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Liisa Paavola

SALLA DISEASE – RARE BUT DIVERSE

A CLINICAL FOLLOW-UP STUDY OF A FINNISH PATIENT SAMPLE

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INSTITUTE OF CLINICAL MEDICINE,
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A clinical follow-up study of a Finnish patient sample

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 4 of Oulu University Hospital, on 26 April 2013, at 12 noon

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Abstract

Salla disease (SD) is a rare lysosomal storage disorder, belonging to the Finnish disease heritage. The condition leads to intellectual disabilities. Two main categories of the disease have been identified – a conventional subtype and a severe subtype. The gene locus of SD has been assigned to a restricted region on the long arm of chromosome 6. The gene *SLC17A5* is responsible for lysosomal-membrane sialic acid transport.

The objective of this study was to describe the neurocognitive developmental spectrum of SD in a long follow-up study. In the original study (1997–1999), the sample consisted of 41 Finnish patients with Salla disease. They were examined by a paediatric neurologist, a psychologist and a speech therapist. The follow-up study (2010–2012) concerned of 27 (66%) patients from the original SD patient sample. The study included neurological and neuropsychological investigations. A case study of a mildly affected female patient was also reported.

In the first study, the typical neurocognitive profile of SD was outlined and the different phenotypes confirmed. The neurocognitive profile of SD consisted of a strong motor handicap, but also well-developed skills in verbal comprehension and interaction. In the follow-up study, the main finding was that the verbal skills related to comprehension did not diminish over time. However, the skills that demanded productive speech were worsened by both dyspraxia and dysarthria, markers of dysfunction of the cerebellum. The neurocognitive and neurological status of the mildly affected female patient remained stable during the long follow-up time. In addition the MRI findings revealed mild dysfunction.

The results indicate that the neurocognitive deficits related to SD are clear in childhood, but the illness does not have a rapid progressive nature after teenage years. The motor handicap is strong but the cognitive skills related to verbal comprehension, and interactive skills, do not deteriorate in adulthood. Four different neurodevelopmental periods can be outlined.

Keywords: dysmyelination, follow-up study, free sialic acid storage, neurocognitive development, rare diseases, Salla disease

Paavola, Liisa, Sallan tauti – harvinainen mutta monimuotoinen.
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Tiivistelmä

Tämän tutkimuksen tavoitteena oli kuvata Sallan tautiin liittyvä neurokognitiivisen kehityksen kulku pitkän seurantatutkimuksen aikana. Sallan tauti, erittäin harvinainen lysosomaalinen kertymäsairaus, kuuluu suomalaiseen tautiperimään. Nämä perinnölliset sairaudet ovat Suomessa yleisempiä kuin muissa maissa. Sallan tauti etenee älylliseen kehitysvammaisuuteen. Kaksi taudin päätyyppiä, tavanomainen ja vakava-asteinen fenotyyppi, on tunnistettu. Sallan taudin aiheuttavan geenin sijainti on paikallistettu kromosomiin 6. SLC17A5-geeni vastaa sialihapon kuljetuksesta solujen lysosomeissa.

Ensimmäisen tutkimuksen (1997–1999) aineisto koostui 41 suomalaisesta Sallan tautia sairastavasta potilaasta. Neurologi, psykologi sekä puheterapeutti tutkivat jokaisen potilaan. Seuranta-aineisto (2010–2012) koostui 27 (66 %) potilaasta. Tutkimukseen kuului neurologin sekä neuropsykologin tutkimus. Lieväoireisen naispotilaan kehityskulku julkaistiin erillisenä tapaustutkimuksena.

Ensimmäisessä tutkimuksessa selvitettiin Sallan taudille ominainen neurokognitiivinen profiili, lisäksi vahvistettiin kahden eri fenotyypin olemassaolo. Neurokognitiivisiin tyyppioireisiin kuuluivat vahvat motoriset defektit, mutta toisaalta hyvin kehittyneet kielelliset taidot puheen ymmärtämisen osalta. Myös vuorovaikutustaidot olivat vahvat. Seurantatutkimuksen päätulos oli puheen ymmärtämisen taitojen säilyminen taudin edetessä. Puheen tuottamiseen liittyvien vaikeuksien osalta sekä dyspraksia että dysartria heikensivät kielellistä toimintakykyä. Nämä kielelliset defektit liittyvät pikkuaivojen toimintahäiriöihin. Lieväoireisen naispotilaan neurologiset ja neurokognitiiviset löydökset eivät olleet edenneet pitkän seurantatutkimuksen aikana. Myös aivojen kuvantamistutkimuksen tulokset olivat lievät.

Sallan tautiin liittyvät neurokognitiiviset muutokset ovat selkeät lapsuusiässä, mutta sairauden luonne aikuisiällä ei ole nopeasti etenevä. Motorisen toimintakyvyn defektit ovat vahvat, mutta kielellisen ymmärtämisen ja vuorovaikutuksen taidot eivät heikkene aikuisilla potilailla. Taudista voidaan erotella neljä erilaista kehityksellistä vaihetta.

Asiasanat: dysmyelinaatio, harvinaiset sairaudet, neurokognitiivinen kehitys, Sallan tauti, seurantatutkimus, vapaan sialihapon kertyminen

For My Grandmother Elina

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This thesis is dedicated to my late grandmother Elina Sirniö. Thank You for believing in me and sharing my dreams.

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Kiiminki, March 2013 Liisa Elina Paavola

Abbreviations

AGA	Aspartylglucosaminidase
AGU	Aspartylglucosaminuria
BSID-II	Bayley Scales of Infant Development-II
CNS	Central nervous system
COH1	Cohen syndrome
CT	Computed tomography
DA	Developmental age
DNA	Deoxyribonucleic acid
DS	Down syndrome
EEG	Electroencephalogram
EPM1	Progressive myoclonus epilepsy, Unverricht-Lundborg type
FDG	2-fluoro-2-deoxy-D-glucose
FINDIS	Finnish disease database
FDH	Finnish disease heritage
FSC	Frontal-subcortical circuit
HIV	Human immunodeficiency virus
H-MRS	Proton magnetic resonance spectroscopy
INCL	Infantile neuronal ceroid lipofuscinosis
IOSCA	Infantile onset spinocerebellar ataxia
ISSD	Infantile sialic acid storage disease
IQ	Intelligence quotient
LD	Learning disabilities
LSD	Lysosomal storage diseases
MEB	Muscle-eye-brain disease
MRI	Magnetic resonance imaging
NANA	N-acetylneuraminic acid
NCLs	Neuronal ceroid lipofuscinoses
NEPSY	Children´s Neuropsychological Test battery
NIH	National Institutes of Health
NLD	Nonverbal learning disabilities
PANESS	Physical and Neurological Examination for Soft Signs
PEHO	Progressive encephalopathy with edema, hypsarrhythmia and optic atrophy
PET	Positron emission tomography
PME	Progressive myoclonus epilepsy
PNS	Peripheral nervous system

SD	Salla Disease
SPSS	Statistical Package for Social Sciences
TS	Turner syndrome
TUG	Timed Up and Go-test
WISC-R	Wechsler Intelligence Scale for Children-Revised
WISC-III	Wechsler Intelligense Scale for Children-III
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised
VMI	Visual-Motor Integration Test
WS	Williams syndrome

List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Varho T, Alajoki L*, Posti K, Korhonen T, Renlund M, Nyman S, Sillanpää M & Aula P (2002) Phenotypic spectrum of Salla disease, a free sialic acid storage disorder. Pediatr Neurol 26(4): 267–273.

II Alajoki L*, Varho T, Posti K, Aula P & Korhonen T (2004) Neurocognitive profiles in Salla disease. Dev Med Child Neurol 46(12): 832–837.

III Paavola L, Remes A, Sonninen P, Kiviniemi V, Korhonen T & Majamaa K (2012) An unusual developmental profile of Salla disease in a patient with the SallaFIN mutation. Case Report Neurol Med vol. 2012 (2012), article 615721, doi:10.1155/2012/615721.

IV Paavola L, Remes A, Harila M, Varho T, Korhonen T & Majamaa K (2012) A 13-year follow-up of Finnish patients with Salla disease. Manuscript.

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Contents

1 Introduction

Salla disease (SD), a free sialic acid storage disorder, belongs to the Finnish disease heritage (FHD), a group of inherited disorders that are more common in Finland than elsewhere. It was first detected in a northeastern part of Finland, Salla, in the late 1970´s (Aula *et al*. 1979). Up to now, approximately 150 SD patients have been diagnosed, mainly in Finland and Sweden (Aula *et al*. 2000, Erikson *et al.* 2002). The high incidence of SD in Sweden could be explained by the common history of the countries, as well as the admixture of these two populations. Only about 30 cases of free sialic acid diseases have been reported in other countries. The disease is caused by mutations in the gene *SLC17A5*, which is responsible for lysosomal-membrane sialic acid transport. About 95% of Finnish SD patients are homozygous for the same missense mutation p.R39C, which is called the $Salla_{FIN}$ mutation (Verheijen *et al*. 1999, Aula *et al.* 2000).

The main neuropathological feature of SD is dysmyelination of the central and peripheral nervous system. Pregnancies and deliveries are usually uneventful in SD. The first symptoms are usually noticed at 3 to 12 months of age as nystagmus, muscular hypotonia, ataxia and delayed motor development (Renlund *et al.* 1983, Renlund *et al*. 1984, Aula & Gahl 2001, Varho 2001). SD leads to intellectual disabilities. Life expectancy is only slightly decreased. The phenotypic variation is wide. Two main categories of the disease are recognized: a conventional subtype and a severe subtype (Varho 2001). Magnetic resonance imaging (MRI) shows dysmyelination in all the cerebral white matter and also corpus callosum hypoplasia (Haataja *et al.* 1994a, Autti *et al*. 1997, Sonninen *et al.* 1999). The neurological spectrum of Salla disease has been described (Varho 2001), but follow-up studies related to the typical neurocognitive course of this dysmyelinating disease are missing.

2 Review of the literature

2.1 Rare diseases

A disease is considered rare when it affects a small amount of people compared with the general population, in Europe one affected person per 2000 (http://www.eucerd.eu/) There are thousands of rare diseases in the world (http://rarediseases.info.nih.gov/). These diseases are often chronic and progressive. They are characterized by a broad diversity of disorders and symptoms that vary from disease to disease, and also from patient to patient suffering from the same disease (www.eurordis.org). Salla disease (SD, OMIM 604369) is a particularly rare lysosomal storage disease, belonging to the Finnish disease heritage, FDH (Aula *et al*. 1979, Renlund *et al*. 1983, Norio 2003a, 2003b). Lysosomal storage disorders (LSD) are a large family of inherited diseases, which have been classified according to the storage material. Infantile sialic acid storage disease (ISSD) and SD are known to be associated with mutations in the gene *SLC17A5* (Verheijen *et al*. 1999, Aula *et al.* 2000). Sialic acids are a family of related compounds which are derived from neuraminic acid. The major sialic acid in humans is N-acetylneuraminic acid (NANA). The gene *SLC17A5* codes for a protein responsible for sialic acid transport across lysosome membrane. This mechanism is required for normal CNS myelination (Prolo *et al.* 2009).

2.2 Finnish disease heritage

The amount of ancient ancestors of the Finns was relatively small, because great migrations of people did not take place in the north. Ancestors brought a random assortment of disease genes to Finland, and the assortment remained unchanged for a long period because of geographic, linguistic and cultural reasons. The strong wave of internal migration in the 1500´s, the late settlement, re-distributed this assortment. Many families from southeastern part of the country moved into the unsettled forest areas in the east and north. Aided by the founder effect and genetic drift, the genes of the settlers formed clusters, which, with little further mixing, have remained to the present day. Most of the diseases belonging to FDH are inherited in an autosomal recessive fashion (Norio 2003a) and many of these

diseases occur concentrated in areas of late settlement as a consequence of the founder effect (Norio 1981, Norio 2003a).

FDH was presented in print for the first time in Finnish in 1972 (Perheentupa 1972) and in English in 1973 (Norio *et al.* 1973). It includes 36 inherited disorders that are more common in Finland than elsewhere (Norio 2003c, Finnish Disease Database Findis, www.findis.org). A great proportion of the genes of FDH are known. Of the diseases, 32 are autosomal recessive, two autosomal dominant and two X-chromosomal. Almost 1/3 of these diseases cause intellectual disabilities and visual handicap. Also epileptic and deteriorating neurological diseases are represented, as well as genital malformations, bone disorders, hearing loss, metabolic disturbances, blood disorders and multisystemic syndromes.

One major mutation has been identified for all the diseases belonging to FDH (Peltonen *et al.* 1999). Other mutations are usually found as compound heterozygotes, together with the major mutation (Norio 2003a). Genetic studies during the last decades have shown that long-term genetic drift and gene flow may also explain the factors behind the FDH and regional differences related to Finnish population (Norio 2003a, 2003b, Palo *et al*. 2009).

2.3 Free sialic acid storage diseases

Three forms of free sialic acid storage disorders are known. Infantile sialic acid storage disease, an intermediate variant of SD, and SD disease are lysosomal storage disorders (LSD) due to impaired function of sialic acid transporter, sialin, at lysosomal membrane (Aula *et al*. 2006, Aula and Gahl 2001, Adams *et al*. 2008). They share the same biochemical mechanism, a defective proton-driven transport of sialin, a protein involved in transport of sialic acid, across lysosomal membrane to the cytoplasm (Aula *et al*. 1986, Aula and Gahl 2001, Suwannarat 2005). All these LSDs are due to mutations in the anion sugar transporter gene, *SLC17A5* (Verheijen *et al*. 1999). Several mutations of the sialin gene are known (Aula *et al.* 2006) and they have great variability in severity. Characteristic symptoms include short stature, coarse faces and neurological dysfunctions. More severe disorders include symptoms related to intellectual disabilities, developmental delays, seizures and behavioral disorders (Brown 2011).

Infantile sialic acid storage disease, ISSD (OMIM 269920) represents the most severe form of these diseases (Hancock *et al*. 1982, Tondeur *et al*. 1982). ISSD patients carry different mutations in the *SLC17A5* gene compared to SD

patients. ISSD children are already severely affected *in utero* or the first signs appear immediately after birth (Aula *et al*. 2000, Salomäki *et al.* 2001, van den Bosch *et al.* 2011). Dysmorphic features, an enlarged liver and spleen, a failure to thrive immediately after birth and severe mental retardation are the clinical manifestations. ISSD is a disease that confers disabilities and the patients usually have a lifespan less than two years. MRI studies (Nakano *et al*. 1996, Pueschel *et al.* 1988) have revealed brain atrophy and high signal intensity in the cerebral white matter and a low signal in the basal ganglia in T2-weighted images.

SD was detected in the parish of Salla in northeastern Finland, in the late 1970´s (Aula *et al.* 1979) and urinary analysis of the first patients revealed a ten-fold increased excretion of free sialic acid (Renlund *et al.* 1979). The diagnostic criteria of SD were proposed on the basis of observations among the first 34 SD patients: 1) moderate to severe psychomotor retardation, 2) defective lysosomal storage and 3) increased urinary excretion of free sialic acid (Renlund 1979, 1983). In order to determine the prevalence of Salla disease and AGU, aspartylglucosaminuria, another member of FDH, screening of urinary oligosaccharides in all mentally retarded patients over 5 years of age was performed in Finland (Aula *et al.* 1986). The estimated carrier frequency of $Salla_{FIN}$ mutation in northeastern Finland is 1:40 to 1:50 (Aula *et al.* 1986, Aula *et al.* 2000) and 1:200 in the whole country.

So far, approximately 150 SD patients have been diagnosed, mainly in Finland and Sweden (Aula *et al*. 2000, Erikson *et al*. 2002). The high incidence of SD in Sweden may be explained by the admixture of Swedish and Finnish population and the common history of the countries. Over 30 cases of free sialic acid diseases have been reported elsewhere, for example in the Netherlands, United Kingdom, France, Argentina, Germany, Egypt, USA and Japan (Echenne *et al.* 1986, Ylitalo *et al*. 1986, Mancini *et al*. 1992, Nakano *et al.* 1996, Sewell *et al*. 1996, Robinson *et al.* 1997, Pueschel *et al*. 1988, Erikson *et al*. 2002, Kleta *et al.* 2004).

2.3.1 The clinical picture of SD

The first symptoms of SD are noticed at 3 to 12 months of age, being nystagmus, muscular hypotonia, ataxia and delayed motor development (Renlund *et al*. 1983, Renlund *et al*. 1984, Aula & Gahl 2001, Varho 2001). Patients under 10 years of age are hypotonic and some of them have distal spasticity. The spasticity increases with aging and is most obvious in severely disabled SD patients. A

severe motor handicap is typical. Peripheral polyneuropathy partly explains the decline in motor skills. One-third of affected children learn to walk. Fine motor skills are worsened by ataxia and athetosis in childhood. The frequency of ambiguous-handedness and left-handedness is as high as 30% among intellectually disabled persons (Bishop 1990), whereas in SD right-handedness is typical (Varho 2001). All patients become intellectually disabled, but life expectancy is only slightly decreased. Though the phenotypic variation is wide, the phenotype of SD has been categorized into two main categories, conventional and severe (Varho 2001, Aula *et al*. 2000, Haataja *et al*. 1994a). Epilepsy is common among both phenotypes (Varho 2001).

2.3.2 Brain imaging

A fairly homogenous dysmyelination pattern in all of the cerebral white matter is typical MRI finding in SD. Hypomyelination in cerebellum has also been documented (Haataja *et al.* 1994a, Sonninen *et al.* 1999). MRI findings correlate with the phenotypic severity (Sonninen *et al*. 1999, Varho *et al.* 2000) and severely affected patients have the most severe pattern and obvious signs of cortical and central atrophy in the cerebrum and cerebellum and brain stem atrophy. The proton magnetic resonance spectroscopy H-MRS, has revealed low choline content in cerebral white matter indicating delayed myelination (Sonninen *et al.* 1999, Varho *et al.* 1999).

Progressive cerebral and cerebellar atrophy is also a typical finding in cases of SD (Robinson *et al*. 1997, Suhonen-Polvi *et al*. 1999, Linnankivi *et al.* 2003, Biancheri *et al.* 2004, Mochel *et al.* 2009). In addition to atrophic changes and dysmyelination, MRI studies have also shown corpus callosum hypoplasia (Haataja *et al.* 1994a, Autti *et al*. 1997, Sonninen *et al.* 1999).

2.3.3 Neuropathological findings

Neuropathological findings have been reported only for two SD patients who died at 41 years of age (Autio-Harmainen *et al*. 1988). The study revealed severe reduction of the cerebral white matter, loss of axons and myelin sheaths and pronounced astrocytic proliferation. Also corpus callosum hypoplasia was described. The observations indicated the possibility of primary axonal degeneration with secondary loss of myelin. The cerebellum showed moderate loss of Purkinje cells.

2.3.4 Molecular findings

In addition to clinical phenotype diagnosis and documentation of increased urinary excretion of free sialic acid, the diagnosis of SD can be established by using DNA analysis, where disease-causing mutations in the *SLC17A5* gene can be identified. The gene locus of SD was assigned to the long arm of chromosome 6 (6q14-6q15) using genetic linkage analyses (Haataja *et al.* 1994b, Schleutker *et al.* 1995a). The first mutations of *SLC17A5* were characterized by Verheijen *et al.* (1999) and Aula *et al*. (2000). Haplotype analyses of Finnish, Swedish and non-Scandinavian SD families were reported by Schleutker *et al*. (1995b). Analysis of Finnish SD chromosomes revealed one common haplotype, which was also seen in most of the non-Finnish patients with the Finnish type of SD.

Among the Finnish SD patients, 95% are homozygous for the founder mutation c.115C->T, p.R39C ($Salla_{FIN}$ mutation) in the *SLC17A5* gene. This suggests a population frequency of ~1/200 (Aula *et al*. 2000). Non-Scandinavian patients have not been reported to be homozygous for the $Salla_{FIN}$ mutation. None of the patients with ISSD have had the $Salla_{FIN}$ mutation. Few patients with SD are compound heterozygotes harbouring the $Salla_{FIN}$ mutation in one allele and a different *SLC17A5* mutation in the other. Compound heterozygotes have a more severe phenotype than the homozygotes (Varho 2001).

2.4 The neuropsychology of intellectual disabilities

Neuropsychology can be defined as the study of brain-behavior relationships. The aim of neuropsychological assessment is to examine these relationships through methods that have been developed for measuring specific cognitive functions. In addition to evaluating general intellectual domains, specific aspects of neurocognitive development are examined. In most cases, skills are related to attention, memory and learning, executive functions and motor development.

In the history of neuropsychology, one main discovery was the localization and lateralization of language in the brain. Early clinical studies by Bouillard (1796–1881) showed that certain verbal functions are localized in the cortex and speech is localized in the frontal lobes. Later on, the studies of Broca (1824–1880) revealed the location of speech in the third gyrus of the frontal lobe on the left side of the brain. Wernicke (1848–1904) provided the first modern model of brain function, the organization of language in the left hemisphere (Kolb and Whishaw 2009).

Also the studies of loss and recovery of functions in animals and people revealed new information about the brain. The role of the cortex in behavior was still unclear. The concept of "hierarchical organization" of brain functions was proposed by neurologist Hughlings-Jackson (1835–1911). He concluded that the nervous system was organized as a functional hierarchy, from lower levels to higher, more complex areas of behavior (Kolb and Whishaw 2009).

The neuropsychological models presented by Luria (1966, 1973) have formed the clinical basis of neuropsychological assessment. He was among the first researchers, who suggested that anatomical criteria could be used to classify the hierarchy of cortical areas. In his theory of high cortical functions, the brain was divided into three blocks or cortical units. These blocks have a hierarchical structure with cortical areas, arranged functionally above the other. Block One, consisting of the brainstem and the reticular system, is responsible for regulating the tone of the cortex, as well as the level of consciousness and arousal. Block Two - the parietal, occipital and temporal lobes of the brain, receives and encodes sensory information. Block Three consists of the frontal lobes and the prefrontal regions and is responsible for executive functions. Christensen (1975) has published Luria´s Neuropsychological Investigation, introduced the evaluation procedures and reported the experiences of its use in the Nordic countries. The clinical and research applications of Luria´s test battery have also been described (Christensen & Caetano 1999).

Kolb & Whishaw (1990) introduced a neurocognitive model related to the organization and functions of the brain. Their model, based on the co-operation and reciprocal connections between sensory and motor systems, included four principles. Posterior parts of the brain were mainly responsible for the sensory tasks and the other, anterior areas for motor functions. The nervous system was organized in a parallel way, so that each of the sensory systems could have their own path into a special motor system. In order to organize the functions of different neurons, the nervous system was built in a hierarchical way. This system enabled the regulation of the more complex behavior. In this model, many of the functions, localized in the posterior part of the brain, were supposed to be lateralized, so that the two hemispheres could function separately. Later on, Kolb and Whishaw (2009) have complemented their principles of lateralization and the functions of the brain. In right-handed people, the right hemisphere has a greater role in the control of certain nonverbal and visual-spatial abilities. Language and the control of complex voluntary movements have a greater impact from the left

hemisphere in right-handed people. Still, it is not known, what processes the two hemispheres are specialized to perform.

In the history of neuropsychology, three phases, structural, theoretical and dynamic, can be outlined. Integration of the structural knowledge of brain development with theoretical neuropsychological models has improved the understanding of neurocognitive phenomena (Frampton 2004). New neurocognitive models of brain functions and domains have complemented the earlier theories of high cortical functions. According to Fuster (2003), developing cognitive networks organize themselves hierarchically, and the cortex can be seen as a part of many networks. These cortical networks, *cognits*, are parts of many items of knowledge: memory functions, perception, attention, language and general intelligence. They contribute to behavior by performing the sensory and the motor functions they represent. In goal-directed behavior, posterior and frontal cognits work together to coordinate the action. At every level, action is guided by feedback from previous actions. This co-operation of integrating stimuli and feedback signals forms the framework of perception-action cycle. The cycle operates at all levels of the nervous system, from the spinal cord to the cerebral cortex. The feedback enables the brain to prepare for both perception and action (Fuster 2009).

Neuropsychological assessment, a paradigm of understanding behavior, is based on the use of age-specific norm-referenced tests. Variation in the tests is wide. Assessment of a patient with intellectual disabilities and learning difficulties is challenging, because deficits in brain-behavior interaction are diverse (Pennington 2009, Goldstein & Reynolds 2011). They are often related to attention, short-term memory span as well as sequential information processing. Language and visuospatial skills tend to vary (Pulsifer 1996). In the field of intellectual disabilities, the neurocognitive characteristics and profiles of Down syndrome DS), Williams syndrome (WS), Turner syndrome (TS) or Fragile X syndrome are well documented. DS is one of the chief causes of intellectual disabilitity. There are several types of DS, the most prevalent being trisomy 21. Other types are translocation 21, partial trisomy 21 and mosaicism. The typical neurocognitive profile consists of delayed motor and cognitive development, especially with language skills. Both receptive and expressive language skills are affected (Hazlett *et al.* 2011). WS is caused by deletion of about 26 genes from the long arm of chromosome 7. The typical neurocognitive findings are good skills in language and verbal short-term memory and difficulties in visual-spatial and constructive skills (Morris 2006, Martens *et al*. 2008). TS is one of the most

studied chromosomal abnormalities in females, linked with a loss of or an abnormality in one of the two X chromosomes (Powell *et al.* 2011). The neurocognitive phenotype is characterized by specific deficits in visual-spatial and executive skills, visual working memory, and mathematics (Mazzocco 2006). Fragile X syndrome is a single gene disorder, caused by an expanded CGG trinucleotide repeat on the long arm of the X chromosome. The full mutation, more than 200 CGG repeats, has a specific phenotype with behavioral, attentional and emotional problems. Neurocognitive deficits can range from mild learning disabilities to severe intellectual disability (Schneider *et al.* 2009). The cognitive profile includes difficulties in arithmetic, short-term memory and sequential processing. Attention and inhibitory control difficulties, as well as fine and gross motor weaknesses have also been reported (Loesch *et al*. 2003).

The neuropsychological test batteries BSID-II and NEPSY (Pääkkönen 1990, Bayley 1993, Korkman 1998, 2007b) as well as Wechsler children´s intelligence scales (Wechsler 2003, 2004) are among the tests typically used with intellectually disabled persons. These test batteries include cognitive tasks related to learning, memory, perception, attention, language and general intelligence. Test selection is complemented with assessment methods concerning various motor tasks as well as tests related to working memory, executive functions and attention regulation.

2.4.1 Neurodevelopmental disorders in FDH diseases

Atypical neurocognitive development has been described in FDH diseases (Norio 2003c) including AGU (aspartylglucosaminuria), Cohen syndrome (COH1), neuronal ceroid lipofuscinoses NCLs (INCL, Northern epilepsy, Jansky-Bielschowsky disease variant and Spielmeyer-Sjögren disease), IOSCA syndrome (infantile onset spinocerebellar ataxia), muscle-eye-brain disease MEB and PEHO syndrome (progressive encephalopathy with edema, hypsarrhythmia and optic atrophy). In addition, progressive myoclonus epilepsies (PME) constitute a heterogeneous group of diseases characterized by myoclonus, epileptic seizures and progressive neurological deterioration (Genton 2010). Unverricht-Lundborg (EPM1, OMIM254800), the most common form of PME, causes neurocognitive dysfunctions, varying from mild to severe states (Koskenkorva *et al.* 2009, 2011).

AGU is a well-documented lysosomal storage disorder with a unique developmental profile (Arvio 1993a, 1993b, Arvio *et al.* 1993). It is one of the most common diseases belonging to FDH. The prevalence is estimated to be at

least 1:18000. The birth places of the grandparents cover most parts of the country (Norio 2003a). It is caused by mutations in the aspartylglucosaminidase (AGA) gene (Ikonen *et al*. 1991). Neurocognitive development in SD differs notably from AGU. The most characteristic feature of AGU is the progressive nature of intellectual disabilities. Children with AGU are mildly affected, fussy and talkative. They are relatively independent in their everyday life. The neurocognitive skills of AGU patients tend to peak at 13–16 years, when their developmental ages correspond to those of healthy 5–6-y-olds. Middle-aged patients are profoundly mentally retarded, quiet and calm, but aggressive when disturbed. They need continuous help from others (Arvio 1993a). In SD, the first neurological symptoms can be seen during the first year of life. Older children are hypotonic, and spasticity starts to increase with aging. Motor handicap is severe. Similar to AGU, adult patients with SD are intellectually disabled.

EPM1 is an epileptic disorder with motility difficulties and myotonic jerks. It is caused by mutations in the cystatin B gene in chromosome 21q22.3 (Pennacchio *et al*. 1996). After the first years of normal development, epileptic seizures start at the age of 5–16 years. Involuntary myoclonic jerks are provoked by various stimuli, such as flashing light or physical exertion. During the first five to ten years, the symptoms progress and stabilize thereafter (Magaudda *et al.* 2006). About one-third of the patients become severely affected and need help in active daily living (Kälviäinen *et al.* 2008). The neurocognitive profiles of adult EPM1 patients vary (Koskenkorva *et al.* 2011).

2.4.2 Neuropsychological aspects of dysmyelination

Human brain development begins in the third gestational week and continues throughout life. Differentiation of the cells shows different spurts and sensitivity changes in both normal and abnormal development. Different populations of neurons form grey-matter structures in many important areas, including cerebellum, midbrain structures and the neocortex. After positioning in the cortex, neurons begin to differentiate. Some of them produce neurotransmitter and neurotrophic factors. Others are specialized in extending the axonal and dendritic processes, forming fibre pathways of the brain neural networks, thus making up the brain white matter. The efficiency of information transmission is strengthened by myelin. Normal myelination of the developing brain begins during the fifth fetal month with the myelination of the cranial nerves (Barkovich *et al*. 1988). It has an orderly pattern in the functional maturation of the neural circuits in white

matter regions, commencing in the brain stem and progressing to the cerebellum and cerebrum (Stiles *et al*. 2010). There are several frontal-subcortical circuits (FSC) in human brain which are activated in both planning and execution of motor acts and in cognitive, emotional and sensory processing (Lichter & Cummings 2001, Tekin & Cummings 2002, Lang *et al*. 2006, Baliki *et al.* 2008). They form reciprocal connections from specific areas of the frontal cortex to certain lower brain networks (Damasio 1988, Davidson *et al*. 2000, Adolphs 2002, Bechara *et al.* 2003, Sheehan *et al.* 2004).

Nonverbal learning difficulties (NLD) are connected with dys- or demyelination of the white matter (Hamadek & Rourke1994, Rourke 1995). A significant dysfunction confined to the right cerebral hemisphere may constitute nonverbal learning difficulty syndrome. The more white matter is dysfunctional, the more likely it is that nonverbal learning difficulty syndrome will occur (Rourke *et al.* 2002). The main defects in neurocognitive development of nonverbal learning difficulty syndrome are connected to non-linguistic skills. The right-hemisphere deficit leads to problems in psychomotor coordination, visual-spatial organization skills, complex tactile-perceptual skills, reasoning, concept formation, mechanical arithmetic and scientific reasoning (Spreen *et al*. 1995, Rourke 1995). These primary deficits are thought to lead to secondary deficits in attention and exploratory behavior, and to tertiary deficits in memory and executive functions (McDonald 2002). The NLD phenotype applies best to disorders in which the white matter dysfunction of the right hemisphere is documented to be prominent, for example agenesis of corpus callosum (Rourke 1995, Panos *et al.* 2001). Nowadays NLD is characterized by three broad areas of dysfunction including visual-spatial organization skills, motor skills and social abilities (Semrud-Clikeman *et al*. 2010).

The neurocognitive profiles of both TS and Fragile X syndrome share characteristics that relate to the spectrum of NLD. Girls with TS have good verbal skills, but they are relatively weak in nonverbal skills. Difficulties with arithmetic and visual-spatial skills are typical and the processing speed is low (Mazzocco 2006). Tasks related to visual-perceptual and visual-constructive skills are difficult (Temple & Carney 1995). Attention deficits and difficulties in social situations have also been described (Rovet *et al*. 1994). Studies have shown that females with TS may have neurocognitive impairment suggestive of diffuse bilateral brain involvement (Yeates *et al.* 2000, Tanji *et al*. 2012). In an MRI study (Yamagata *et al.* 2012), TS girls demonstrated significant white matter aberrations in brain regions responsible for face processing, visual-spatial

abilities, and sensorimotor and social abilities compared with controls. The findings indicate that absence of an X chromosome in girls with TS is associated with white matter abnormalities in specific regions implicated in characteristic neurocognitive features of TS.

The neurocognitive deficits of fragile X syndrome especially in girls are related to visual-spatial, visual-perceptual and visual-constructive skills, executive skills, visual working memory, and mathematics. A long response time is a consistent finding across neurocognitive tasks (Kwon *et al.* 2001, Mazzocco 2006). MRI studies of fragile X have revealed delayed white-matter development during early brain development. These abnormalities are located in the left ventral frontostriatal pathway. The primary function of this neural pathway is to regulate cognitive inhibition (Irwin *et al*. 2001, Harnea-Goraly *et al*. 2003, Haas *et al*. 2009).

Children with white matter abnormalities are vulnerable to neuropsychological deficits. However, the relationship between dysmyelination and cognitive functions is non-linear (Semrud-Clikeman *et al*. 2010, Spreen 2011). Children with NLD tend to score poorly in non-verbal tasks, but there is a sizable minority of children who do not. It has been suggested that difficulties are presented in the right-hemispheric white matter in NLD (Rourke 1995) but imaging studies that could confirm the right hemispheric white matter hypothesis have not been published.

Deficits in brain-behavior relationship vary remarkably among intellectually disabled people. It is difficult to define the role of abnormal brain development in neurodevelopmental and genetic disorders with dysmyelination. It may be that the white matter aberrations need to be widespread before neurocognitive impairments can be seen (Anderson *et al*. 2004, Spreen 2011). The sensitivity of the brain to abnormal development may also vary with time. Different brain regions are particularly sensitive to different changes. In SD, for example, the perinatal history and the first months after birth are usually normal. Mature myelination is seen in the brain stem, hemispheres, cerebellar peduncles and stria medullaris thalami but the myelination seems to cease between the birth and the first months (Haataja *et al.* 2004a).

To conclude, learning disabilities (LD) in general are often associated with specific neurodevelopmental disorders or genetic syndromes. Comorbidity in neurocognitive disorders and LDs is high (Goldstein *et al.* 2011). Both the development of brain structures and the level of functions influence learning. Deficits in the genetic program may lead to errors of development that contribute

to severe deficits. Two types of abnormal development, corpus callosum hypoplasia and dysmyelination of cerebrum and cerebellum are typical in SD.

Myelination can be seen as an index of cerebral maturation. It is mainly a postnatal process and continues until nearly 18 years of age (Kolb & Whishaw 2009). The earlier myelinated areas of the brain control sensory analyses and simple movements, whereas the late progress of myelination is seen in the areas that control the highest cognitive functions. With age, cortical areas become more specific in organizing cognitive tasks.

To sum up, neurocognitive development is a continuous process. Main stages of cognitive development have earlier been identified by psychologist Piaget (Kolb & Whishaw 2009). In the model, the child´s strategies for understanding and problem-solving are constantly changing. These changes are connected with the level of myelination in the brain, as well as the growth spurt periods. Cognitive and behavioral abilities follow the sequences of development, from the sensorimotor level to the preoperational level, and further to the stages of concrete and formal operations. White matter development is an important factor in motor, cognitive, behavioral and emotional development during childhood. Maturation of the myelinated pathways has a great impact on the neurodevelopmental changes in brain regions that organize motor skills, memory functions, attention regulation, executive functions and cognitive abilities, for example reading skills (Fuster 2002, Nagy *et al*. 2004, Barnea-Goraly *et al.* 2005, Casey *et al.* 2007, Edin *et al*. 2007, Yeatman *et al*. 2012).

3 Aims and objectives of the study

The aim of the study was to examine and describe the neurocognitive developmental spectrum of SD and to clarify the severity of cognitive changes related to dysmyelination. The specific objectives of the study were:

1. To characterize in detail the developmental age profiles of patients with SD as a function of chronological age, and to describe the typical pattern of their neurocognitive development (Study I-II)
2. To describe a patient with conventional $Salla_{FIN}$ mutation but a unique neurodevelopmental profile (Study III)
3. To identify the developmental milestones of SD patients in a follow-up study over ten years (Study IV)
4. To describe a typical neurocognitive profile and main findings in neurological examination of SD in a follow-up (Study IV)

4 Patients and methods

4.1 Patients

4.1.1 The baseline study

In the baseline study, the subjects consisted of 41 Finnish patients with SD, 19 females and 22 males (median age 19 years, range 11 months to 63 years) with varying severity of clinical symptoms. In the sample, 35 patients were homozygous for the Finnish founder mutation p.R39C. Six patients were compound heterozygous harbouring the p.R39C mutation in one allele (Aula *et al.* 2000, Aula and Gahl 2001). Thirty-seven patients presented with the so-called conventional phenotype with a wide clinical variation. Seven of these cases (age, 3–25 years) constituted a subgroup of mildly affected patients. Four of the most severely disabled patients (age, 15–28 years) constituted a clearly distinguishable group, the so-called severe phenotype. They had spasticity and athetosis and were nonambulant and unable to speak. All of them and 12 of the other patients had epilepsy. All patients had developmental disabilities and needed help in their active daily living.

4.1.2 The follow-up study

The follow-up study concerned 27 patients from the baseline study (12 females, 15 males). The median age was 30 years (range, 16–65 years). Fourteen patients were not examined in the follow-up study. Six female and two male patients had died after the baseline study, seven of them from pneumonia. The mean age at death was 52 years. Six other patients were unwilling to participate in the follow-up study.

In the follow-up study, 22 patients were homozygous for the founder mutation p.R39C and five were compound heterozygous. Six patients, five with the severe phenotype and one with the conventional phenotype, were non-ambulatory. Seven patients needed a walking aid, while 14 patients were able to walk independently. Epileptic seizures were present in 10 of the cases.

4.2 Methods

In the baseline studies (I, II), all patients were clinically examined by the same psychologist, pediatric neurologist and speech therapist. The methods of neuropsychological evaluation are presented in Table 1. Because patients with SD formed a heterogeneous group with a varying level of neurodevelopmental disabilities, different age-related neuropsychological tests were needed. In 37 cases the mental and motor parts of the Bayley Scales of Infant Development II (BSID-II) were used. BSID-II is used to assess the fine and gross motor, receptive and expressive language, and cognitive development of toddlers and infants aged 0–42 months. BSID versions are widely used with different groups of small children, for example with those who are intellectually disabled (Pääkkönen 1990), preterm (Msall 2010, Vohr *et al.* 2012), HIV-positive (Smith 1997), or have neurodevelopmental difficulties due to somatic diseases (Walker *et al.* 2012). BSID versions have proved to be among the most useful instruments in giving comprehensive assessment of the development of infants (Thompson et al. 1991, Harris and Langkamp 1994, Jackson *et al*. 2012).

The Wechsler Preschool and Primary Scale of Intelligence –Revised (WPPSI-R) was performed with three patients with conventional phenotype of SD (two females aged 7 and 20, one male aged 9 years). One mildly affected 16-year-old girl was able to achieve the Wechsler Intelligence Scale for Children – Revised test (WISC-R). Wechsler tests include verbal and performance subtests. Full scale intelligence quotient (IQ) is based on the tests included in verbal and nonverbal IQ scales.

Beery's Visual-Motor Integration Test (VMI) was used to evaluate visual-motor integration skills. Subtests of the Neuropsychological Assessment of Children (NEPSY) were also performed. The handedness of the patients was assessed separately by psychologist and pediatric neurologist observation. The assessment of handedness was also assisted by information from the families of the patients and nursing staff.

Language development (comprehension and expressive speech) of all 41 patients was assessed by a speech therapist using the Symbolic Play Test (Lowe and Costello 1988) and Reynell developmental language scales (Reynell and Huntley 1987).

Brain MRI results were available for 15 patients (Sonninen *et al.* 1999, Varho *et al.* 2000).

In the follow-up studies (III, IV), all the patients were examined by the same neurologist and neuropsychologist. The methods of neuropsychological evaluations are presented in Table 1. BSID-II was used for 26 patients, in order to evaluate the neurocognitive spectrum of development in SD further. Two patients had managed the tasks of WPPSI-R in the baseline study, but were able to perform only the BSID-II tasks in the follow-up study. Their neurocognitive symptoms had progressed. A 30-year-old female patient with a remarkably mild phenotype of SD was able to solve the cognitive tasks of WISC-III. Visual-Motor Integration Test (VMI) was excluded, because it turned out to be too challenging for the adult patient group with a severe motor handicap. New methods, verbal subtests of NEPSY, PANESS test, TUG test and Cerebellar tests were included for evaluation of the atypical developmental pattern in detail. PANESS is widely used in measuring the corpus callosum dysfunctions: lateral preference, gaits, postures as well as repetitive and patterned movements. TUG test is a practical test that has been used in clinical practice as an outcome measure to assess basic or functional ambulatory mobility, or dynamic balance. Cerebellar tests include both static (muscle tone, arm displacement, postural stability, limb shake) and dynamic (finger to thumb, toe tapping, pegboard, beads to thread) tasks. Test selection was based on the information of the earlier brain imaging studies of SD (chapter 2.3.2).

Table 1. Methods used in neuropsychological evaluation.

Abbreviation	Full name of test	Reference	Focus of test / chosen parts	Baseline study	Follow-up study
WISC-R	Wechsler Intelligence Scale for Children-R	Wechsler (1984)	Verbal and perceptual cognitive skills	X	
WISC-III	Wechsler Intelligence Scale for Children-III	Wechsler (1991)	Verbal and perceptual cognitive skills		X
NEPSY	Children´s Neuropsychological Test Battery (3-6 years)	Korkman (1988), Korkman *et al*. (1997)	*Comprehension of Instructions		X
			*Oromotor Sequences		X
			*Repetition of Nonsense Words		X
			*Handedness	X	
			*Fingertip Tapping	X	
VMI	Visual-Motor-Integrating task	Beery (1989)	Visual-motor development	X	
BSID-II	Bayley Scales of Infant Development 2nd ed.	Bayley (1997)	Motor and mental skills	X	X
PANESS	Physical and Neurological Examination for Soft Signs	Denckla (1985), Roeder *et al*. (2008)	Corpus callosum dysfunctions		X
CEREBELLAR tests	Static and Dynamic Cerebellar Tests	Fawcett *et al*. (2001)	Dysfunctions of cerebellum		X
TUG-test	Timed Up and Go-test	Williams *et a*l. (2005)	The basic and functional mobility		X

In the follow-up study, neurocognitive development, progression of symptoms, and neurological findings of a mildly affected 30-year-old female patient were atypical in comparison with the other patients with the same $Salla_{FIN}$ mutation. There was no deterioration in her neurological condition during the follow-up. The case report related to her unique neurodevelopmental profile (III) included neuropsychological investigation, neurological examination and a MRI study. The

methods of neuropsychological investigation were the same as in the follow-up study IV.

4.3 Statistical methods

In the baseline study, BSID-II sum variables were calculated and tested for reliability by calculating Cronbach´s alpha. The probable differences between two age groups (0 to 25y, over 25y) and the sex distribution in cognitive development were tested using a Student's *t*-test procedure. Pearson's correlation coefficients were used to analyze the correlation between expressive and receptive speech and language development, as well as between developmental ages of BSID-II in motor and mental scale. The proportion of left- and right-handedness among SD patients compared with the whole population of those with intellectual disabilities was assessed with a $\chi 2$ test.

In the follow-up study, two of the 26 patients did not complete the BSID-II test in the baseline study and were excluded from the follow-up analysis. The ranges, means and standard deviations of SD patients´ performance (raw scores) of BSID-II test in the first and the follow-up study are presented in Table 2. Probable differences between two age groups ($\leq$ 30 and 30 years) and the sexes in neurocognitive development were tested using Student´s *t*-test or Mann-Whitney *U*-test, as appropriate. In order to study differences between the developmental ages and the results of BSID-II mental and motor scales after the follow-up period, the paired-sample *t*-test was used.

Table 2. Raw scores in mental and motor assessment of 24 patients with SD in the baseline study and in the follow-up study (BSID-II). SD, standard deviation.

Study	Assessment	Raw scores			
		Median	Range	Mean	SD
Baseline	Mental	115	65–164	114	28
	Motor	69	32–101	68	17
Follow-up	Mental	132	40–168	118	44
	Motor	71	24–90	62	23

The NEPSY, TUG test and cerebellar tasks were rated in three levels (no deficits - mild to moderate deficits – clear deficits) according to the reference values of each test (Korkman 1988, Korkman *et al.* 1997, Fawcett *et al.* 2001, Williams *et*

al. 2005). Median was used as the summary statistic as it is less susceptible to the effects of outliers in small data.

All the statistical analyses were conducted using IBM SPSS Statistics v. 20.0 for Windows.

4.4 Ethical considerations

This study was approved by the Ethics Committee of the Oulu University Hospital. Written informed consent was requested from the patients and carers before performing the studies.

5 Results

5.1 The baseline study

Detailed neuropsychological profiles of 41 Finnish patients with SD were examined in the baseline study (I, II). Developmental ages (DA) on the BSID-II mental and motor scales revealed that cognitive development was better than motor development up to the second decade of life, but thereafter the difference between the mental and motor skills diminished (Study II, Figure 1). Mean DAs of the SD patients differed between the severity of the phenotypic findings ($p=0.005$). A severe motor handicap was seen from early infancy. Motor development showed a more rapid decline compared with mental skills after 30 years of age. The DAs of four severely affected patients were markedly lower than those of the remaining patients on both the mental and motor scales. Four of the seven mildly affected patients (age, 7 - 19 years), tested by using the WPPSI-R/WISC-R, had DAs between 3 years 5 months and 6 years 4 months. Their verbal IQ, ranging from 42 to 57, was better than their performance skills ($r=0.79$, $p=0.001$).

Similar to the study by Varho *et al.* (2000), abnormalities in MRI of fifteen SD patients showed a significant correlation with phenotypic severity ($r=0.79$, $p=0.001$).

Neurocognitive profiling of BSID-II mental and motor scale (Study II, Figures 2, 3), showed a typical neurodevelopmental pattern of both conventional and severe phenotype of SD. Receptive language skills were notably better than expressive speech. Difficulties in expressive speech had a stronger association with the phenotypic severity ($r=0.45$, $p=0.003$) than deficits in speech comprehension ($r=0.35$, $p=0.026$). Oral motor difficulties, both dyspraxia and dysarthria were evident especially with adult patients and severely affected. The patients' interactive and non-verbal communication skills were relatively fluent. One mildly affected 16-year-old girl had fluent skills in technical reading, but she could not understand the text.

Most of the patients with SD were right-handed (40/41). Spatial and visual-constructive disabilities were common. Visual and tactile discrimination of forms was poor. Hand-eye coordination, visual attention, short-term visual memory and executive tasks were performed better.

In the baseline study, the characteristic neurocognitive profiles of SD patients showed weaker non-verbal performance compared with linguistic skills. Common features related to nonverbal learning disabilities, NLD, were found (Hamadek *et al.* 1994, Rourke 1995).

5.2 The follow-up study

5.2.1 Neurological features and motor functions

A severe motor handicap was a consistent finding among all the 27 patients, showing a rapid decline after the second decade of life (Study IV). Interestingly, ten patients did not show clear deterioration of motor skills. In the follow-up study, the younger group (≤ 30 years) performed better than the older patients. The differences between the two age groups were significant in tasks demanding visual-motor skills (p=0.030) and walking up and down stairs with help (p=0.023). Motor skills had not decreased significantly between the two examinations.

Fourteen patients were able to walk independently, but only one was able to walk alone in good coordination. Six patients (severe phenotype, 5; conventional phenotype, 1) were non-ambulatory. Seven patients needed a walking aid. Maintaining balance in standing and walking was difficult for most patients (n=26). Motor impairment was also notable in tasks that demanded raising oneself to sitting or standing position or starting a movement. Mirror movements were typical. Non-ambulatory patients suffered from spasticity and were able to sit only with support.

Some patients used pre-walking methods, like crawling, in moving. Non-ambulatory patients were able to make early stepping movements, when helped from a wheelchair to bed. Patients, who needed a walking aid, were able to move short distances independently but had problems in coordination. Ability to walk had deteriorated in patients over 40 years of age, due to increasing spasticity in lower limbs. Tendon reflexes in upper limbs were normal, but patella reflex was abnormally brisk in all cases. All patients suffered from severe planovalgus and Achilles reflex was absent. Babinski sign was positive in 10 cases.

Ataxia was diminished and disappeared between ages of 10–15 years. However, mild to moderate athetosis was present in 25 patients and two of them had suffered from severe athetosis since puberty. Nystagmus was not seen in

adulthood. Instead of nystagmus, all the patients had moderate to severe strabismus at the time of the follow-up.

The typical coarse facial features related to SD developed during teenage years. In addition to epileptic seizures (n=10), three other patients had startle-type reactions to auditory stimulus, for example a loud noise.

Fine motor skills varied notably. Most of the patients (n=25) were able to use partial thumb opposition to grasp an object. Some of the patients (n=16) also used the pads of fingertips in grasping or holding a pen. Copying tasks were difficult, as only four of the patients were able to copy a plus sign but none could draw a circle or trace designs. All the patients were right-handed.

5.3 Neurocognitive development

Both in the baseline study and in the follow-up study the younger patients (≤ 30 years) performed better in almost all tasks of the BSID-II mental scale. The differences were significant in tasks related to constructive skills (p=0.026), basic counting (p=0.016) and immediate visual recognition (p=0.026).The findings were similar in the tests of visual attention and interactive skills between the two age groups.

Receptive language skills were notably better than speech production. All the patients were able to vocalize sounds, but the patients with a severe phenotype could not imitate words. Other patients were able to use at least two different words appropriately. Arithmetic tasks were difficult as only 12 patients were able to name numbers and 9 patients performed correctly the task of counting in order. Pre-reading and pre-writing tasks (e.g. attending to scribbling, imitation of strokes, attending to story, producing utterances in response to picture book) were performed better than arithmetic tasks.

The patients were social, well-tempered and interactive both verbally and non-verbally. All of them recognized familiar faces and voices. They responded to smile and showed different emotional states either verbally or nonverbally. Most of them (n=26) had a definite sense of humor.

Basic verbal memory functions varied between the patients. Talkative patients were able to remember songs and phraseologies and learn new ones. They were also able to learn daily routines and keep short instructions in mind. Concentration skills among the patients varied notably. They were sensitive to loud and sudden noises. Visual tracking and visual attention tasks were performed well.

Tasks that demanded eye-hand coordination (e.g. use of a spoon or a comb) were performed well. The patients had major problems in tasks related to construction of blocks, drawing or spatial planning. Tasks with geometric shapes and spatial orientation showed deficits in visual-spatial reasoning for all patients. Visual-motor performance was slow, but not worsened by ataxia.

The patients were unable to perform the tests that measure the dysfunctions of the corpus callosum (PANESS). Static cerebellar tests (muscle tone, arm displacement, postural stability, limb shake) were too demanding as well. Performance in the dynamic cerebellar tests (finger to thumb, toe tapping, pegboard, beads to thread), verbal tasks of NEPSY and the TUG-test is shown in Table 3. All the patients were able to perform tasks that demanded comprehension of instructions fairly well, though many of them were unable to repeat nonsense words or oromotor sequences. The basic and functional mobility of the patients was severely affected. Dynamic cerebellar tests showed severe deficits in motor sequencing and timing.

Table 3. Frequency of deficits in language and fine motor skills of 27 SD patients.

Test	No deficits (%)	Mild-moderate deficits (%)	Clear deficits (%)
NEPSY			
*Comprehension of instructions	63	10	27
*Oromotor sequences	3	7	90
*Repetition of nonsense words	10	3	87
Dynamic cerebellar tests			
*Finger to thumb	3	4	93
*Toe tapping	33	20	47
*Pegboard task	0	43	57
*Bead threading	13	24	63
TUG-test	10	38	52

5.3.1 Developmental ages of SD patients

Developmental ages of 24 SD patients were determined by using the BSID-II at the baseline and at the follow-up visit (Table 2). The profiles of mental and motor developmental ages of these patients are presented in Fig. 1 and 2. The patients were divided into six groups according to their chronological age (10 years/group) and the group median was calculated. In the follow-up, the median

of mental developmental ages was 27 months (range 2 - 42 months). The median developmental ages of the motor scale was 16 months (range 1–27 months).

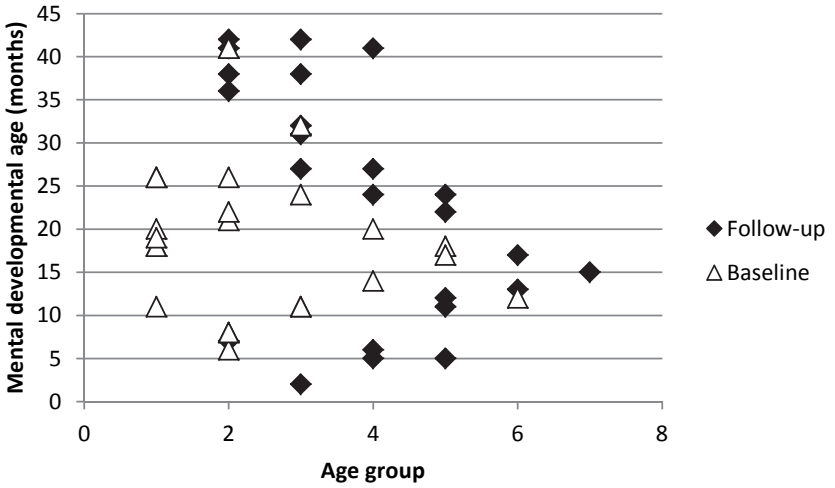

Fig. 1. Developmental ages of 24 SD patients determined by the mental scales of BSID-II. Δ, baseline study; ♦, follow-up study. Chronological ages are presented in 10 years / group.

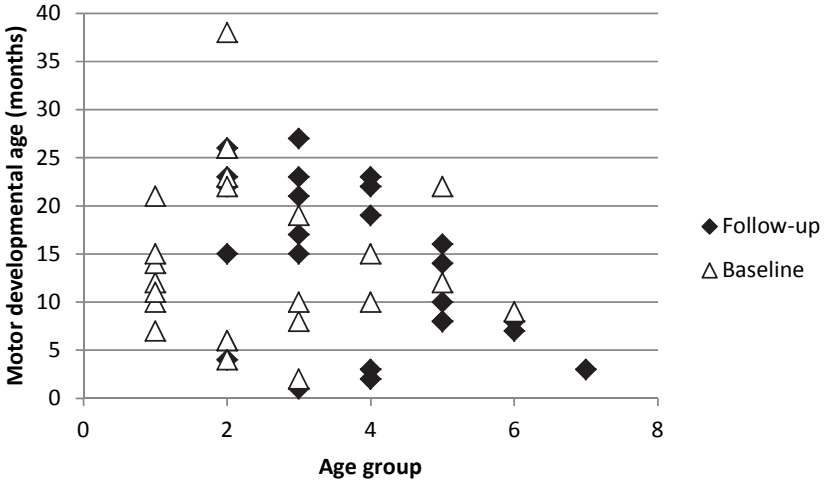

Fig. 2. Developmental ages of 24 SD patients determined by the motor scales of BSID-II. Δ, baseline study; ♦, follow-up study. Chronological ages are presented in 10 years / group.

Neurocognitive development started to decline mildly after the second decade of life. Among adult patients with SD, the neurocognitive development varied notably. After the fourth decade of life, the skills showed a clear decline. On the other hand, young patients with SD learned new cognitive skills during the follow-up time. A severe motor handicap was a constant finding among all the patients and the remaining motor functions declined rapidly after the second decade of life.

5.3.2 Mental and motor assessment of SD patients at baseline and follow-up visit

The twelve most informative sum variables of the BSID-II mental scales with Cronbach´s alpha values between 0.58–0.95 were chosen for the analysis in the follow-up study of 24 patients (Fig. 3). The mean achievement percentages had not increased notably between the baseline study and the follow-up. The main symptoms had not progressed significantly. Some neurocognitive abilities had even slightly improved. Immediate visual recognition skills decreased during the follow-up significantly (p=0.001).

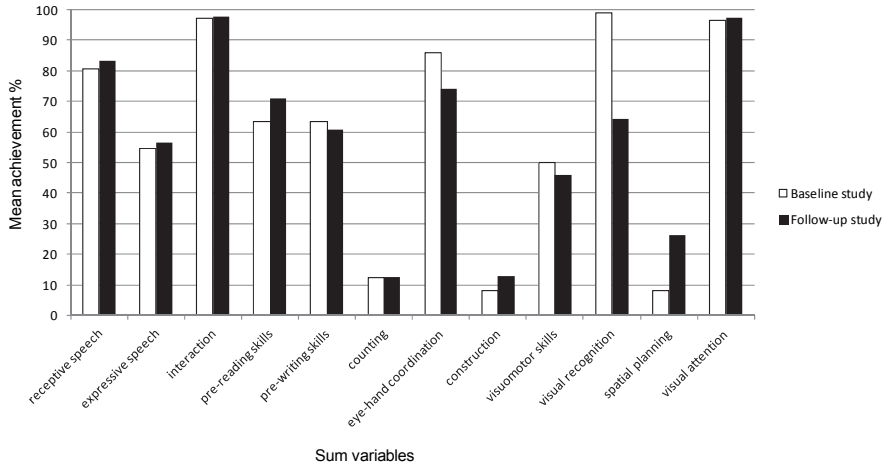

Fig. 3. Mean achievement of 24 patients with SD in 12 tasks of BSID-II mental scale. □, baseline study; ■, follow-up.

All ten sum variables of the BSID-II motor scale had Cronbach´s alpha values greater than 0.67. The motor skills had not decreased significantly between the baseline and the follow-up examination. (Fig. 4).

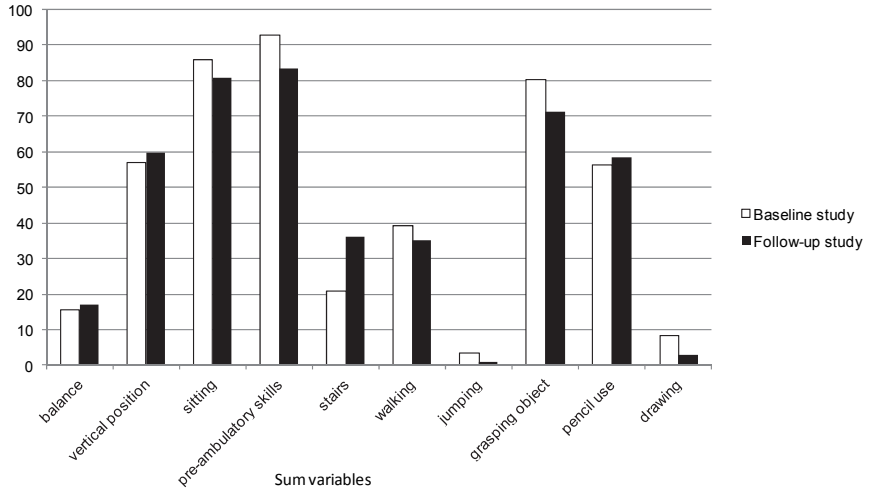

Fig. 4. Mean achievement of 24 patients with SD in 10 tasks of BSID-II motor scale. □, baseline study; ■, follow-up.

5.4 A unique neurodevelopmental profile of a woman with the Salla$_{FIN}$ mutation

A 30-year-old, mildly affected woman was described in Study III. The neurocognitive development during her first year of life was relatively normal. The early neurological symptoms were an unstable crawling, muscular hypotonia and nystagmus. She was able to walk by 1½ years of age, but her balance and gait were developing slowly. First words were spoken at 1 year of age and first sentences at 2 years of age. A year later, the neurocognitive development was assessed as normal, except for mild clumsiness. On the basis of clinical findings and increased level of free sialic acid in the urine, SD was diagnosed at 3 years of age.

In the childhood, mild delays in motor tasks and eye–hand coordination were reported. The patient had problems with concentration and attention tasks. Verbal development was slightly delayed and verbal dyspraxia was described. At the age

of six years, the developmental delay in neurocognitive skills was approximately 2 years.

Ataxic symptoms, prominent in childhood, disappeared by the teenage years. Neurocognitive development fluctuated notably during the primary school. Achievement in verbal subtests of neuropsychological evaluations was better than visual performance or fine motor skills. The problems with balance and body awareness were evident. The level of developmental disability was considered to be mild.

In early puberty, the verbal skills in the WISC-R test were at the level of 7 years of age and the achievement in non-verbal subtests varied between 5½ - 6½ years of age. In the follow-up evaluation at the age of fourteen, no progression was reported in her neurocognitive deficits, the verbal skills had even improved. The DA in WISC-R test varied between 4 and 8 years. Verbal skills were notably better than her achievement in visual or fine motor tasks.

5.4.1 Neurocognitive and motor development

At the age of 30 years, the patient participated in the follow-up study. She was living alone with support. Her performance on neuropsychological tests is presented in Table 4. The DA, as assessed by WISC-III, was 6 years 6 months (7 years 9 months for the verbal scale and 5 years 4 months for the non-verbal scale). Neurocognitive profiles of her performance in WISC-R test at the age of 16 and in WISC-III test in the follow-up are described in Fig. 5. In adulthood, her neurocognitive skills were remarkably better than those of other patients with the conventional type of SD and the $Salla_{FIN}$ mutation. In a reference group of ten patients with a median age of 26 years (range, 23–29 years) the median developmental age was 2 years 8 months (range, 1–42 months; mental scale in BSID-II) and 1 year 5 months (range, 1–27 months; motor scale in BSID-II).

Table 4. Results of neuropsychological evaluation of the female patient with the Salla$_{FIN}$ mutation at 30 years of age.

Full name of test	Abbreviation	Reference	Subtests	Performance[a]
Wechsler Intelligence Scale for Children-III	WISC-III	Wechsler (1991)	*Verbal tasks	1
			*Perceptual tasks	1
Children´s Neuropsychological Test Battery	NEPSY	Korkman *et al*. (1997)	*Comprehension of instructions	0
			*Oromotor sequences	2
			*Repetition of nonsense words	2
Physical and Neurological Examination of Soft Signs	PANESS	Denckla 1985)	Tests of corpus callosum dysfunction	2
Static and Dynamic Cerebellar Tests	Cerebellar tests	Fawcett *et al*. (2001)	Tests of cerebellar dysfunctions	1
Timed Up-and-Go-test	TUG-test	Williams *et al*. (2005)	Tests of basic and functional mobility	1

[a]0=among average, 1=mild impairment, 2=severe impairment.

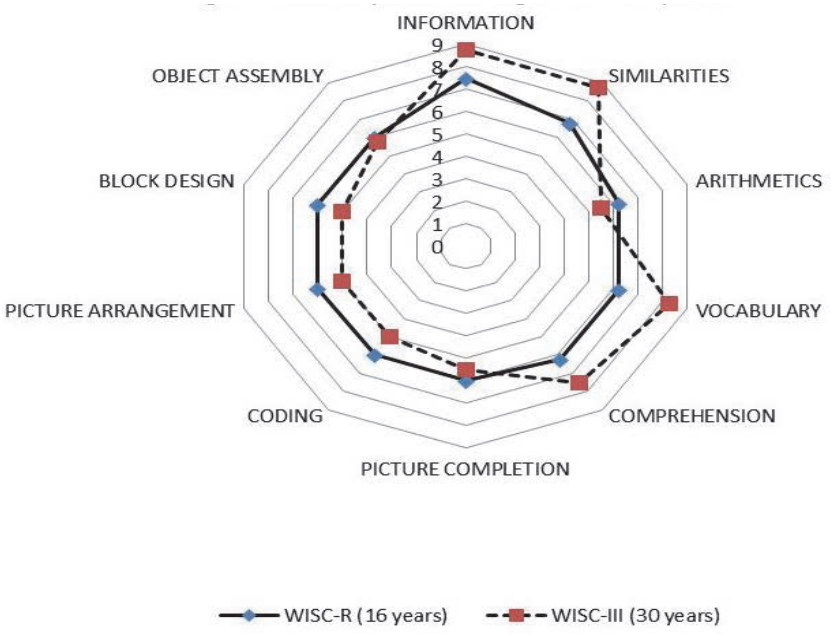

Fig. 5. Developmental age of the proband. Solid line, WISC-R at 16 years of age; dotted line, WISC-III at 30 years of age.

Spatial orientation and visual reasoning were mildly delayed and visual-constructive skills diminished during the follow-up time. There was also a slowing in eye–hand coordination and in a speed of motor actions. Verbal skills had slightly improved. The patient was able to learn and repeat long, logical stories. Repetition of oromotor sequences and nonsense words (NEPSY subtests) were difficult because of oral and verbal dyspraxia.

Motor deficits were evident but the progression of the symptoms was not significant during the follow-up period. Skills had improved with respect to balance, coordination of body movements and reciprocal motor actions. However, motor actions had become slightly slower. Static cerebellar tests were performed with slight problems with balance. Two of the dynamic cerebellar tests, toe tapping and finger-to-thumb tapping, were performed correctly. The test of basic functional mobility (TUG) was performed quite well.

5.4.2 Neurological examination

At the age of 30 years, the patient was 157 cm in height and weighed 56 kg. Auscultation of the heart and lungs was unremarkable; her blood pressure was 114/74 mmHg and the electrocardiogram was normal. The patient´s facial features were slightly coarse. She was able to walk without aid, but both legs were in a pes planus position. She had some athetotic movements in her upper extremities. Muscle strength and skin sensation were normal. Tendon reflexes were normal and symmetrical. The plantar responses were in flexion. There was mild spasticity in both legs and Achilles tendons were slightly shortened.

In neurological examination, only mild ataxia was revealed. There was mild instability in the Romberg test. The patient was unable to stand with eyes closed. Coordination tests showed no ataxia or dysmetria, but hand movements were clumsy. In her right eye, clear outward strabismus was seen. Eye movements were normal and nystagmus was not detected. The patient´s neurological condition had not deteriorated during the previous 10 years.

5.4.3 Neurophysiological studies

The electroencephalogram (EEG) was normal in early childhood. At five years of age, mild generalized background abnormality with occasional spikes and sharp waves at the left temporo-parieto-central region was shown. At 15 years of age, quantitative EEG was normal. In adulthood, the patient was taking no medication. She had no history of epileptic seizures. However, symptoms that resembled the startle reflex were noticed in response to sudden or loud noises.

5.4.4 Brain imaging

At 15 years of age, MRI results showed dysmyelination. The cerebellum, pons and the proximal part of the cervical cord were normal. The corpus callosum was hypoplastic. No enlargement of the ventricles or signs of cortical atrophy was reported. At 30 years of age, MRI findings were mild. There was no progression in atrophy (Study III, Fig. 1).

6 Discussion

The aim of this study was to describe the neurocognitive developmental spectrum of SD over a long follow-up time. The study reports the developmental milestones of SD patients and describes a patient with a conventional $Salla_{FIN}$ mutation but a very unique developmental profile. As far as is known, this is the first published follow-up study of neurocognitive development in SD. Detailed neuropsychological profiles of 41 Finnish patients with SD were described in the baseline study. Twenty-seven (66%) of them participated in the follow-up study, where the follow-up time was 13 years. The results show that the neurocognitive deficits of SD are clear in childhood, but the disease does not have a rapid progressive nature after the teens. The motor handicap is severe but the cognitive skills related to verbal comprehension and interactive skills do not deteriorate in adulthood.

Based on the results of this study, four neurodevelopmental periods in SD can be outlined. 1) The perinatal history and the first months after birth are normal in most of the patients. Mature myelination is seen in the brain stem, hemispheres, cerebellar peduncles and stria medullaris thalami. The myelination seems to cease between the birth and the first months (Haataja *et al*. 2004a). 2) The first symptoms, typically hypotonia and delayed motor development, are present from the first year of life. Slow but positive development continues to puberty. During this developmental stage ataxia will decline and disappear. 3) A quite constant period of neurocognitive skills and neurological findings can be seen between 15–40 years. The development of neurocognitive skills is slow but positive till age 40 years. 4) The progressive decline in mental abilities starts after 40 years of age. After age 20 years there is an apparent decline in motor skills. Similar neurocognitive periods have been described in another lysosomal storage disease, AGU (Arvio 1993a, 1993b).

MRI findings in Salla disease differ from those reported in AGU, where the thalamus is affected (Autti *et al.* 2008). In contrast, cerebral and cerebellar atrophy and dysmyelination are consistent findings in SD. In addition, corpus callosum hypoplasia has been described.

The patients with SD share some characteristics that are typical in nonverbal learning difficulties (Rourke 1995) that are associated with dys- or demyelination of the white matter. On the other hand, some characteristics related to NLDs, especially corpus callosum dysfunction, differ significantly from the phenotypes of SD. Autism as well as attention-deficit symptoms are associated with

developmental abnormalities of corpus callosum (Cao *et al*. 2009, Hardan *et al.* 2009, Verhoeven *et al.* 2009) that are highly atypical in SD patients.

Corpus callosum hypoplasia among patients with SD may partly explain their right hand preference as well as difficulties in mirror movements and left-right differences in timed motor activation in PANESS-test. The frequency of ambiguous handedness and left-handedness is as high as 30% among intellectually disabled persons (Bishop 1990), whereas right-handedness is typical in SD. The loss of axons in corpus callosum may be the factor that affects developmental hand preference and cerebral dominance (Sonninen *et al.* 1999, Witelson 1985). Special characteristics of SD, such as severe motor deficits, the special characters of speech and language development as well as strong interactive skills, can be seen as a continuum of the exceptional brain maturation and dysmyelination of the CNS.

Difficulties and deterioration of speech production skills are partly related to dysarthria and dyspraxia. Both of these symptoms are typically related to cerebellar dysfunctions (Stoodley & Schmahmann 2009). Cerebellum is more than the regulator of the motor control (Pulsifer 1996, Strick *et al*. 2009). It has an important role in timing and sequencing both non-motor and motor actions (Xu *et al.* 2006, Leggio *et al*. 2008, Molinari *et al.* 2008), as well as motor cognition (Fuentes & Bastian 2007), Furthermore, it is involved in cognitive functions and behavior in many ways (Rapoport *et al.* 2001, Glickstein & Doron 2008). The cerebellum regulates verbal short term memory functions (Durisko & Fiez 2009, Majerus *et al.* 2009, Misciagna *et al*. 2009) as well as language functions (Stoodley & Schmahmann 2009). There is also evidence for cognitive and motor fronto-cerebro-cerebellar circuits, links or loops in the brain (Krienen & Buckner 2009, Strick *et al*. 2009, Tavano & Borgatti 2010).

Neurobiological and hormonal changes are common in the neurodevelopment of teenagers in general. These changes might partly explain the appearance of coarse facial features, typical of SD patients, from early teenage years. Neuropsychiatric symptoms and psychotic episodes were described by the carers of a few teenagers and young adults with SD during the follow-up visits. These symptoms might reflect the rapid changes of brain structures and neural networks in puberty (Brand & Kirov 2011).

Most SD patients are very sensitive to pain. This may be partly related to the atypical functions of the neural network. The neuropathology of intellectual disabilities affects pain-related grey and white matter - the amygdala, insula, hippocampus and the anterior cingulate cortex, which may alter the experience of

pain (Jernigan *et al.* 1993, Hallahan *et al.* 2011). Clinical studies on pain experience in patients with intellectual disabilities are limited (de Knegt *et al.* 2011). Long-term pain alters the functional connectivity of cortical regions known to be active at rest (Baliki *et al.* 2008). The sensitivity for pain should be taken into consideration in clinical settings, when treating a patient with intellectual disabilities. Many SD patients are unable to express themselves verbally. It is, therefore, important to interview the caregivers of SD patients in order to determine, how the patient reacts to pain stimulus and expresses it non-verbally.

SD is a very rare disease and its special characteristics can be outlined, but the individual differences within the phenotypes are large. The identification of a patient with a unique, mild phenotype of SD in this study is interesting. Her neurocognitive and neurological status has remained stable over the long follow-up time. She has participated actively in sports since childhood and received regular physiotherapy. She is able to participate in sports that are difficult for patients with motor handicap, for example floorball and oriental dance. The brain is responsive to physical exercise. Exercise benefits neural health and improves cognitive capacity of the brain (Colcombe & Kramer 2003, Cotman *et al.* 2005). The anatomical, functional, cellular and molecular changes can be seen in brain areas that are critical to higher executive-control processes, learning and memory functions as well as to mood regulation (Alonso *et al.* 2002, Brene *et al.* 2007). Physical activity has positive effects on the brain and on the neural capacity to process information (Kamijo *et al*. 2007). Also unknown genetic and environmental variation may explain the unique phenotype of the proband. Further studies related to SD are still needed. The heterogeneity of the clinical severity and progression is a challenge for both diagnostic work and rehabilitation in SD. It is also important to note the different phenotypes, personality characters and the temperaments of SD patients at every stage of the disease.

The heterogeneity of the clinical picture of SD sets specific demands for neuropsychological assessment. As earlier described, the assessment is based on the use of age-specific norm-referenced tests. The variation of the tests is wide. A patient with intellectual disabilities and learning difficulties has diverse deficits in brain-behavior interaction. In this study, most of the patients were evaluated by using the BSID-II test battery, typically used for infants aged 0–42 months. Only a few patients could complete Wechsler children´s tests. Instead of defining the IQ:s of the SD patients, the developmental profiles were assessed in this study, as were developmental ages of neurocognitive skills and motor skills. The neurodevelopmental profiles that describe both weaknesses and abilities of SD

patients, give new information about the typical characteristics of neurocognitive development in this rare disease.

To conclude, the results indicate that neurocognitive deficits in SD are prominent in childhood, but the illness does not have a rapid progressive course after the teenager years. The motor handicap is severe but the cognitive skills related to verbal comprehension and interactive skills do not deteriorate in adulthood.

7 The strengths and the weaknesses of the study

The present study is the first follow-up study of SD. A further strength of this study is the long follow-up time of the patients with SD. Twenty-seven of the patients examined at baseline cohort participated in the follow-up study. SD is rare, but the phenotypic variation is wide. Therefore, it is important to describe both typical and special characteristics of the neurocognitive development in order to understand the changing needs of the patients. Even though many of the patients are unable to speak, they can understand spoken language relatively well.

In this study, the earlier MRI results of SD patients guided the selection of the most suitable test methods for the baseline study and the follow-up. BSID-II and the Wechsler tests provided information about the typical neurocognitive and motor development of SD patients. The subtests of NEPSY as well as the PANESS and the cerebellar tests provided new information on the special features of verbal skills, dynamic and static motor functions and special neurocognitive deficits related to corpus callosum hypoplasia in SD.

The weaknesses of the present study are related to the small number of SD patients, although we succeeded to recruit 41 of the ca. 100 Finnish patients in the original study and to evaluate 27 of them in the follow-up study. The small sample size sets limits to the statistical analysis of the data. Furthermore, this study has a narrow view of special deficits related to language development in SD. More specific test methods for analyzing the structure and type of verbal difficulties related to speech production and comprehension would have been informative. Neuropsychological test methods used in the present study give a general description of these neurocognitive factors, but are non-specific compared to the methods used by a qualified speech therapist.

This study lacks of information related to rehabilitation perspectives. SD patients who live in or close to urban areas are able to receive regular therapies while others are not. It is important to notice that physical activity in the form of physiotherapy, for example, improves the well-being of the brain, also with patients who have intellectual disabilities. SD patients, who become spastic and have a strong motor handicap in adulthood benefit from regular exercise.

8 Conclusions and future aspects

Four neurodevelopmental periods can be outlined in SD. Neurocognitive deficits, especially in motor skills, are evident in childhood, but the disease does not have a rapid progressive nature after the teenage years. A quite consistent period of neurocognitive skills and neurological findings can be seen between 15–40 years. The progressive decline in mental abilities starts after 40 years of age. After the age of 20 years there is an apparent decline in motor skills. Motor handicap is severe, but the cognitive skills related to verbal comprehension and interactive skills do not deteriorate in adulthood.

Individual differences within the phenotypes are large. One patient with a mild phenotype had a unique neurodevelopmental profile and her neurocognitive performance was remarkably better than those of other patients in her age group. There was no progression in atrophy or neurocognitive symptoms at 30 years of age. Physical activity, in the form of regular physiotherapy or otherwise, may partly explain the differences in motor development. Also unknown genetic and environmental variation may explain the individual differences among patients with the $Salla_{FIN}$ mutation. Further studies of these factors in SD are needed.

In the future, patients with SD are in a need for specific, individually planned rehabilitation practices. It would be important to study the effectiveness of different therapies (e.g. physiotherapy, occupational therapy, speech therapy) with SD patients from the early childhood. Patients should also have regular neurological follow-ups. At the moment, adult patients have contact to a neurological unit mainly because of their treatment-resistant epilepsy.

Patients with SD have undergone many brain imaging studies. It would be informative to have the results analyzed in order to test the hypothesis that there are as yet unknown brain areas that have undergone atypical development. The results could be combined with what is known about the neurodevelopmental and neurocognitive profiles of SD.

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IV Paavola L, Remes A, Harila M, Varho T, Korhonen T & Majamaa K (2012) A 13-year follow-up of Finnish patients with Salla disease. Manuscript.

Original publications are not included in the electronic version of the dissertation.

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