Healthcare industry BW

Metabolic diseases

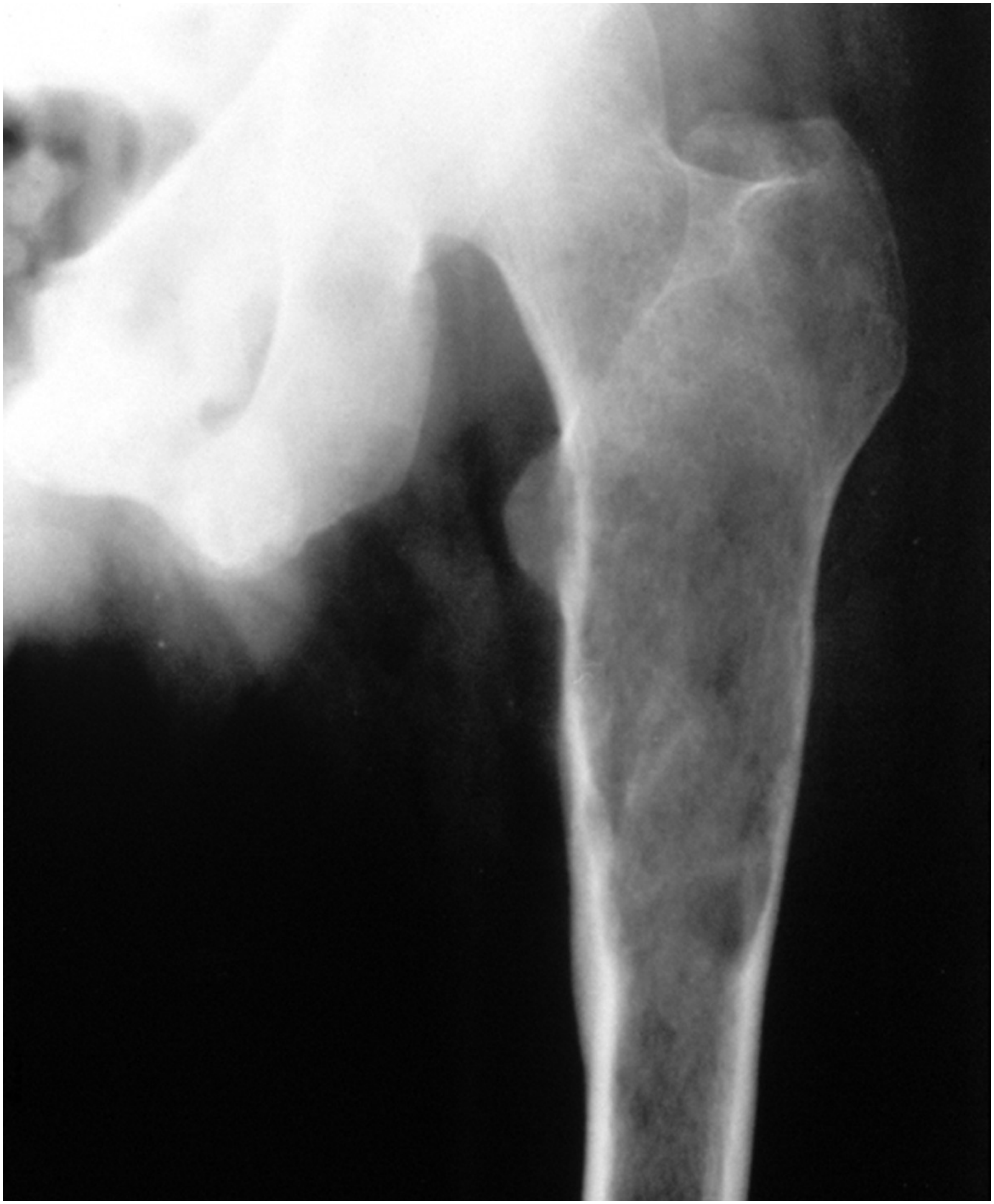
Metabolic diseases are characterised by disorders of the intermediary metabolism, which can either be inherited or acquired. The extent and incidence of metabolic diseases can differ considerably and can range from widespread diseases such as diabetes to rare congenital diseases that frequently have a fatal outcome. Through new approaches in genome research, amongst other things, science and industry are increasingly focusing on metabolic diseases.

Congenital metabolic diseases are mainly characterised by genetic enzyme defects which can lead to organ failures, depending on the function of the reaction product. Acquired metabolic diseases of the intermediary metabolism are often caused by a deficiency in certain substrates or by exogenously induced enzyme deficiencies. Around 11,000 human congenital metabolic disorders are known and characterised; about 200 of these disorders are associated with fits and epilepsy (e. g., phenylketonuria) (*1).

Rare vs. widespread diseases

Metabolic diseases can vary considerably in their incidence. There are very rare diseases such as Gaucher's disease (incidence: 1:100,000), as well as very widespread diseases such as diabetes (7% of the population), gout, adult lactose intolerance and many other intolerances to foodstuffs. Around 500 enzymatic defects are known to affect the metabolism of intracellular organelles (lysosomes, peroxisomes and Golgi apparatus) and the energy metabolism as well as the synthesis and degradation of proteins and lipids.

“Light“ and “severe” disease symptoms



Metabolic disorders often lead to secondary diseases such as osteopenia, which is a pre-stage of osteoporosis, generating loss of bone.

In general, metabolic diseases affect the entire organism. Some of them may only be associated with "light" (such as intolerance to lactose) consequences or symptoms, whereas some are associated with "severe" consequences or symptoms. Many metabolic disorders lead to the dysfunction of organs and other body systems. For example, in people suffering from Gaucher's disease, which is

characterised by the lack of an enzyme required to degrade sugar-containing substances, organs such as the spleen, the liver or the lungs swell, potentially leading to irreparable damage that could eventually have fatal consequences. Some metabolic diseases are characterised by the body's inability to degrade certain storage and signalling substances, which in turn leads to metabolic disorders.

If several fatty metabolism disorders occur simultaneously, this has a drastic effect on the brain. Disorders in the sugar metabolism often entail disorders in the skeletal muscles. Primary metabolic myopathies include muscular diseases that result from genetic disorders of the anaerobic and aerobic energy metabolism. People with such diseases suffer from muscle cramps, amyotrophia, stress-induced amyotrophia and an increase in creatine kinase concentrations. Metabolic myopathies include glycogen storage diseases such as Pompe's disease (1 of 40,000 life births), a genetic disorder characterised by a defect in a gene that encodes an enzyme called alpha 1,4-glucosidase (GAA). The disorder is caused by the accumulation of glycogen in certain tissues that impairs their proper function. Other metabolic myopathies are lipid myopathies, metabolic diseases arising from a disorder in individual enzymes (e.g., MAD deficiency). Metabolic diseases are often the consequence of celiac disease and associated vitamin deficiencies. Vitamin deficiency can lead to anaemia or to an individual's increased susceptibility to infections. On the other hand, metabolic diseases might also be the cause of diseases such as arteriosclerosis.

Neurometabolic diseases

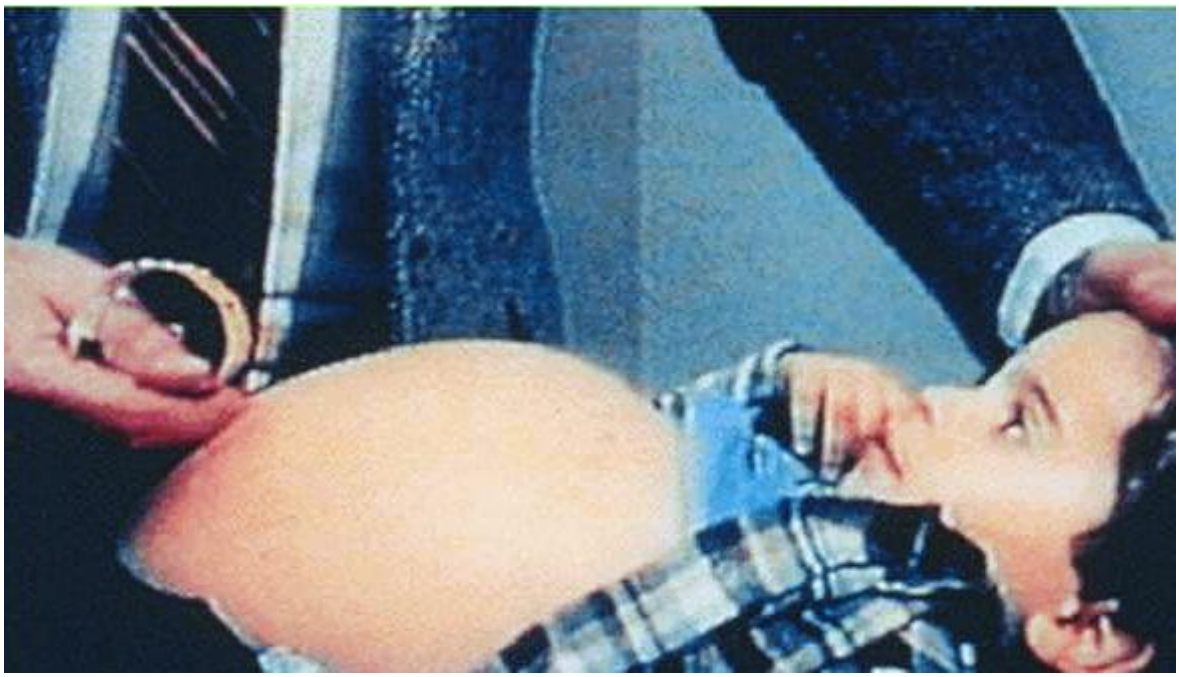
When metabolic diseases occur in the first few months of life, they are frequently associated with severe neurological dysfunctions. The central nervous system, which is not fully developed until adolescence, is particularly susceptible to developing metabolic encephalopathies, since the enzymatic defect leads to the lack of vital metabolic components and/or the accumulation of toxic metabolites and pathological degradation products. Hereditary metabolic defects such as Crigler Najjar syndrome (which affects the bilirubin metabolism) often results in damage to the nervous system. That is why these disorders are called neurometabolic and heredodegenerative diseases.

"Deadly quartet" as the first signal

Metabolic disorders, in particular the metabolic syndrome (otherwise known as the "deadly quartet" - obesity, fatty metabolism disorders, high blood pressure and insulin resistance), are characterised by a broad range of metabolic changes that can be detected and treated long before the onset of the actual disease. Metabolic syndrome is a combination of medical disorders that increase the risk of developing diabetes and cardiovascular diseases. Early and independent treatment of the medical disorders is required. The non-medical approaches for treating these diseases are very similar, including weight reduction, physical activity and muscular work. Medication (e. g., fibrates or cholesterol synthesis inhibitors/statins) is only considered in cases when the aforementioned strategies have not been successful.

Great expectations? Stem cells and gene therapy

Medical progress over the last few years has shown that functional and medical genome research can make a considerable contribution to major advancements in the diagnosis and therapy of metabolic diseases. Scientists and physicians recently succeeded in using gene therapy to treat a young child suffering from a deadly congenital metabolic disease. The child was suffering from a disease in which the deficiency of the molybdenum co-factor (MoCo) leads to the accumulation of



Congenital metabolic disorders such as Gaucher's disease might have severe effects, for example a considerably enlarged abdomen

toxic sulphite deposits in the brain. The scientists found a way to introduce the missing genetic information that once again enabled the child to produce functional quantities of MoCo.

Cystic fibrosis, which is also known as mucoviscidosis, is a common hereditary disease which often causes premature death. New strategies for the development of cause-related treatments are being investigated, for example functional and pharmacological CFTR correction. Alternative ion channels are used to take over or replace the function of defective chloride channels. Another method, referred to as "transfection", is also being talked about as a potential way to treat the disease. Foreign DNA is introduced into bacteria or viruses which then transfer the introduced gene. For many sufferers of metabolic disorders, for example those suffering from cystic fibrosis, stem cell therapy is the only hope for an improvement in their health. However, stem cell therapy throws up ethical concerns, both in medical research as well as in the public arena.

Potential approach: identification of metabolism genes

Genome-wide association studies with metabolic products are now being used to determine the genetic variations of individuals. These studies use DNA microarrays (DNA chips) to determine hundreds of thousands of genetic variations. Higher frequencies of certain genetic variations in a particular group enables researchers to determine the genomic locus where the candidate genes might be located and to use other DNA analysis methods to identify genes or functional gene variants. The identification of genes involved in such diseases is regarded as a prerequisite for developing therapies for the treatment of metabolic diseases.

Research on the advance

One third of all research projects carried out by German biotech companies deal with cancers. However, increasing focus is being put on research into metabolic diseases. About 2 to 5% of all research projects now focus on metabolic diseases (*2). On the European level, the field of oncology is still the medical field of greatest research and therapy interest (516 drug candidates), however,

128 drugs are currently available for the treatment of metabolic diseases (for comparison: 262 pharmaceutically active substances are available for the treatment of infectious diseases). In terms of revenues achieved with biopharmaceuticals, a study carried out in Germany in 2008, found that the metabolic drug market achieved 768 million euros, whereas the field of infectious disease treatment achieved 528 million euros (*3).

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Literature:

(*1) Leary LD, Nordli DR, De Vivo Jr, De Vivo DC. Epilepsy in the setting of inherited metabolic and mitochondrial disorders. In:
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(*2) Comparison Between German and Swiss Biotech Companies. In: Novumed Biotech Finder, Novumed GmbH Life Science Consulting, Dr. Jörn Leewe

(*3) Boston Consulting Group (BCG) - study on behalf of VFA Bio

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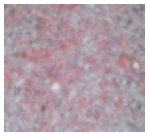

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