

Setting up an Infra-Structure of Healthcare for Alkaptonuria in Germany by Dissemination and Networking

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AKU-Symptoms^{1,7}

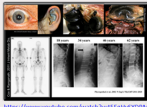
Chronological Phases of AKU:

1. Asymptomatic: Darkening of urine upon exposure to air from birth to adulthood.
2. First pain / functional impairments from 3rd decade by back- and joint pain. Adjusted lifestyle and physiotherapy as well as occupational therapy can help in this phase.
3. Deterioration of quality of life from 5th decade and the necessity of surgical interventions as well as tailored pain therapy for improvement.



Symptoms:

- Darkening of urine from birth
- Backpain and Spondylarthrosis (± 30 years)
- Ochronosis: Auricles of ear / sclerotic of eyes (± 30 years)
- Joint pain / degeneration of joints by ochronotic arthritis (± 40 years)
- Amyloidosis A / Inflammation / oxidative stress
- Rupture of tendons / ligaments / muscles
- Hearing impairments by ochronosis in tympanic membrane / auditory ossicles
- Kidney- / prostate-stones (± 50 years)
- Aortic stenosis (± 60 years)



Abstract:

Alkaptonuria (AKU, ochronosis) is an inborn metabolic disease, resulting in the accumulation of the metabolic intermediate homogentisic acid (HGA). Oxidation of HGA by air or within connective tissue causes darkening of the urine, pigmentation of eyes and ears, kidney- and prostate-stones, aortic stenosis, but most severely an early onset of arthritis called ochronotic arthropathy (ochronosis) due to deposition in the cartilage. Ochronosis is very painful, disabling and progresses rapidly. Starting in the thirties with the spine and affecting large joints in the forties, patients frequently require joint replacements in their fifties and sixties⁷⁻⁹. Like many of the rare diseases, AKU-patients undergo a long odyssey of several years until their diagnosis.

The German AKU-Society "Deutschsprachige Selbsthilfegruppe für Alkaptonurie (DSAKU) e.V." was founded in 2012 and became subsequently registered as a non-profit patient organization. First of all, the DSAKU identified AKU-patients, set up a homepage and designed flyers with information for patients, their families, medical professionals and healthcare services. Second, it offered workshops on AKU-related issues and enabled personal exchange. Third, it raised awareness of AKU, both nationally and internationally by information booths, presentations and posters at scientific congresses as well as rare disease days (RDD). Fourth, in response to the needs of patients, it established collaborations and built up national networks for a better health care accordingly. Thus, patients were encouraged to visit the centres for metabolic diseases at the Charité (Berlin), Hannover Medical School (MHH), University of Düsseldorf and Institute of Human Genetics at the University of Würzburg to bundle knowledge and expertise. The DSAKU is member of AchSE e.V., NAKOS, EURORDIS and MetaERN and registered in the databases SE-Atlas, ZIPSE and Orphanet. Finally, the DSAKU is nationally and internationally active in health politics regarding training in drug safety and evidence-based medicine.

The Challenge:

Visible Symptoms:
Disease-specific signs & symptoms



Dissemination

DSAKU-Homepage: www.dsaaku.de

AKU-Informationen for Patients and Healthcare Providers

Flyers

Informationen on Disease Management for AKU⁸⁻¹²

Age (y)	Possible symptoms / problems	Recommended interventions - treatment methods
Infancy <	Urochrotonuria Chalked < "Dirt"	Laboratory analysis HGA. Survival rate of kidney function Healthy life program
Childhood <	Darkening of urine Back pain<	Avoidance of high activity with high impact Avoidance of jobs with heavy labour
Adolescence <	Choice of occupation< Family planning<	Genetic counselling Family planning
30 <	Back pain< Fat taches<	Physiotherapy, physiotherapy, physical exercise Contacts with other AKU-patients via DSAKU e.V.
40 <	Joint pain< Joint pain<	Tailored pain therapy, physical therapy Surveillance of kidney / prostate<
50 <	Survelliance of kidney / prostate< Working with AKU< Stiffness / joint pain<	Annual ultrasound + laboratory diagnostics Annual ECG + Echokardiogramm Support by DSAKU + Deutsche Rheuma-Liga Occupational assistance, support if required such as joint replacement
60 <	Kidney - / prostate-stones< Aortic stenosis< Possible occupational disability<	Surgical removal of kidney / prostate-stones if required Occupational assistance, support if required such as joint replacement Support by DSAKU + Deutsche Rheuma-Liga + Unabhängige Patientenberatung

Informationen on Diagnostic Surveillance for AKU^{14, 9}

Symptoms	Age	Diagnostic
Link urine	0 <	HGA determination; HbA1c analysis; kidney function; Bone metabolism
Darkening of urine, urine on air	0 <	Quantitative determination
Back pain, stiffness, tenderness	30 <	1-rap. MRI, bone scintigraphy
Joint pain	40 <	1-rap. MRI, bone scintigraphy
Kidney-stones	60 <	Ultrasound, CT, laboratory diagnostics
Prostate-stones	60 <	Ultrasound, CT
Aortic stenosis	60 <	Echocardiography, ECG
Depression / Isolation	30 <	Medical history, clarification of the disease

Summary and Translation of Literature

Treatments, Therapies and Counselling^{2,13, 14}

Therapy / Counselling / Treatment	Treatment	Summary
Symptomatic therapies	Vitamin C	Efficacy unproven
Nutrition	Low Protein Diet	Efficacy in adults unproven, compliance problematic
Natural Therapies	Exercise	Implemented on patients, demand, efficacy unproven
Life style counselling	Family Planning	Professional Genetic Counselling
Therapies by health professionals	Occupational therapy	Underused, usually not AKU-specific
Pain management	Relaxation techniques	Underused, implemented in rehabilitation clinics
Surveillance	Diagnosis	Lack of knowledge prevents utilisation
Surgery	Organ replacement	Unjustified due to relatively preserved lifespan
Curative, HGA-lowering Therapies	Enzyme replacement	Submitted to EMA
Substrate reduction therapy	HGD-gene	Not yet available
Enzyme replacement	HGD-enzyme	Not yet available

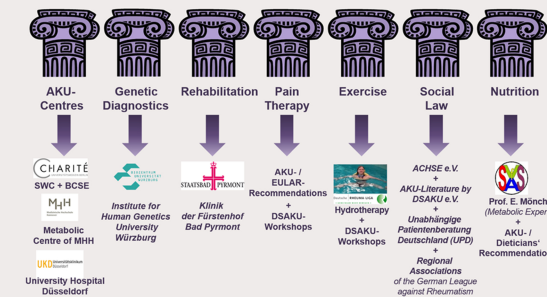
Translation of

AKU-Severity Score Index (AKUSSI)^{2,4-15}

Organ	Feature	Points	Points	
Reproduction system	Nasal Conjectiva ² (0, 1, 2, 3)	0-3	Nasal Conjectiva ² (0, 1, 2, 3)	0-3
	Nasal Sclera ² (0, 1, 2, 3)	0-3	Nasal Sclera ² (0, 1, 2, 3)	0-3
	Temporal Sclera ² (0, 1, 2, 3)	0-3	Temporal Sclera ² (0, 1, 2, 3)	0-3
Hearing	Hearing impairment ²	0-4	Hearing impairment ²	0-4
	Prostate stones ² (Episodes)	0-4	Kidney stone ² (Episodes)	0-4
Cardiovascular	Aortic stenosis ² moderate	10	Aortic stenosis moderate	10
	Aortic stenosis mid	10	Aortic stenosis severe	12
Bone	Osteoporosis	0-4	Stiffness (Rheumatic)	0-8
	Muscle rupture (Rheumatic)	0-4	Tendon rupture (Rheumatic)	0-8
Soft Tissue	Clinical Joint Pain Score (2 for each joint, 14 large joint areas)	14	Sclerographic skin Joint Score (2 for each joint, 14 large joint areas)	28
	Number of past joint replacements (2 for each joint, 14 large joint areas)	28	Total Score of Clinical Features	40
Spine	Clinical Spinal Pain Score (2 for each vertebra, 14 large joint areas)	14	Clinical Spinal Pain Score (2 for each vertebra, 14 large joint areas)	14
	Number of past joint replacements (2 for each vertebra, 14 large joint areas)	28	Pain or Isotope Bone Scan Score (pain, isotope)	4
Spine	Spinal Pain Score (2 for each vertebra, 14 large joint areas)	14	Spinal Pain Score (2 for each vertebra, 14 large joint areas)	14
	Total Score of AKUSSI (Sum of scores from clinical features + points + spine)	20	Total Score of AKUSSI (Sum of scores from clinical features + points + spine)	20

Networking

Networks for Disease Management

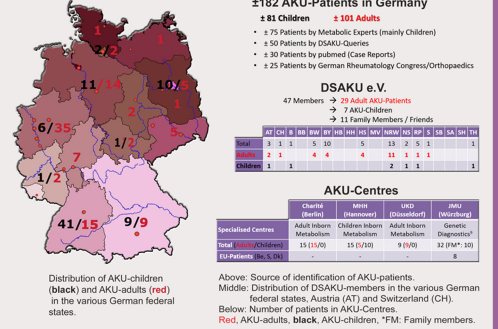


Memberships, Partners and Databases

Year	Membership / Partners / Database	Organization / Location
2012	VFSS e.V.	Patient Organization (PO), Germany
2012	International AKU-Societies	PO, worldwide
2012	Deutsche Rheuma-Liga	PO, Germany
2012	EULAR	PO/Medical/Scientific, Europe
2012	Disiplanet	Database, Europe
2013	DSaR & DGBm	Medical, Germany
2013	AchSE e.V.	PO, Germany
2014	ASIM e.V.	Medical, Germany
2014	UFDP	PO/Medical/Scientific, Germany
2015	SE-Atlas	Database, Germany
2015	ZIPSE	Database, Germany
2015	MSDD (MedDRA-Lizenz)	Database, worldwide
2015	EuroRIMS	PO, Europe
2015	NAKOS	PO, Germany
2018	EURATI	IMI-Project (EC), Europe
2018	MetaERN (ePAGE)	PO/Medical, Europe
2018	SIEM	Medical/Scientific, worldwide
2020	AAPS e.V.	Medical, Germany
2020	DISEM	Medical/Scientific, Germany

Cochrane-Workshops - GRADE for guideline development - Basic EBM-course: Systemic reviews evidence-based health care

Identification of AKU-Patients



Raising Awareness

Public Awareness Days

Scientific Congresses

DSAKU-Workshops

Conclusion

In a federal healthcare system such as in Germany, treatment and care for AKU patients was scattered. Centralising AKU-patients to only a few Metabolic Centres, enabled bundling of expertise, and increase of knowledge. Additionally, by dissemination and networking a holistic healthcare for AKU could be established.

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