

Neurological assessment and nerve conduction study findings in 22 patients with alkaptonuria from Jordan

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Abstract

Alkaptonuria is a rare metabolic disease characterised by accumulative deposition of homogentisic acid in the connective tissue of the body. This results in early degeneration of tendons, cartilages, heart valves, and other tissues. The main objective of the study is to examine the possibility of the nervous system involvement in patients with alkaptonuria. The sample consists of two groups; 22 patients with AKU and 20 controls. A neurological assessment has been carried out including detailed medical history, neurological examination, and a nerve conduction study of the nerves of the dominant hand. The prevalence of any abnormality was compared between the two groups using chi square test. The mean values of the nerve conduction study were compared between the two groups using student t-test. There was a higher prevalence of low back pain, hearing problems and tinnitus, numbness and neuropathic pain in alkaptonuria patients. There was no significant difference between the two groups in other conditions such as seizures, headache, and syncope. The values of the nerve conduction study did not show significant difference between the two groups. Neurologically related symptoms in alkaptonuria mostly represent complications of the connective tissue degeneration rather than direct involvement of the nervous system. This has been supported further by the normal findings of the neurophysiology study in patients with alkaptonuria.

Introduction

Alkaptonuria (AKU) is a rare metabolic disease that is inherited as autosomal recessive trait. It has a worldwide prevalence of 1 in 250,000 to 1 million. The prevalence is highest in Slovakia where it reaches 1 in 19,000.¹

The disease is due to a defect in the gene coding for an enzyme called homogentisate 1,2

dioxygenase.² This enzyme helps in breaking down tyrosine and phenylalanine. As a result of malfunction of this enzyme, levels of homogentisic acid are increased in the blood. Excess products are then excreted in urine producing dark urine. There is an accumulation of homogentisic acid in the connective tissue in a process known as ochronosis.³ Deposition of these ochronotic pigments produces dark colour cartilage and early spondyloarthropathy, kidney stones, prostate stones, dark sclera,⁴ valvular heart disease and other conditions.⁵ However, urine discoloration is frequently minimal and can be unnoticed by the patient. In addition, patients usually present with general symptoms of connective tissue involvement that are not peculiar to AKU such as low back pain, joint pain, and numbness or pins and needles of the extremities. Therefore, AKU patients often remain undiagnosed until they present with advanced complications. AKU patient may attend neurology clinics as their first presentation. It is not very uncommon for AKU to be diagnosed intraoperatively, such as during joint replacement, during valvular heart replacement, or during spine surgery.⁶ From the nature of the disease, deposition of ochronotic pigments is generalised and can affect any area of the body that has connective tissue, including deep (aortic valve, intervertebral discs) or more superficial structures (sclera, external ear cartilage).⁷

AKU related myeloid deposition in the central nervous system and the relation of AKU with Parkinson disease and stroke have been already established.^{8,9} To our knowledge, possible effects of AKU on the peripheral nervous system have not been investigated previously. In the present study we will try to find out if there are neurological symptoms that are more prevalent in AKU patients compared to normal population by obtaining thorough medical history and conducting complete neurological examination. Investigating the direct effect of AKU on peripheral nerves will be achieved by performing nerve conduction studies in both AKU and control groups.

Aims

To study the possible neurological manifestations in 22 patients with AKU and the prevalence of these manifestations in AKU compared to 20 controls.

Materials and Methods

The sample includes 22 patients (19 males and 3 females) who have confirmed diagnosis of AKU and 20 controls (10 males and 10 females). For patients with AKU, the age ranges from 22 to 59 years (mean \pm SD = 39.86 \pm 9.54 years). For the control sample, the

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age ranges from 22 to 60 years (35.15 \pm 9.80 years; Table 1).

The study was conducted at the neurology unit in Alkarak governmental teaching hospital in the south of Jordan and in association with the Faculty of Medicine Mutah University. All patients who accepted to participate in the study were initially contacted via the Jordanian AKU society. The study was approved by the local research ethics committee. On initial presentation, participants had to fill a questionnaire about their medical history and in particular for the presence of any neurologically related symptoms. Symptoms included in the questionnaire have been considered based on the most common presentations to the neurology clinic.

The physical examination and nerve conduction study were performed by one of the authors (O.A) who was blinded to the information obtained in the questionnaires. A neurological examination was carried out for stance, gait, balance, cranial nerves examination, deep tendon reflexes, and superficial reflexes, assessment of tremor, coordination, upper and lower limbs power and sensation.

After that, a nerve conduction study was performed at another occasion. The study involved the median and ulnar nerves of the dominant hand. Values obtained were the distal sensory latencies, the onset motor latencies, the conduction velocity, and the sensory and motor

amplitudes of both nerves. If an abnormality was found in any of the participants, further procedures were carried out in other nerves or other limbs including electromyography.

Interpretation of results and statistics

To find if there is a significant correlation between the abnormality and AKU, the ratio of the abnormality in AKU was compared with the ratio of the abnormality in the control group using chi square test. The medians of values obtained from the nerve conduction study were compared with those obtained from controls using student T test (SPSS 14).

Results

All participants have attended the clinical evaluation session but only 12 AKU patients and 8 controls attended the nerve conduction study sessions.

None of the AKU patients has diabetes mellitus and only two males have hypertension. There were 6 AKU patients with previous surgical history; 3 patients had surgeries that are believed to be due to AKU; a male had a surgery due to disc prolapse between L3-L4, a male had knee replacement at age of 52 years, and a male had a repair of spontaneous Achilles tendon rupture at age of 39 years. 3 females had surgeries that are mostly not related to AKU; two females had caesarean sections and a female had a pituitary macroadenoma removed 2 years ago.

Neurological symptoms and signs

The most common symptom that has been reported by 100% of AKU patients was low back pain. Low back pain has been reported by 25% of the control group (P 0.005). Symptom of numbness in any of the limbs was described by 72% of patients and 15% of controls (P 0.005). Neuropathic pain in either the upper or lower limbs was described by 53% of patients and in 15% of the controls (P=0.018).

About 49% of patients with AKU reported hearing problems with none of the controls reported any symptoms related to hearing (P=0.002). Another AKU related symptom is tinnitus which has been described by 34% of AKU patients and none of the controls (Chi square P=0.004). Approximately 40% of AKU patients experience occasional blurring of vision while none of the controls complained about vision (P=0.002). About 35% of patients with AKU were concerned about shaking (tremor) but none of the controls group had this symptom (P=0.004). Feeling of general weakness also appears to be more prevalent in AKU where it was reported by 40% of patients and 10% of controls (P=0.028).

There was no significant difference between the two groups in the prevalence of headache, syncope, loss of consciousness, involuntary movements, epilepsy, dizziness, dysphagia, speech problems, diplopia or problems with taste (Table 2).

Physical examination

There were variable positive signs related to musculoskeletal problems such tenderness and limitation of knee movement, low back pain, and positive straight leg raise test. Generally, neurological examination of patient did not reveal significant signs that are different between the two groups. Patients and controls who reported symptoms such as tremor, balance problems, numbness, blurring of vision, diplopia, taste problems, speech problems, dizziness and vertigo were not found to have objective signs on physical examination. Only one AKU patient described later in this study showed a number of positive signs.

Nerve conduction study

The mean median distal sensory latency was 3.2 milliseconds (ms) in AKU patients and 3.46 ms in controls (P=0.522). In AKU, the mean median onset motor latency was 4.1 ms and in controls was 3.51 ms (P=0.361). The ulnar sensory peak latency was 2.38 ms in AKU and 3.1 ms in controls (P=0.06). The mean ulnar motor latency was 2.96 ms in AKU and 2.84 ms in controls (P=0.805). Although the forearm conduction velocity of the motor median nerve was slightly lower in AKU (47.51 meters/second) than in controls (52.56 meters/second), the difference did not reach statistical significance (P 0.179).

Other nerve conduction values including sensory and motor amplitudes did not also show significant differences between the two groups (Table 3).

Alkaptonuria patient with severe polyneuropathy

Among AKU patients, a 36 year old male was complaining of progressive weakness for the

Table 1. Summary of the sample.

Sample type	Gender	Age, min.	Age, max.	Mean	SD (years)
Control	Male	27	60	39.30	9.346
	Female	24	47	31.00	8.781
Alkaptonuria	Male	27	59	40.22	8.755
	Female	22	54	38.25	14.104

Table 2. Prevalence of neurological symptoms in alkaptonuria (AKU) patients and controls.

Symptom	Ratio in controls %	Ratio in AKU %	Chi square
Imbalance	00	20	0.035
Tinnitus	00	35	0.004
Tremor	00	35	0.004
Numbness of any of the limbs	15	70	0.0001
Neuropathic pain	15	50	0.018
General weakness	10	40	0.028
Vision problems	00	40	0.002
Lower back pain	25	100	0.0001
Hearing problems	00	40	0.002
Headache	15	35	0.144
Amnesia	15	10	0.633
Dizziness	00	15	0.072
Syncope	0	5	0.311
Loss of consciousness	00	5	0.311
Involuntary movements	00	30	0.147
Diplopia	00	15	0.072
speech problems	00	5	0.311
Nausea and/or vomiting	00	00	-
Taste problems	0	5	-
Dysphagia	0	0	-

last two years but he did not seek medical help. On examination, he had abnormal posture, ataxic gait, impaired coordination, bilateral weak dorsiflexion and bilateral hypothenar and first dorsal interosseus atrophy. There was generalised reduction in muscle power and reflexes including upper and lower limbs. Speech was normal with no signs of cranial nerves lesions.

The neurophysiological study of the patient has shown signs of severe generalised polyneuropathy of both axonal and demyelinating types. The study has been extended to include the lower limbs and EMG study. There was absence of sensory and motor responses in a number of nerves with a very slow conduction velocity ranging from 16 m/s to 24 m/s. The EMG has shown signs of active and chronic denervation. The patients underwent further investigations and an initial diagnosis of idiopathic progressive polyneuropathy was considered.

Discussion

This study is possibly the first study that investigated the neurological symptoms and signs in patients with AKU. Results from the study may increase awareness of neurologists to certain symptoms presenting to the neurology clinic and the possibility of AKU. Because of the extremely wide range of neurological symptoms, it was not possible to analyse all symptoms. Symptoms were selected depending on the frequency of symptoms attending a general neurology clinic.

AKU results in accumulation of homogentisic acid in the connective tissue. There is a possibility that accumulation may take place in other tissues such as the nervous system. Progressive accumulation of the acid usually results in degeneration of the connective tissue and consequently pain especially in weight bearing areas such as the spine and knees. Therefore, it is not surprising that 100% of patients with AKU patients in this study complain of low back pain. Three of them had surgeries that are directly related to AKU compli-

cations; a patient had a disc prolapse surgery, a patient was diagnosed intraoperatively during knee replacement surgery at age of 52 years when the surgeon noticed that the knee cartilage is dark in colour, and another patient had a spontaneous rupture of the Achilles tendon which has been repaired surgically. The ruptured Achilles tendon presentation has been reported recently as a case report.¹⁰ Spontaneous tendon rupture has been also reported in AKU patients in two previous occasions and can be a presenting symptom of AKU.^{11,12} Clinicians should therefore consider AKU diagnosis in young patients who have early degenerative changes in weight bearing areas.

Two related symptoms that have been described by most patients with AKU are numbness and/or neuropathic pain in any of the extremities. These symptoms reported in the lower limbs and are most likely due to degeneration of the spine causing disc prolapse and osteophytes that compress proximal roots. Patients with AKU may experience neuropathic pain that is not related to degeneration of the spine. We described in this report a patient with severe polyneuropathy. In fact, myopathy and neuropathy have been reported previously as a case report in a patient with AKU.¹³ In this study, 50% of cases complain of reduced hearing and 35% complain of tinnitus. Hearing loss appears to be a common problem in patients with AKU. In fact, high frequency hearing loss and conduction hearing loss have been reported in a patient with AKU.¹⁴ ENT manifestations was described by 90% of cases according to a previous case series of 20 patients.¹⁵ A previous case report has described a patient with tinnitus and bilateral high frequency hearing loss.¹⁶ According to these published reports, deposition of the homogentisic acid results in hardening of tissue such as the tympanic membrane and the ossicular chain which may result in hearing loss and tinnitus. In this study, hearing has been tested by performing whispering test which did not show significant abnormality. Whispering test may not be enough to evaluate minimal hearing loss due to reduced mobility of the tympanic membrane and the ossicular

chain. Once diagnosed, AKU patients may need frequent ENT examinations including regular tympanogram to monitor their hearing function and to offer disease modifying therapy for those who show deterioration.

Interestingly, a significant number of AKU patients described feeling of imbalance and tremor. Feeling of imbalance can be related to either polyneuropathy or myelopathy due to spinal degeneration, involvement of the vestibular system in the inner ear, and cerebellar pathology. However, apart from the AKU patient with severe neuropathy, none of AKU patients have shown physical signs suggestive of neurological involvement. We performed examination of normal gait, tandem gait, Romberg's sign, rapid alternating movement, finger nose test, rebound phenomena, heel to shin test, examination for nystagmus, and Dix-hallpike test. Although these clinical tests may be sensitive to detect cerebellar or spinal cord pathology, they are less sensitive to detect subtle balance problems produced by pathology of the vestibular system. For accurate assessment of the vestibular system, additional investigations are required such as, electronystagmography, videonystagmography, Vestibular evoked myogenic potential, and other tests.

Patients in the present study were concerned about frequent feeling of blurring of vision and this was significantly higher than normal controls. There was no previous evidence in literature that AKU affects visual acuity. Similarly in this report there was no evidence of abnormality in the physical examination including pupillary reflexes, confrontation visual field defect, funduscopic retinal examination, and visual acuity test using Snellen chart. It is possible that this feeling of visual distortion is related to deposition of the material in the connective tissue of the eye ball rather than direct involvement of the retina or the optic nerve. It is established that AKU results in deposition of homogentisic acid in the sclera or the Bowmans membrane of the cornea,¹⁷ and may also result in uveitis.¹⁸ A complete ophthalmological assessment including retinal optic coherence tomography and visual evoked potential may reveal AKU related

Table 3. Summary of the of nerve conduction study values in alkaptonuria patients and healthy controls.

	Sample type	Mean	SD	SE mean	Sig t-test
Median compound muscle action potential in millivolt	Alkaptonuria	5.28	1.96	0.59	0.134
	Control	6.37	00.93	0.35	
Ulnar compound muscle action potential in millivolt	Alkaptonuria	5.92	2.05	0.62	0.104
	Control	7.86	2.40	0.91	
Median sensory nerve action potential (Peak to Peak in microvolt)	Alkaptonuria	40.44	22.03	6.64	0.547
	Control	46.44	18.81	7.11	
Ulnar sensory nerve action potential (peak to Peak in microvolt)	Alkaptonuria	35.99	27.32	8.24	0.345
	Control	47.73	23.17	8.76	
Median motor conduction velocity (forearm) in meter/second	Alkaptonuria	52.56	1.77	0.67	0.179
	Control	47.51	11.42	3.44	

retinal or optic nerve pathology.

A number of patients reported episodes of diplopia but the physical examination of the extraocular muscles showed no apparent strabismus. It is possible that deposition of ochronotic pigments may include the connective tissue of the orbit, especially the annulus of Zinn. This may result in minimal malalignment of the eyes causing clinical diplopia that is not detectable using the routine test of extraocular muscles. Therefore, it may be necessary to exclude subtle changes by performing other tests such as cross cover test and prism alternate testing.

Symptoms such as seizures, headache, loss of consciousness, that may reflect direct central nervous system involvement showed normal prevalence among AKU patient when compared to controls.

Nerve conduction study

There is no previous evidence that AKU alters the function of the peripheral nerves. This has been supported further in this study by comparing neurophysiological results between AKU and healthy controls. There was no significant difference in the nerve conduction results between the two groups. Although amplitudes of action potential and nerve conduction velocities were higher in controls, the difference seems to be minimal and insignificant statistically. However, number of patients with AKU who were diagnosed to have subclinical carpal tunnel syndrome (CTS) were 6 patients (50% of the examined patients) compared to 1 patient with subclinical CTS from normal controls (14% of examined healthy controls). All of the AKU patients showed values suggestive of minimal to mild subclinical CTS. Subclinical CTS is considered in asymptomatic patients with nerve conduction study changes suggestive of CTS. The median nerve passes in the carpal tunnel with 9 tendons and deposition of AKU pigments in these tendons may produce changes in the tunnel such as swelling and consequently compression on the nerve.

In this study we have also presented a patient with AKU who has severe polyneuropathy. In a previous case report of AKU, a patient was found to have both myopathy and severe neuropathy.¹³ Such coexistence may be accidental but neuropathy remains a possible complication of AKU.

Conclusions

Number of participant in the study may not be representative but may be indicative of marked complications. There was higher prevalence of certain symptoms and signs in AKU patients compared to controls such as hearing loss, tinnitus, numbness, neuropathic pain, tremor, imbalance, and visual complaints. However, these symptoms may not reflect direct neuronal involvement. There was similar prevalence of headache, involuntary movements, seizures, dizziness, and a number of other neurological symptoms and signs. The study also did not demonstrate a significant difference in the nerve conduction study findings of the peripheral nerves between the two groups.

One of the important limitation is that clinical assessment was based on clinical examination without further investigations apart from nerve conduction study of the dominant hand. Additional neurophysiology investigations are also required to detect other nerves specifically the lower limbs nerves, optic nerve, and the vestibulocochlear nerve.

Although the study did not demonstrate a direct involvement of the nervous system in AKU, neurologists should be aware that patients with AKU may present to the neurology clinic for the first time with neurological symptoms such as low back pain, neuropathic pain, numbness, balance problems, tinnitus, and hearing problems.

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