics, and L-dopa. Deep brain stimulation (DBS) causes mild improvement in dystonia severity [44], and no definite result has been achieved by iron-chelating agents (such as deferiprone) in clinical trials [45].

4.7 Neuroacanthocytosis

A 41-Year-Old Man with Unsteadiness and Memory Impairment

Clinical Presentations

A 41-year-old male presented to us with a 4-year history of increasing unsteady on his feet. At first, he noticed "heaviness" in his legs, particularly while climbing up stairs. Sometimes, he felt his knees bent forward involuntary while walking. These symptoms were subtle at the beginning and progressed gradually. His wife reported that he had difficulties in concentrating and felt that he was increasingly forgetful for the latest 2 years, and he lost his job due to the memory impairment. He reported no sensory symptoms and no symptoms of bladder or bowel dysfunction. He was admitted to our Neurology Department for further examinations. He has been systemically well with no weight loss, change in appetite, or sleep habit. He takes no alcohol or cigarette or regular medications. On examinations, the general systemic examinations including blood pressure was unremarkable. His Mini-Mental State Examination (MMSE) score was 29/30 dropping only 1 point for attention and calculation. His cranial nerves were entirely normal. The limbs were normal on inspection, with no wasting or fasciculations. Tone was normal; power was symmetrically normal 5/5 in all muscle groups in the legs and throughout the arms. All reflexes were decreased and plantars were mute. The coordination was generally good with slight clumsy of hands rotation.

The blood tests were all grossly normal apart from a creatine kinase (CK) of 2244 U/L (reference < 171 U/L) and CK-MB 50 U/L (reference < 24 U/L). His ECG and echocardiogram were normal. Electromyography (EMG) showed widespread slowing of conduction in sensory and motor nerves (Table 4.1). An MRI scan of the brain demonstrated slight cortical atrophy.

The electromyography findings showed that the motor conduction velocities of common peroneus were slow, and motor-induced amplitudes were reduced. The sensory conduction velocities of sural were slow, and sensory-induced amplitudes were also slightly decreased.

Primary Diagnosis

The history and examination findings suggest that this patient has a diffuse impairment of the nervous system including peripheral nerves, muscles, and possibly cortical function. This is far more likely to be a certain complex syndrome. Because the most severe impairment was the elevated CK level, we considered myopathy to be the first diagnosis, of which mitochondrial encephlomyopathyis of great possibility. Further questioning revealed that he was not good at sports since a child, and his unsteadiness always developed when he felt tired. Although the decrease in exercise tolerance may simply represent fatigue, in this case it may highly signify neurological muscle weakness affecting the limbs that argue strongly in favor of a possible diagnosis of mitochondrial encephalomyopathy. We tested the serum lactic acid level after

Table 4.1 Nerve conduction study

Nerve	Stimulate point	Latency (ms)	Amplitude (mV)	Velocity (m/s)
Motor nerve conduction velocity (MCV)				
Peroneus (L)	Ankle	6.25	1.51	
	Capitula fibula	14.1	0.94	34.3
Peroneus (R)	Ankle	3.76	4.0	
	Capitula fibula	10.5	3.5	40.9
Sensory nerve conduction velocity (SCV)				
Sural (L)	14 cm above heel	2.18	7.1	39.0
Sural (R)	14 cm above heel	2.07	5.0	36.2

exercise. The lactic acid levels were1.6 mmol/L at rest, 5.2 mmol/L immediately after exercise, 4.6 mmol/L 10 min after exercise, and 2.2 mmol/L 30 min after exercise, while the reference range is 0.7–2.1 mmol/L. Although these results meet the minimum diagnosis criteria for mitochondria disease, the lactic level is often much higher. Muscle biopsy is considered to perform in the patient.

Additional Tests or Key Results

Before muscle biopsy was scheduled, on further physical examinations, we noticed that there were some involuntary fidgeting, writhing, and twitching movements of the distal of limbs. The movements appear semi-purposeful but in a random pattern. They were very subtle thus could only be noticed on a long time careful observation. These involuntary movements were chore form, thus reminding us the possibility of Huntington's disease (HD). However, the increased CK level and peripheral neuropathy could not be explained by HD. HD genotyping was requested and negative, which excluded the diagnosis of HD. The complex presentations that include peripheral neuropathy, cortical function impairment, chore form involuntary movements, as well as an increased CK level raise the suspicion of a rare inherited disorder, neuroacanthocytosis (NA). Peripheral blood smear was performed, and an increased number of acanthocytes (>5%) were found (Fig. 4.12) and supported the diagnosis of NA. A detailed family history reveals that no one in his family experienced similar symptoms reminding us the possibility of an X-linked recessive inheritance. McLeod syndrome (MLS) is one of NA syndromes and an X-linked recessive disorder caused by mutations of *XK* gene located on the X chromosome [46]. Therefore, mutations of *XK* were screened in the patient, and the c.942G>A (p.W314X) mutation was found (Fig. 4.13), which further confirmed the diagnosis of MLS.

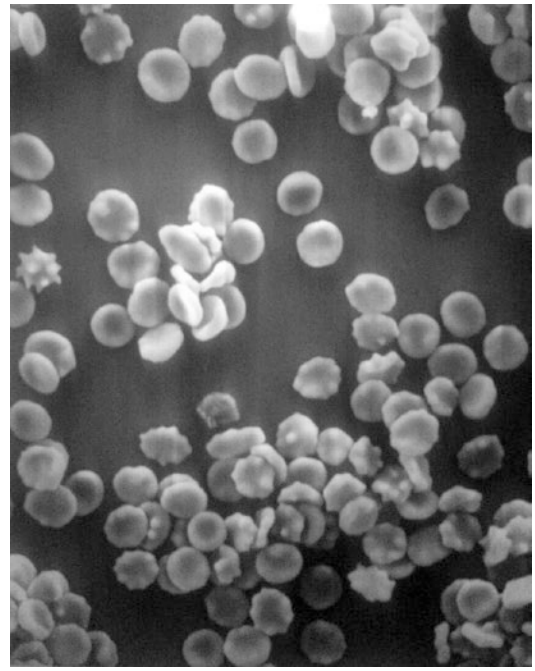

Fig. 4.12 Peripheral blood smear on electron microscope showed an increased number of acanthocytes (>5%)

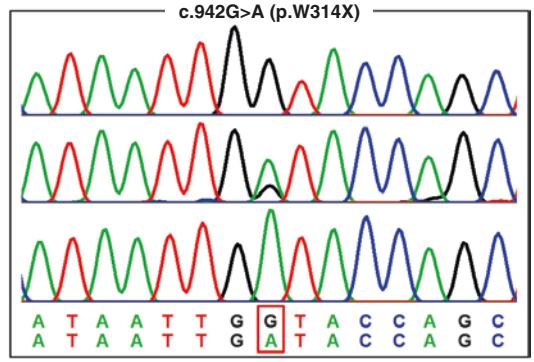

Fig. 4.13 Mutation analysis of the patient. Chromatogram of c.942G>A (p.W314X) mutation in *XK* gene. The *upper panel* is normal sequence of the control, the *middle panel* represents the heterozygous c.942G>A sequence, whereas the *lower panel* represents hemizygous c.942G>A sequence of the patient

Discussion

NA is a group of very rare disorders estimated to have affected 1000 people worldwide. There are four core NA syndromes including chorea-acanthocytosis (ChAc), MLS, Huntington's disease-like 2 (HDL2), and pantothenate kinase-associated neurodegeneration (PKAN) [47]. MLS typically presents in men in their midlife with hyperkinetic involuntary movements, specifically chorea, peripheral sensorimotor neuropathy, psychiatric or cognitive issues, and an elevated CK or liver enzymes. Fifty percent

of subjects have seizures, which usually respond well to standard anticonvulsant medications. The main observation on brain imaging is atrophy of the caudate nucleus and putamen [48].

Our diagnosis of MLS was first based on clinical features and laboratory findings. Clinically, the patient had midlife onset illness. Hence, our diagnosis was restricted to either ChAc or MLS because HDL2 and PKAN have a childhood or juvenile onset. However, because the characteristic phenotype of ChAc including a very peculiar "feeding dystonia" with tongue protrusion, orofacial dyskinesias, and involuntary tongue/lip biting was absent in our patient, our first diagnosis was MLS. In addition, an important distinction between MLS and the other NA disorders is the presence of cardiomyopathy [49], which is seen in approximately 2/3 of patients. Although the ECG and echocardiogram of this patient were normal, he did have an increased CK-MB level (50 U/L, reference <24 U/L).

The diagnosis of this patient was quite difficult at beginning because his chore form movement was too subtle to be recognized. However, on retrospection, the combination of symptoms should raise our suspicion of NA even without the hyperkinetic involuntary movements. In conclusion, although NA disorders are rare, the clinical presentations are very characteristic that should be recognized [50].

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