Early detection of ESSENCE in Japanese 0–4–year–olds

Studies of neurodevelopmental problems in the community and in clinics

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Gothenburg 2018

Cover illustration: Azusa Hashimoto

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ISBN ISBN 978-91-629-0416-6 (PRINT)
ISBN 978-91-629-0417-3 (PDF)

Printed in Gothenburg, Sweden 2018
Printed by BrandFactory

To my wife Mariko

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ABSTRACT

Background: Early identification of children with neurodevelopmental problems/ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) is a critical issue both in the community and in clinical settings. **Aims:** Approach early identification of ESSENCE from three different angles; training for health professionals, early concern regarding motor development, and the development and preliminary validation of a new one-page screening questionnaire, the ESSENCE-Q. **Methods:** (Study I) Evaluate the effect of seminars and materials developed for the training of health professionals engaging in child 18-month check-ups, using a before-and-after questionnaire. (Study II) Explore whether concern about early motor development may be an indication of ESSENCE, using a prospective clinical cohort of children under age two years. (Study III) Develop and examine the ESSENCE-Q as a parent screening questionnaire in a clinical setting, in the context of an explorative study of the ESSENCE-Q used for one year in a neurodevelopmental clinic. (Study IV) Validate the ESSENCE-Q in a community setting targeting mothers, public health nurses, and psychologists in routine child-health check-ups. **Results:** (Study I) Overall subjective evaluation was positive, and self-confidence of public health nurses improved after the seminar. (Study II) The majority of children with concern about early motor delay had ESSENCE. (Study III) The ESSENCE-Q appeared to have good psychometric properties as a parent questionnaire in a clinical setting. (Study IV) The ESSENCE-Q when used by public health nurses and psychologists appeared to have good psychometric properties in a public health setting. **Conclusion:** Neurodevelopmental disorders/problems can often be identified in very early childhood. Careful observation of motor development would seem to be crucial, and the ESSENCE-Q would be a useful tool in screening for ESSENCE both in clinics and in the general preschool population of children. Public health nurses may be the most appropriate professionals in the screening process, and providing training for them in the field of ESSENCE is critical.

Keywords: ESSENCE, public health nurse, motor development, ESSENCE-Questionnaire

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SAMMANFATTNING PÅ SVENSKA

ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) är ett begrepp som lanserades 2009 av Christopher Gillberg och som syftar på den samexistens och ”samsjuklighet” samt den överlappning av symptom som föreligger vid utvecklingsneurologiska funktionsnedsättningar. ESSENCE är inte en diagnostisk term utan konceptualiserar detta kliniska faktum.

Forskning rörande tidiga insatser för barn med utvecklingsneurologiska funktionsnedsättningar ger stöd för att tidiga, anpassade insatser kan ge positiva effekter. Följaktligen är tidig identifiering av barn med utvecklingsneurologiska problem en mycket viktig fråga både i samhället och inom kliniska verksamheter. Det är viktigt att ha i åtanke att tidig identifiering inte betyder att en specifikt avgränsad funktionsnedsättning måste diagnostiseras, utan snarare att problem som faller in under paraplybegreppet ESSENCE kan identifieras.

Det övergripande målet med denna studie är att utforska avgörande aspekter när det gäller tidig identifikation av ESSENCE-problem i kliniska sammanhang utifrån följande tre synvinklar: utbildning för vårdpersonal, tidiga frågeställningar rörande motorisk utveckling som ett problem inom ESSENCE, samt utveckling och preliminär validering av ett nytt kort frågeformulär avseende för screening, ESSENCE-Q.

Studie I utvärderade effekten av seminarier och material som utvecklats för utbildning av vårdpersonal som deltar vid 18-månaderskontroller för barn, med hjälp av frågeformulär, ifyllda före och efter. Samtliga personer i studien deltog i seminarierna. Seminarierna var inriktade på att ge information om hur barn med misstänkt autismspektrumtillstånd (AST), under ett till två års ålder, kan identifieras. Fokus låg dels på ”typisk” social kommunikationsutveckling under den aktuella åldersperioden, snarare än på avvikande autistiska beteenden, dels på att utveckla det utbildningsmaterial som användes i seminarierna. Man genomförde även en metodenkät med hjälp av självskattningsformulär. Den övergripande subjektiva utvärderingen av seminariet var positiv, och efter seminariet ökade självförtroendet hos sjuksköterskor inom japansk barnhälsovård. Genom att erbjuda möjligheter

att lära sig om typisk barnutveckling och tidig a tecken på AST bidrog man till att problem skulle kunna upptäcktas tidigare och därmed till bättre tidiga insatser.

Studie II gick ut på att studera huruvida bekymmer i fråga om tidig motorisk utveckling kan vara ett tecken på ESSENCE. Studiegruppen omfattade en kohort av alla barn under två års ålder, som under en ett-årsperiod besökte en japansk utvecklingsneurologisk länsmottagning med anledning av försenad eller avvikande grovmotorisk utveckling. Den stora majoriteten av barn med motoriska problem hade ESSENCE-relaterade symptom eller funktionsnedsättningar vid fortsatt uppföljning. Detta pekar mot att små barn som tidigt uppvisar motoriska problem alltid skulle behöva en bred klinisk bedömning, inte enbart relaterad till motorisk funktion, och också även en fortsatt klinisk uppföljning.

Studie III gick ut på att utveckla och undersöka ESSENCE-Q som ett föräldraformulär i kliniskt sammanhang, i en explorativ studie. ESSENCE-Q användes under ett år på en utvecklingsneurologisk mottagning. Frågeformuläret är kortfattat, ”snabbt och enkelt” och täcker 12 områden: allmän utveckling, kommunikation/språk, social ömsesidighet, perception, motorisk koordinationsförmåga, uppmärksamhet/”lyssnande”, aktivitet, ”beteende”, humör, matvanor, sömn och ”episoder”/absenser. Det utvecklades för att enkelt kunna fånga upp problem inom ESSENCE-gruppen. ESSENCE-Q är inte inriktat på någon specifik utvecklingsneurologisk diagnos och detta är sannolikt dess styrka som ett screening- instrument för hela området av ESSENCE-problem. En psykiatriker inom området utvecklingsneurologi vid ett japanskt länscenter använde sig av ESSENCE-Q under en ett år lång forskningsperiod för alla nya patienter under sex års ålder som remitterats dit. Föräldrarna fyllde i ESSENCE-Q-formuläret innan de första kliniska bedömningarna ägde rum. ESSENCE-Q hade goda psykometriska egenskaper då det användes som föräldraformulär i klinisk miljö.

Studie IV validerade ESSENCE-Q inom den japanska barnhälsovården där formuläret användes till mödrar, sjuksköterskor och psykologer vid barnhälsovårdens kontroller. Studiepersonerna utgjordes av mödrar som kom med sina barn till kontrollerna då barnen var 18 respektive 36 månaders ålder, samt sjuksköterskor och psykologer som specialiserat sig på

barnutveckling och utvecklingsneurologiska funktionsnedsättningar och som varit involverade i kontrollerna under samma period. ESSENCE-Q besvarades av mödrarna, sköterskorna och psykologerna oberoende av varandra. Resultaten från dessa tre gruppers respektive ESSENCE-Q jämfördes. ESSENCE-Q, då det användes av sjuksköterskor och psykologer inom japansk barnhälsovård, hade goda psykometriska egenskaper.

Utvecklingsneurologiska funktionsnedsättningar/problem kan ofta identifieras mycket tidigt under barndomen. Noggrann observation av motorisk utveckling verkar ha en avgörande roll, och ESSENCE-Q kan vara ett användbart screeningformulär. Sjuksköterskor inom barnhälsovården skulle kunna vara den mest lämpade yrkeskategorin att använda detta screeninginstrument och därför är det av stor vikt att tillhandahålla utbildning inom området ESSENCE till denna grupp.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Hatakenaka Y. & Hiarano S. Training Health Professionals Engaging in 18-Month Check-up for Early Detection and Early Intervention of Autism Spectrum Disorder. Journal of Social Policy and Social Work 2015; 19:45-57.

II. Hatakenaka Y, Kotani H, Yasumitsu-Lovell K, Suzuki K, Fernell E, & Gillberg C. Infant Motor Delay and Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations in Japan. Pediatric Neurology 2016; 54:55-63.

III. Hatakenaka Y, Fernell E, Sakaguchi M., Ninomiya H, Fukunaga I, & Gillberg C. ESSENCE-Q - a first clinical validation study of a new screening questionnaire for young children with suspected neurodevelopmental problems in south Japan. Neuropsychiatric Disease and Treatment 2016; 12:1739-1746.

IV. Hatakenaka Y, Ninomiya H, Billstedt E, Fernell E, Gillberg C. ESSENCE-Q - used as a screening tool for neurodevelopmental problems in public health checkups for young children in south Japan. Neuropsychiatric Disease and Treatment 2017; 13:1271-1280.

CONTENT

ABBREVIATIONS

AD/HD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
AUC	Area Under the Curve
ASD	Autism Spectrum Disorder
BIF	Borderline Intellectual Functioning
CI	Confidence Interval
CP	Cerebral Palsy
CT	Computed Tomography
DCD	Developmental Coordination Disorder
DISCO	Diagnostic Interview for Social and Communication Disorders
DQ	Developmental Quotient
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EEG	Electroencephalography
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
ESSENCE-Q	ESSENCE-Questionnaire
ID/IDD	Intellectual Disability/Intellectual Developmental Disorder
ICD-10	Intelligence Classification of Diseases, Tenth Edition
IQ	Intellectual Quotient
KSPD2001	Kyoto Scale of Psychological Development 2001
LD	Learning Difficulties

MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
ODD	Oppositional Defiant Disorder
PHN	Public Health Nurse
PPV	Positive Predictive Value
RAD	Reactive Attachment Disorder
ROC	Receiver Operating Characteristic
SAD	Social Anxiety Disorder
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SLD	Speech and Language Disorder
T-B test	Tanaka-Binet Scale of Intelligence
TD	Tic Disorder

1 INTRODUCTION

Neurodevelopmental disorders encompass a group of disorders that affect diverse developmental aspects including motor, language and speech, learning and memory, imagination, social interaction, and self-regulation, including behavioral control. The most common forms of these disorders are autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (AD/HD), intellectual disability (ID)/intellectual developmental disorder (IDD), and developmental coordination disorder (DCD). In 2010, Gillberg published a paper, "The ESSENCE in child psychiatry: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations", in which the ESSENCE concept, launched in 2009 was explicate (Gillberg, 2010). ESSENCE is the acronym for Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. ESSENCE is not a diagnostic term, but rather a concept that alerts clinicians and researchers to the very common coexistence and overlap of neurodevelopmental disorders. When a child has been identified with a neurodevelopmental disorder or developmental problems, there is a need to also consider the possibility of other concurrent neurodevelopmental disorders. The ESSENCE concept implies the almost universal coexistence of neurodevelopmental disorders and problems in child psychiatry and in pediatrics (Gillberg, Fernell, & Minnis, 2014). This clinical reality was already mentioned in the 1970s and early 1980s, in papers discussing results suggesting that Deficits in Attention, Motor control and Perception (DAMP), currently equivalent to AD/HD with DCD, were generally associated with some social, language and behavioral impairments; i.e., in some cases consistent with ASD or autistic symptoms as conceptualized today (Gillberg, 1983; Gillberg, Rasmussen, Carlstrom, Svenson, & Waldenstrom, 1982). However, this reality of sharing symptoms across diagnoses has come to be largely ignored because of a preference for categorical "diagnostic boxes" with mutually exclusive diagnostic criteria.

1.1 What is included in ESSENCE?

Some of the most common disorders subsumed under the ESSENCE concept are; ASD, AD/HD, ID/IDD, DCD, speech and language disorder (SLD), oppositional defiant disorder (ODD), and tic disorder (TD). ESSENCE also covers difficulties/problems not meeting criteria for a certain diagnosis, including borderline intellectual functioning (BIF) and other non-specific learning difficulties (LD). If a child before age 3 (-5) years has one or more (usually several) major problems, lasting more than several months, in the

following 12 fields: general development, motor development/milestones, senosory reactions, communication/language, activity or impulsivity, attention/"listening", social interaction, behavior (e.g. repetitive, routine insistence), mood, sleep, feeding, and episodes/absences in the first years of childhood, this should be seen as a red flag for possible ASD, AD/HD, ID/IDD, DCD, SLD, ODD, TD, BIF and LD. If problems are unrecognized and not intervened for, ESSENCE may predispose to chronic or lifelong neurodevelopmental disorders, other mental and psychiatric problems, drug abuse, physical disorders (including obesity and chronic pain), antisocial behaviors, and premature death (Hirvikoski et al., 2016; London & Landes, 2016). With regard to prevalence, ESSENCE can be estimated to affect at least 10% of children under age 18 years (Gillberg, 2010). About a half of the whole group are currently probably discovered already by age 6 years. It can also be expected that half or more of all "chronic" adult psychiatric patients suffer from disorders that are linked to ESSENCE (Nylander, Holmqvist, Gustafson, & Gillberg 2013).

Autism Spectrum Disorder (ASD)

ASD is the name of a group of neurodevelopmental conditions characterized by impaired social communication and restricted behaviors and interests. Clinical manifestations of ASD are quite heterogeneous, depending on the severity of ASD per se, on cognitive level, and on other comorbid neurodevelopmental disorders (Coleman & Gillberg, 2012; Waterhouse, Fein, & Modahl, 1996; Waterhouse, London, & Gillberg 2017). The prevalence is around 1% (Lundstrom, Reichenberg, Anckarsater, Lichtenstein, & Gillberg, 2015).

Attention-Deficit/Hyperactivity Disorder (AD/HD)

AD/HD is a neurodevelopmental disorder marked by attention deficits with or without concurrent hyperactivity and impulsivity, which are clearly inappropriate for a person's age. The prevalence is 5-8% of the young population (Barbaresi et al., 2002; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) and most of the cases have one or more comorbid neurodevelopmental problem(s) (Faraone et al., 2015). Although it has been believed that AD/HD mainly affects boys rather than girls, girls with AD/HD might be misdiagnosed and undertreated (Sassi, 2010). At least some symptoms of AD/HD persist into adult life and about half of those diagnosed with AD/HD in childhood still meet full criteria for AD/HD as adults (Faraone, Biederman, & Mick, 2006).

Intellectual disability (ID)/Intellectual developmental disorder (IDD)

ID/IDD is defined with both a cognitive impairment (IQ is at or below 70) and deficits in adaptive behaviors with onset before 18 years of age (Patel & Merrick, 2011). According to a meta-analysis, the prevalence of ID/IDD would be estimated around 2% of all populations (Gillberg, 2010; Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011). Comorbidity with ASD is high (Matson & Shoemaker, 2009), and AD/HD is also often a comorbid disorder (Dekker & Koot, 2003). It has been estimated that 30-80% of children and adolescents with ID/IDD have comorbid mental/psychiatric disorders (Einfeld, Ellis, & Emerson, 2011; Steffenburg, Gillberg, & Steffenburg, 1996).

Speech and Language Disorder (SLD)

Delay in speech and language is one of the most common developmental problems that affects 10-14% of 2-year-old children, and half of them still have speech and language problem at 5 years (Hart, 2004). SLD would be an early red flag for neurodevelopmental disorders/problems such as ASD, AD/HD, ID/IDD, BIF, and LD (Miniscalco, Nygren, Hagberg, Kadesjö, & Gillberg, 2006).

Developmental Coordination Disorder (DCD)

If a child shows poor motor skills including clumsiness, slow and inappropriate performances, below expected level, and these motor coordination problems significantly affect their daily life, DCD may be given as the diagnosis. DCD is common, affecting 5-10% of all children (Henderson & Henderson, 2003; Kadesjö & Gillberg, 1999). This phenomenon was already known as part of Deficit in Attention, Motor control and Perception (DAMP) umbrella in the early 1980s (Gillberg, 1983).

Oppositional Defiant Disorder (ODD)

ODD is a persistent behavior pattern in which a child displays angry or irritable mood, defiant or argumentative behaviors towards authorities, such as parents and teachers. These behaviors severely interfere with the child´s daily life and the child´s developmental functions. Keenan & Wakschlag (2002) reviewed evidence for the construct validity of ODD in preschool children and discussed that typical and atypical behavior problems can be differentiated in the preschool period (Keenan & Wakschlag, 2002). ODD has been found to be almost always comorbid with other neurodevelopmental disorders, such as AD/HD and ASD (Connor, Steeber, & McBurnett, 2010; Kadesjö, Hägglöf, Kadesjö, & Gillberg 2003; Kerekes et al., 2014; Loeber,

Burke, Lahey, Winters, & Zera, 2000; Simonoff et al., 2008; Waschbusch, 2002).

Tic Disorder (TD)

TD is characterized by sudden, recurrent, and brief movements or sounds that appear repetitively (Ganos, Münchau, & Bhatia, 2014). TD is common particularly in middle childhood, and affects at least 15% of all children at some time (Gillberg, 2010). Severe, chronic and disabling motor and vocal tics, referred to as Tourette syndrome affects around 1% of school age children (Kadesjö & Gillberg, 2000).

Borderline intellectual functioning (BIF) and non specific learning difficulties (LD)

BIF is the border zone between ID/IDD and average IQ according to standardized IQ test results (Zetlin & Murtaugh, 1990). Children and adolescents with BIF have relatively higher rates of mental health problems (Emerson, Einfeld, & Stancliffe, 2010; Fernell & Ek, 2010) and get relatively higher rates of diagnoses of mental disorders (Dekker & Koot, 2003). LD refers to persistent difficulties in learning and academic achievement, despite an intellectual level within the "normal variation". The difficulties include problems with reading and mathematics and some children may meet criteria for dyslexia and/or dyscalculia and some have coexisting ADHD.

1.2 Early detection of and early intervention for children with ESSENCE

In Japan and in many other parts of the world, early detection of and early intervention for children with ESSENCE are among the most important issues in public health services (Gillberg, 2010). Early intervention has especially been studied and discussed in the context of ASD (Estes et al., 2015; Nygren et al., 2012; Zwaigenbaum et al., 2015; Zwaigenbaum et al., 2015). Early assessment and identification of the child´s cognitive deficits and resulting behavioral problems opens up possibilities to inform parents and preschool staff about how to help and guide the child´s development in an intervention program. Early intervention also includes the possibility to explain and discuss with parents and preschool teachers how different behavioral problems may stem from deficits in intellectual ability, theory of mind problems and/or from deficits in attention and executive functioning. It should also be emphasized that children with neurodevelopmental problems under the umbrella of ESSENCE are important to identify, even in cases

where a precise diagnosis at the time of assessment is not possible to pinpoint.

The role of public health nurses (PHNs) in Japan

In Japan, most of the work of PHNs in municipal or prefectural governments is for the purpose of assisting in preventing illness and promoting citizens' health (Saeki, Izumi, Uza, & Murashima, 2007). Their public activities have expanded from disease prevention to community health promotion activities (Hirano, Saeki, Kawaharada, & Ueda, 2011). More particularly, maternal and child health issues, including early detection of neurodevelopmental disorders/ESSENCE, have come to be recognized as one of the crucial missions for PHNs because they meet children at key stages of their development. Nurses working in communities have been recognized as the key professional in developmental surveillance in western countries (Curry & Duby, 1994; Dworkin, 1989; Sim et al, 2015), and recently, especially their role in ASD and in speech and language screening has been emphasized (Barbaro, Ridgway, & Dissanayake, 2011; Carlson et al 2013; Halpin & Nugent, 2007; Miniscalco et al., 2006; Miniscalco, Westerlund, & Lohmander, 2005; Nadel & Poss, 2007; Nygren et al., 2012; Pinto-Martin, Souders, Giarelli, & Levy, 2005). This trend is the same in Japan, because the PHNs meet all newborn children in the community and are responsible for child health check-ups (Ide-Okochi & Tadaka, 2016).

18-month check-up and ASD screening in Japan

All parents of children in Japan are invited to take part in health checks, the first at child age 18 months (18-month check-up, range 18-24 months) and the second at three years of age (36-month check-up, range 36-48 months). Every municipality provides these check-ups based on the Maternal and Child Health Act. Contemporaneously with the American Academy of Pediatrics (AAP) (Johnson & Myers, 2007), recommendation of screening of ASD, at least two times before the age of two years, has been advocated also in Japan to promote early diagnosis and early intervention in ASD (Hashimoto et al., 2005). Under the Act on Support for Persons with Developmental Disabilities from April 2005, early detection of children with ASD has become one of the most important responsibilities for maternal and child health in municipalities. Considering that several symptoms of ASD often are present by the age of 18 months, especially in the area of social communication development (Bryson et al., 2007; Kleinman et al., 2008), the 18-month check-up would be one of the best opportunities to find children with suspected ASD (Honda et al., 2009). The earliest signs of ASD would be the delayed attainment of social communication developmental milestones

(Barbaro & Dissanayake, 2012, 2013; Carbone, Farley, & Davis, 2010; Dahlgren & Gillberg, 1989). Such early identification is possible if professionals, engaging in ASD surveillance in a community-based setting, know the early signs of ASD. If there is knowledge about these signs, e.g. lack or delay of "normal" or "typical" development of social communication, they can identify correctly and refer infants and toddlers with a suspicion of ASD (Barbaro & Dissanayake, 2010; Barbaro et al., 2011; Carlson, Gillberg, Lannero & Blennow 2010).

Motor development

For a quarter of a century, it has been well documented that several of the groups of disorders included in the concept of ESSENCE are associated with early motor developmental problems, such as early onset motor control problems, ranging from general clumsiness and reduced fine motor skills to coordination difficulties and visuomotor/visuoperceptual function abnormalities (Bishop, North, & Donlan, 1995; Gillberg, 1983, 2003; Gillberg et al., 1982; Gillberg & Soderstrom, 2003; Gillberg & Gillberg, 1989; Rasmussen, Gillberg, Waldenstrom, & Svenson, 1983; Reilly, Menlove, Fenton, & Das, 2013; Wing, 1981). The motor control problems are nowadays increasingly diagnosed separately as DCD (at least from school age, more rarely in the first few years of life), which, in itself, is also subsumed under the ESSENCE concept. There is growing evidence that many cases of ESSENCE may actually first be manifested by early signs of atypical motor-perceptual development (Allely, Gillberg, & Wilson, 2013; Billstedt, Gillberg, & Gillberg, 2007; Dahlgren & Gillberg, 1989; Fernell et al., 2010; Gillberg & Coleman, 2000; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998). Gross motor delay in early child development is easy to recognize by nurses and general practitioners, and it could, potentially, become one of the core signal, "screening symptom" for very early recognition of not just ASD, but ESSENCE more generally.

ESSENCE-Q

For early detection of developmental delay or problems, using validated screening tools is indispensable (Glascoe, 2005; Mackrides & Ryherd, 2011). To capture problems within the ESSENCE group, the ESSENCE-Questionnaire (ESSENCE-Q) was developed in 2011 and revised (Gillberg, 2012). ESSENCE-Q is a brief, simple "quick and easy" questionnaire consisting of 12 items covering 12 areas: general development, communication/language, social interrelatedness, perception, motor coordination, attention/"listening", activity, "behavior", mood, feeding, sleep and episodes/absences. In the ESSENCE-Q, the questions are about

"concern" for each of the ESSENCE domains, not about specific symptoms or behaviors. "Yes", "No" and "Maybe/A little" are the response alternatives. It may appear to be somewhat unspecified and vague, but this is actually the unique strength of the ESSENCE-Q. Behaviors of young children are very varied, and there is a need to use a broad view and not to focus only on a specific behavior. Using the ESSENCE-Q provides an opportunity to catch non-specified but critical information about the child's development. ESSENCE-Q is not geared towards a specific neurodevelopmental diagnosis and this could be the strength for screening across the whole range of ESSENCE problems. (see Appendix I)

2 AIM

The overall aim of this thesis is to explore critical aspects for the early detection of ESSENCE problems in clinical and in general population setting from different angles: training for health professionals engaging in the 18-month check-up, motor development, and validity of the ESSENCE-Q. More specific aims of the thesis are to;

- Evaluate the effect of seminars held and materials developed for the training of health professionals (PHNs) engaging in the 18-month check-up (Study I);

- Explore whether or not early motor delay may be a frequent indication of ESSENCE (Study II);

- Validate the ESSENCE-Q as a parent questionnaire in a neurodevelopmental clinic for children (Study III);

- Validate the ESSENCE-Q in routine public health check-ups of young children (Study IV).

3 METHODS

An overview of the participants and the methods used in Study I-IV is shown in Table 1.

Table 1. *Study groups and methods used in Study I-IV*

Study	I	II	III	IV
	Seminar study	Motor delay study	ESSENCE-Q Clinic study	ESSENCE-Q Public Health study
Object of Study	Evaluate effect of seminars held and materials developed for training of health professionals engaging in the 18-month check-up	Explore whether early motor delay often is an indication of ESSENCE	Validate the ESSENCE-Q as a parent questionnaire in a neurodevelop-mental clinic for children	Validate the ESSENCE-Q in public health check-ups
Target group	288 health professionals	47 (24 boys) with motor delay	145 (120 boys) with concern in clinic	152 (79 boys) at 18 months 158 (77 boys) at 36 months
Group examined	288	30 (20 boys)	130 (109 boys)	143 (75 boys) at 18 months 149 (73 boys) in 36 months
Study design	Anonymous survey	medical record clinical study	Prospective clinic-based investigation	Prospective, population-based, observational cohort study
Instrument	Anonymous self-rating questionnaire	KSPD2001, T-B test	ESSENCE-Q, KSPD2001, T-B test, ADHD-RS	ESSENCE-Q, KSPD2001, DISCO, SDQ

3.1 Instruments

Anonymous self-rating scale (Study I)

The questionnaire consisted of three questions (Q1, Q2 and Q3) and was designed for this specific study by the author. Q1 was about the understanding of the meaning of early detection of ASD and the role of

health professionals in this assignment, which consisted of 8 items rated on a five-point Likert scale with the anchor for the level of agreement ("1: Strongly disagree" to "5: Strongly agree"). Q2 was about the most crucial things with regard to early detection of ASD in infants in public check-ups, which consisted of 11 items (participants were asked to choose three items among these 11 items in the order of the importance for the early detection of ASD). Q3 was about the understanding of the contents of the seminars, which consisted of 12 items rated on a five-point Likert scale for the level of quality ("1: Very low" to "5 Very high").

Kyoto Scale of Psychological Development 2001 (KSPD2001) (Study II, III and IV)

KSPD2001 was the latest version of the Kyoto Scale of Psychological Development, standardized for 2677 Japanese children and adults. This is an individualized face-to-face test to assess a child's development in the area of fine and gross motor functions, the area of non-verbal reasoning and visuospatial perceptions, and the are of interpersonal relationships, socializations and verbal abilities (Koyama, Osada, Tsujii, & Kurita, 2009). A sum score each area is converted into a developmental age (DA). An overall DA is also obtained. These DAs (DAs in the three areas and the overall DA) are divided by the child's chronological age and multiplied by 100 to calculate DQ. KSPD2001 has excellent psychometric properties, and results are closely correlated these obtained using the Bayley Scales of Infant Development (Nakai et al., 2004).

Tanaka-Binet Scale of Intelligence (T-B test) (Study II and Study III)

T-B test is a modified version for Japan of the original Binet-Simon test, being a method by which mental age is evaluated and IQ is calculated from the ratio of mental age to chronological age (Tanaka, 1987).

ESSENCE-Questionnaire (ESSENCE-Q) (Study III and IV)

In Study III, the ESSENCE-Q was used as a parent screening questionnaire. In Study IV, it was used both as a parent questionnaire and also as a brief interview by a public health nurse (PHN) and a specialized psychologist. It consists of 12 items that covers concerns related to the following 12 areas: general development, communication/language, social interrelatedness, perception, motor coordination, attention/"listening", activity, "behavior", mood, feeding, sleep and/or episodes/absences. The responses are checked as either Yes (Y), Maybe/A little (M/AL) or No (N) (Gillberg, 2012). In the

Study III, we used the first version of the ESSENCE-Q, consisting of 11 items (without the item 12).

Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) (Study III)

The ADHD-RS is an instrument to help in the assessment of AD/HD in children and adolescents. It can be used both as an observer rating scale and as a self-report rating scale. There are 18 items and each item is rated on a four-point scale (not at all, a little, pretty much, and very much) (Zhang, Faries, Vowles, & Michelson, 2005). In this study, it was used as a parent and preschool teacher rating scale.

Diagnostic Interview for Social and Communication Disorders (DISCO) (Study IV)

The DISCO is used as an assessment tool for ASD. The interview is semi-structured and covers a wide range of behaviors associated with the ASD phenotype. It is suitable for use with all ages and levels of ability. It enables to identify specific features found in ASD (Wing, Leekam, Libby, Gould, & Larcombe, 2002).

Strengths and Difficulties Questionnaire (SDQ) (Study IV)

The SDQ covers child mental health and developmental aspects, including child behavior, emotions and relationships. It also addresses impact and duration of symptoms, distress in the child, impairment in different settings and burden to others. SDQ can be used as a screening tool for several types of neurodevelopmental disorders, including ASD and AD/HD (Goodman, 1997). In this study, it was used as a parent and preschool teacher rating scale.

3.2 Study I. Training health professionals engaging in 18-month check-up for early detection and early intervention in ASD

Participants

The participants were professionals who attended the seminars for early detection of children with suspected ASD. The seminars were held in 6 different places of Kochi Prefecture, in the south of Japan. A total of 288 professionals participated in the seminars. They were divided into four

groups. Of these 288, 133 (46.2%) were public health nurses (PHNs) in the municipalities, 19 (6.6%) were PHNs at the prefecture level, 39 (13.5%) were physicians (pediatricians and child psychiatrists), and 97 (33.7%) were other specialists (nurses, speech therapists, occupational therapists, preschool teachers, psychologists, social workers, and dieticians). The rates of participating professionals did not differ across regions.

Procedure

The main goals of the seminars were to get the participants to understand their role in the early detection of ASD and to provide knowledge to the participants so that they might better be able to identify children, aged 1 to 2 years, with suspected ASD. The seminars focused on "typical" social communication development during the age period rather than on aberrant autistic behaviors, and for this purpose training materials used in the seminars were newly developed. An anonymous self-rating questionnaire was handed out to all seminar participants. Before the seminars, at a seminar room, the participants were asked to respond to all the questions, and after the seminars, at the same place, they were asked to respond the same questions and the results were analyzed statistically.

Statistical analysis

Statistical analysis was done using non-parametric methods.

For the Q1, total rating scores before and after the seminars were compared by using Wilcoxon signed rank test. For each item, differences in pre-post change on subjective scales were examined using the Wilcoxon signed rank test. The numbers of the participants who decreased the scoring scale (e.g. 4 before the seminars and 2 after the seminar) and who increased scoring scale (e.g. 2 before the seminars and 4 after the seminars) in each items were also compared. Additionally, the Kruskal-Wallis test was used to determine differences in four professional groups (PHNs in municipalities (mPHN), PHNs in the prefecture (pPHN), medical doctors (MD), and others (Oth)) on each of the items before the seminars and after the seminars, and if significant, then Steel-Dwass test was applied.

In the Q2, the number of the item chosen as the most important thing was compared with the McNemar's test.

In the Q3, total rating scores before and after the seminars were compared by using Wilcoxon signed rank test. For each item, differences in pre-post change on subjective scales were examined using the Wilcoxon signed rank test. The number of the participants who decreased the scoring scale (e.g. 4

before the seminars and 2 after the seminar) and who increased scoring scale in each items (e.g. 2 before the seminars and 4 after the seminars) were also compared.

Statistical significance was defined as $p < .05$.

Ethics

We obtained informed consent by written documentation containing the research use of the data from the participants. This is a survey of health professionals done by Kochi Prefectural government, which is not required to get approval from an ethical committee. For ethical consideration, we referred to the department managing personal information in the prefecture, and we confirmed our compliance of the Personal Information Protection Act (Act No, 57 2003).

3.3 Study II. Infant Motor Delay and Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations in Japan

Participants

The sample studied comprised a one (fiscal)-year cohort (April 1, 2007, through March 31, 2008) of all children (n=47, 24 boys, 23 girls) who were referred to the Kochi Prefectural Medical and Welfare Centre before their second birthday because of delayed or abnormal gross motor development. Of these 47 children, eight (2 boys and 6 girls) were regarded to be functioning within the normal variation, and parents of nine children (2 boys and 7 girls) stopped coming before the child had reached two years of age. These 17 children did not have any assessment regarding ESSENCE and they were therefore excluded from the further analyses in the present study. Data from the remaining 30 children (20 boys and 10 girls) are presented with special regard to the concept of ESSENCE.

Procedure

The study was based on retrospective data (from collected medical and other records) and on prospectively recorded data. The children were followed up from the ESSENCE viewpoint.

Full clinical examinations were done at the first visit. Whenever a major neurodevelopmental problem was identified or suspected at clinical

examination during follow-up, further assessments were initiated. Motor function assessments with regard to DCD and cerebral palsy were done repeatedly. Cognitive assessments were carried out using validated tools at least twice. Clinical assessment for ASD was performed when the child presented symptoms that raised concern about coexisting social-communication deficits. This assessment concentrated on identification of social-communication and repetitive behaviors, characteristic of very young children with ASD, including impairments of social interest, joint attention, imitation, play, reciprocal affective behavior and insistence on sameness/stereotypies (Charman & Baird, 2002; Charman et al., 2005). In children with autistic symptoms, an evaluation of the diagnostic criteria for ASD was performed. The clinical assessment of AD/HD was done by unstructured clinical observations at the clinic and unstructured report or interviews from parents and preschool teachers, combined with interviews using structured diagnostic criteria. The International Classification of Diseases, Revision 10 (ICD-10), and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for diagnoses of child psychiatric and neurodevelopmental disorders were used throughout. Medical investigations were tailored to each child on clinical grounds by taking account of medical history, heredity, and the results of physical and neurological examinations. MRI, CT, EEG, chromosomal analysis, and muscle biopsy had been performed on clinical ground, not systematically.

Analysis

A descriptive analysis was done by information retrieved from clinical records. Information gathered comprised gender, gestational age, referrer (e.g. pediatrician, mother, PHN etc.), age at the first visit, motor delay/motor-related problem causing referral, motor disorders, neurological abnormalities, brain imaging findings, etiological diagnosis, and ESSENCE diagnosis.

Ethics

The study was submitted for ethical review and approved by the Kochi prefectural Medical and Welfare Centre.

3.4 Study III. ESSENCE-Q – a first clinical validation study of a new screening questionnaire for young children with suspected neurodevelopmental problems in south Japan

Participants

The ESSENCE-Q was used by a psychiatrist at a prefectural representative neurodevelopmental center. Of the 182 patients assessed during the research period (from 21st May 2012 to 8th May 2013), 145 children under the age of six years were included in this research. Of these 145, 15 children were excluded since a nurse forgot to provide the ESSENCE-Q, implying that the questionnaire could not be used in five children, and ten children stopped to come to the center before a final decision with regard to diagnosis had been made. The study subjects were the remaining 130 children (mean age 3.5 years, boys: girls=5.2:1), assessed with the ESSENCE-Q and given a full clinical evaluation, and with a final decision regarding diagnosis/no diagnosis.

Procedure

This was a clinically-based investigation using the Japanese version of the ESSENCE-Q (the first version consisting of 11 items). After getting the author's permission, a child psychiatrist in Japan, who has been working in the field of neurodevelopmental disorders for more than 25 years and very familiar with the concept of ESSENCE, translated the ESSENCE-Q into Japanese. A native English speaker who has been living in Japan for the previous 14 years and has been working as a lecturer of Japanese literature in a university for 5 years and with enough knowledge of the Japanese language, conducted the back-translation into English. The author reviewed and compared the back-translation to the original instrument. After repeating this process, we established the Japanese version of the ESSENCE-Q.

The ESSENCE-Q was completed by a parent (or a caretaker) of the referred child before the first clinical examination. The independent clinical assessment aimed at examining all kinds of developmental areas and disorders included under the ESSENCE umbrella. The following diagnostic categories were covered in the assessment; ASD, AD/HD, IDD, DCD, SLD, ODD, BIF and LD. It also included unstructured clinical observations at the clinic and unstructured reports/interviews from parents and preschool teachers, combined with interviews using the ADHD-RS (Zhang et al., 2005). Cognitive assessments were performed mainly by using KSPD2001 (Koyama

et al., 2009; Nakai et al., 2004), and the T-B test (Tanaka, 1987) was also used in several cases. For a diagnosis of DCD, children were examined while standing, walking, throwing and catching a ball along with performing other fine motor skills (Hamilton, 2002; Kirby, Sugden, & Purcell, 2014; Missiuna, Gaines, & Soucie, 2006; Tsai, Wu, & Huang, 2008; P. H. Wilson, 2005). The evaluations were repeatedly done over at least two different sessions separated by a minimum of a few weeks (Battaglia & Carey, 2003). The ICD-10/DSM-IV criteria for diagnoses of child psychiatric/neurodevelopmental disorders were used throughout.

Statistical analysis

To estimate the reliability of the ESSENCE-Q, Cronbach's Alpha for internal consistency was used. The sensitivity and the specificity at the cut-off level suggested by the author of the ESSENCE-Q, which is Y≥1 or M/AL≥3, were calculated. To explore cut-off levels of the ESSENCE-Q that have the sensitivity and the specificity both in 0.7-0.8 ranged and also sensitivity>specificity, ROC curves were established for all possible sum scores of Y (1-11) and M/AL (1-11) separately. Youden index was also calculated. Youden index is [(sensitivity+specificity)-1] and ranges from 0 to 1 (Youden, 1950).

Ethics

The study was approved by the Ethics Review Board of Kochi Prefectural Medical Welfare Center.

3.5 Study IV. ESSENCE-Q – used as a screening tool for neurodevelopmental problems in public health check-ups for young children in south Japan

Participants

Data on two separate groups of children who came to health care centers in Kami City, Kochi, Japan, from April 2014 through March 2015 were collected. Participants were mothers who came with their children to the 18-month and the 36-month check-up and municipal PHNs and psychologists specialized in child development and neurodevelopmental disabilities and engaged in the check-ups during the same period. A total of 152 children (79 boys and 73 girls) were invited to the 18-month check-ups and 143 children (75 boys and 68 girls, mean age 18.7 months, SD 0.9) participated. A total of 158 children (77 boys and 81 girls) were invited to the "36-month check-ups"

(which, in reality, occurred at 42 months in the majority of cases) and 149 children (73 boys and 76 girls, mean age 42.0 months, SD 1.0) participated.

Procedure

All ESSENCE-Q data from mothers who came with their child to the 18-month or the 36-month check-up and ESSENCE-Q data from the PHNs and the specialized psychologists, engaged in these check-ups were gathered. The mothers, PHNs and the specialized psychologists scored the child´s ESSENCE-Q blind to each other.

The ESSENCE-Q had been sent to mothers before the check-up, and they were asked by letter to complete the questionnaire. Mothers' ESSENCE-Qs (ESSENCE-Q-M) were collected by receptionists at the check-ups. Then, at the check-ups, the PHNs completed the ESSENCE-Q (ESSENCE-Q-N) by interview with the mothers and by direct observation of the child without any knowledge about the ESSENCE-Q-M. Thirdly, specialized psychologists also completed the ESSENCE-Q (ESSENCE-Q-P) by an interview with the mothers and by direct observation of the child without any knowledge about the ESSENCE-Q-M and the ESSENCE-Q-N. The PHNs and the specialized psychologists used the ESSENCE-Q statements as a template for their interviews, and sometimes added simple questions (e.g. "When did your child start walking?"). After the interview and the observation, they noted their concerns in the ESSENCE-Q.

At the end of the check-ups, pediatricians with training in the field of ESSENCE examined the child and interviewed the mother. The child´s entire records with regard to development from birth were checked as were the three ESSENCE-Qs. Taking all this information into consideration, the pediatrician made a decision as to whether or not the child needed to go for further neurodevelopmental examinations. Children targeted for further examinations were then examined - on another day at the same health center - by a specialized child neuropsychiatrist (including interview with the mother). If there was any remaining concern regarding neurodevelopmental disorders, the child was referred to a neurodevelopmental clinic for further investigation by the psychiatrist and a team including occupational therapists and psychologists. The child neuropsychiatrist was not blind to the results of the ESSENCE-Qs, but these results did not form part of his referral decision.

At the neurodevelopmental clinic, assessments covered all developmental areas included under the ESSENCE umbrella. Overall development, motor and perceptual performance, social communication and related behaviors, social interest, joint attention, imitation, play, reciprocal affective behavior

and insistence on sameness/stereotypies (Charman & Baird, 2002; Charman et al., 2005; Corsello, Akshoomoff, & Stahmer, 2013) were assessed for all children at the first 2 to 3 visits. For cognitive assessment, KSPD2001 (Koyama et al., 2009) was used. For the assessment of social and communication development, the DISCO (Wing et al., 2002) was used. SDQ (Goodman, 1997) for parents of 2-4 year olds was also used. Unstructured clinical observations at the clinic and reports/interviews from parents and preschool teachers were collected throughout the examination period. Motor-perceptual performance was examined at clinical observations. The diagnositic evaluations were done at least at five different session separated by a minimum of two weeks (Battaglia & Carey, 2003). For the children who were referred from the 18-month check-ups, definite diagnoses were given at or after 30 months. The ICD-10 and DSM-IV were used throughout.

Statistical analysis

ESSENCE-Q items were rated 0 for N, 1 for M/AL and 2 for Y. The range of possible scores was 0-24. If four or more (more than 10%) of the 36 items, collapsed from the three ESSENCE-Qs, were unchecked by a mother, a PHN or a specialized psychologist, then this case was excluded. Unchecked items were otherwise rated as 0. We used these overall ESSENCE-Q scores as continuous variables, and generated ROC curves and compared the AUC to evaluate the validity of ESSENCE-Q-M, ESSENCE-Q-N and ESSENCE-Q-P separately. Additionally, we explored the optimal cut-off values for screening in health check-ups from the ROC curves. For a developmental screening, the best sensitivity and specificity balance is around 0.70-0.80 for both (Glascoe, 2005; Mackrides & Ryherd, 2011). Sensitivity should be higher than specificity so as not to miss children with problems (Worobey, 2005). When an optimal cut-off value fulfilling these conditions was found, sensitivity, specificity, PPV, and NPV were calculated. Sensitivity, specificity, PPV and NPV were expressed with a 95% CI.

Ethics

The institutional ethical boards of Kochi Prefectural Medical and Welfare Centre approved the study with parents' written informed consent.

4 RESULTS

4.1 Study I

The response rate to the questionnaire was 100%. On the Q1, the total score of the understanding of the meaning of early detection of ASD was significantly higher ($Z=-11.78$, $p< .001$, by Wilcoxon signed rank test) post-seminar (mean 35.69, SD 3.89) than pre-seminar (mean 33.51, SD 4.11). In each item of the Q1, the post-seminar score was significantly higher than pre-seminar score. The number of the participants who chose 5 (strongly agree) and 4 (agree) increased, while 2 (disagree) and 1 (strongly disagree) decreased (Table 2).

Table 2. *The changes of answer in each item of the Q1*

Q1	Question items		1 (Strongly Disagree)	2(Disagree)	3(Neutral)	4(Agree)	5(Strongly Agree)	unmarked		
			N *(%)*	*N* *(%)*	*N* *(%)*	*N* *(%)*	*N* *(%)*	*N* *(%)*	*median*	*Z*
1	Early detection of ASD suspect children in public health check-ups in infants is one of the most crucial things in public health.	pre	0 (0.0)	3 (0.1)	28 (1.0)	108 (3.8)	147 (5.1)	2 (0.1)	5	**-7.91*****
		post	0 (0.0)	1 (0.0)	11 (0.4)	52 (1.8)	222 (7.7)	2 (0.1)	5	
2	I have enough knowledge and skills for early detection of ASD suspected children.	pre	72 (2.5)	99 (3.4)	76 (2.6)	36 (1.3)	3 (0.1)	2 (0.1)	2	**-10.99*****
		post	16 (0.6)	57 (2.0)	103 (3.6)	96 (3.3)	11 (0.4)	5 (0.2)	3	
3	I want to participate in seminars or training for early detection of ASD as much as I can.	pre	0 (0.0)	1 (0.0)	19 (0.7)	84 (2.9)	184 (6.4)	0 (0.0)	5	**-4.80*****
		post	0 (0.0)	0 (0.0)	11 (0.4)	55 (1.9)	219 (7.6)	3 (0.1)	5	
4	I am interested in the current findings about child development.	pre	0 (0.0)	2 (0.1)	12 (0.4)	84 (2.9)	189 (6.6)	1 (0.0)	5	**-3.05*****
		post	0 (0.0)	0 (0.0)	12 (0.4)	60 (2.1)	214 (7.4)	2 (0.1)	5	
5	I understand the meaning of early detection of ASD.	pre	0 (0.0)	2 (0.1)	18 (0.6)	80 (2.8)	186 (6.5)	2 (0.1)	5	**-5.80*****
		post	2 (0.1)	1 (0.0)	6 (0.2)	49 (1.7)	226 (7.8)	4 (0.1)	5	
6	I notice that cooperation and coordination with other organizations are very important for early detection and follow-up after that.	pre	0 (0.0)	5 (0.2)	19 (0.7)	94 (3.3)	167 (5.8)	3 (0.1)	5	**-5.88*****
		post	1 (0.0)	1 (0.0)	8 (0.3)	63 (2.2)	212 (7.4)	3 (0.1)	5	
7	The early detection must be accompanied with community-based early intervention for ASD children.	pre	1 (0.0)	4 (0.1)	13 (0.5)	60 (2.1)	209 (7.3)	1 (0.0)	5	**-3.36*****
		post	1 (0.0)	2 (0.1)	4 (0.1)	49 (1.7)	230 (8.0)	2 (0.1)	5	
8	Working in the field of early detection of ASD suspected children, being key person for leading children to diagnostic process and early interventions are important responsibilities in my profession.	pre	3 (0.1)	31 (1.1)	66 (2.3)	121 (4.2)	66 (2.3)	1 (0.0)	4	**-10.34*****
		post	0 (0.0)	5 (0.2)	18 (0.6)	107 (3.7)	155 (5.4)	3 (0.1)	5	

Z: Results of Wilcoxon signed rank test (According to signed-rank post < pre) $^{*}p < .05$ $^{**}p < .01$ $^{***}p < .001$

Before the seminar, scores were significantly different among the occupational groups in five questions by Kruskal-Wallis test (Q1-1, Q1-2, Q1-4, Q1-5, and Q1-8). In post-hoc test by Steel-Dwass test, On Q1-1 and Q1-8, other specialists (Oth) was significantly higher than PHNs in municipalities (mPHN), and on Q1-4, Oth was significantly higher than mPHN and PHNs in prefecture (pPHN). On Q1-5, there was no significant difference among each group. On Q1-2, which was "I have enough knowledge and skills for early detection of ASD suspected children", pPHN, MD, and Oth were significantly higher than mPHN. After the seminars there was no significant difference among these four groups in all questions ($p > .05$, Kruskal-Wallis test) (Figure 1).

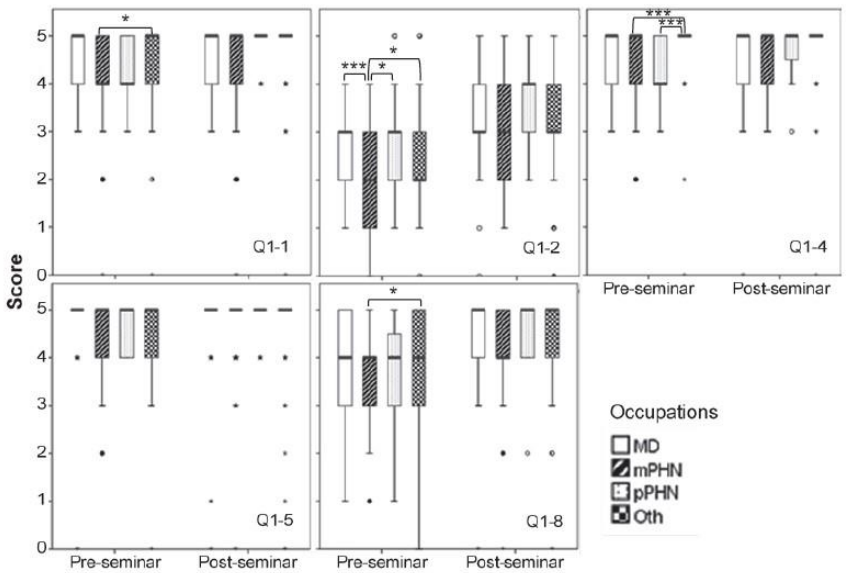

Figure 1. *Differences in scores of understanding between occupations in each question of Q1. Bar in each box is the score of median.*
**: p< .05, **: p< .01, ***: p< .001 (Steel-Dwass test)*

The Q2, the knowledge of autistic features (item 8) was thought as the most important aspect for early detection of ASD in public health check-ups before the seminars (31.60%). After the seminars, the knowledge about typical child development (item 7) was thought as the most important aspect (46.18%). Both the decrease of choosing the item 8 and the increase of choosing item 7 were statistically significant ($p < .001$). The rate of choosing the item 1

(cooperation with other organizations) also significantly decreased (p< .001) (Table3).

Table 3. *Pre-post changes*

Q2	items	pre		post		χ^2	
		N	(%)	*N*	(%)		
1	Cooperation with other organizations	**36**	**(12.5)**	**9**	**(3.13)**	**19,31**	***
2	Information from parents	28	(9.72)	18	(6.25)	2,70	
3	Nurturing environment	2	(0.69)	0	(0)	*a*	
4	Direct observation	66	(22.92)	72	(25.00)	0,34	
5	Continuous training for early detection	5	(1.75)	5	(1.75)	-	
6	Occupational experience	0	(0)	0	(0)	-	
7	Knowledge about typical child development	**38**	**(13.19)**	**133**	**(46.18)**	**78,20**	***
8	Knowledge of autistic features in early age	**91**	**(31.60)**	**41**	**(14.24)**	**25,54**	***
9	Items in questionnaire	2	(0.69)	1	(0.35)	*a*	
10	Collaboration among staffs(e.g. MD and PHN)	19	(6.60)	4	(1.39)	*a*	***
11	Others	1	(0.35)	3	(1.04)	*a*	
N/A		0	(0)	2	(0.69)	-	
	Total	288	(100)	288	(100)		

χ^2*:* Results of McNemar's test *a:* calculating *p* from binomial distribution
(N<25) $^{*}p < .05$ $^{**}p < .01$ $^{***}p < .001$

On the Q3, the total score of the understanding of the contents of the seminars was significantly higher (Z=−13.26, p< .001, by Wilcoxon signed rank test) post-seminar (mean 39.76, SD 8.88) than pre-seminar (mean 29.23, SD 9.86). On each item of the Q3, the post-seminar score was significantly higher than the pre-seminar score. The number of the participants who chose 5 (strongly agree) and 4 (agree) increased, while 2 (disagree) and 1 (strongly disagree) decreased (Table 4).

Table 4. *Response change for each item of Q3*

Q3	Question items		1(Very Low) N (%)	2(Relatively Low) N(%)	3(OK) N (%)	4(Relatively High) N (%)	5(Very High) N (%)	unmarked N (%)	*median*	*Z*
1	**Knowledge about ASD**	pre	49 (1.7)	86 (3.0)	114 (4.0)	30 (1.0)	4 (0.1)	5 (0.2)	3	-
		post	3 (0.1)	46 (1.6)	149 (5.2)	74 (2.6)	12 (0.4)	4 (0.1)	3	**10.38^{***}**
2	**Knowledge about typical development to 2 years old**	pre	27 (0.9)	67 (2.3)	140 (4.9)	48 (1.7)	5 (0.2)	1 (0.0)	3	**-9.26^{***}**
		post	3 (0.1)	32 (1.1)	135 (4.7)	95 (3.3)	19 (0.7)	4 (0.1)	3	
3	**Response to others in typical development**	pre	38 (1.3)	86 (3.0)	121 (4.2)	32 (1.1)	6 (0.2)	5 (0.2)	3	-
		post	2 (0.1)	31 (1.1)	130 (4.5)	101 (3.5)	20 (0.7)	4 (0.1)	3	**11.22^{***}**
4	**"Showing" in infancy**	pre	86 (3.0)	93 (3.2)	77 (2.7)	24 (0.8)	3 (0.1)	5 (0.2)	2	-
		post	1 (0.0)	34 (1.2)	133 (4.6)	92 (3.2)	22 (0.8)	6 (0.2)	3	**12.61^{***}**
5	**Development of sharing affection**	pre	76 (2.6)	83 (2.9)	91 (3.2)	25 (0.9)	5 (0.2)	8 (0.3)	2	-
		post	2 (0.1)	36 (1.3)	127 (4.4)	98 (3.4)	19 (0.7)	6 (0.2)	3	**11.81^{***}**
6	**Development of social routine**	pre	42 (1.5)	79 (2.7)	125 (4.3)	35 (1.2)	3 (0.1)	4 (0.1)	3	-
		post	1 (0.0)	33 (1.1)	119 (4.1)	109 (3.8)	21 (0.7)	5 (0.2)	3	**11.13^{***}**
7	**Development of joint attention**	pre	92 (3.2)	91 (3.2)	73 (2.5)	23 (0.8)	2 (0.1)	7 (0.2)	2	-
		post	1 (0.0)	40 (1.4)	127 (4.4)	97 (3.4)	17 (0.6)	6 (0.2)	3	**12.75^{***}**
8	**Interactive play in infancy**	pre	49 (1.7)	91 (3.2)	104 (3.6)	37 (1.3)	3 (0.1)	4 (0.1)	3	-
		post	2 (0.1)	34 (1.2)	122 (4.2)	100 (3.5)	24 (0.8)	6 (0.2)	3	**11.36^{***}**
9	**Development of imitation**	pre	41 (1.4)	79 (2.7)	126 (4.4)	37 (1.3)	3 (0.1)	2 (0.1)	3	-
		post	1 (0.0)	33 (1.1)	121 (4.2)	109 (3.8)	18 (0.6)	6 (0.2)	3	**10.87^{***}**
10	**Range of facial expression in infancy**	pre	46 (1.6)	84 (2.9)	115 (4.0)	37 (1.3)	4 (0.1)	2 (0.1)	3	-
		post	1 (0.0)	25 (0.9)	130 (4.5)	100 (3.5)	27 (0.9)	5 (0.2)	3	**11.55^{***}**
11	**Development of communication**	pre	36 (1.3)	77 (2.7)	127 (4.4)	41 (1.4)	2 (0.1)	5 (0.2)	3	-
		post	2 (0.1)	35 (1.2)	130 (4.5)	95 (3.3)	21 (0.7)	5 (0.2)	3	**10.27^{***}**
12	**Characteristic autistic behaviors to 2 years old**	pre	64 (2.2)	83 (2.9)	97 (3.4)	38 (1.3)	3 (0.1)	3 (0.1)	2	-
		post	3 (0.1)	41 (1.4)	134 (4.7)	90 (3.1)	12 (0.4)	8 (0.3)	3	**10.50^{***}**

Z: Results of Wilcoxon signed rank test (According to signed-rank post < pre) $^{*}p < .05$ $^{**}p < .01$| $^{***}p < .001$

4.2 Study II

A total 47 children (24 boys and 23 girls) had been referred during the 1-year study period. Of these 47, 8 (2 boys and 6 girls) were regarded to be functioning within the normal variation, and parents of 9 children (2 boys and 7 girls) stopped coming before the child reached age 2 years.

The remaining 30 children were assessed with regard to ESSENCE. Fifteen (10 boys and 5 girls) of the children had either a verified medical or etiological underlying developmental disorder (four trisomy 21, one 9p partial trisomy, one hereditary congenital myopathy, one spina bifida with hydrocephalus, three periventricular leukomalacia, two had a low-density area according to CT, and another three children had neuroimaging abnormalities with probable etiological relevance). The other 15 (10 boys and 5 girls) had no definite medical or etiological diagnosis or risk factors that could be related to a causal condition.

Of the 15 children with an identified or strongly suspected etiology, 13 (8 boys and 5 girls) (87%) had ESSENCE diagnoses (one CP, 6 IDD, 4 IDD with CP, one ASD with AD/HD, and one ASD with IDD and AD/HD). Of the 15 children without a known etiology, all had ESSENCE diagnoses (one CP, one IDD, one ASD, one SLD, one IDD with CP, one ASD with DCD, one ASD with IDD, one ASD with IDD and DCD, one ASD with AD/HD and DCD, and one ASD with IDD and epilepsy).

Of the 21 children with IDD, 14 (67%) had two or more ESSENCE diagnoses. Of the 13 children with ASD, 12 (92%) had two of more ESSENCE diagnoses. All cases with AD/HD, all with DCD, and the child with epilepsy had at least one other ESSENCE diagnosis. Of the seven children with CP, five also had IDD.

The ESSENCE diagnoses were established between 5 and 98 months (mean 40.2, median 36), IDD (n=21) was diagnosed between 9 and 66 months (mean 32.5, median 27), ASD (n=13) between 18 and 98 months (mean 46.4, median 40), AD/HD (n=3) at 57, 89 and 98 months (mean 81.3, 89), DCD (n=3) at 32, 37, and 88 months (mean 52.3, median 37), and SLD (n=1) at 47 months. Cerebral palsy (n=7) was diagnosed between 5 and 53 months (mean 26, median 20). The diagnosis of epilepsy (n=1) was given at 54 months. The results revealed that the majority of children with concerns about early motor delay had ESSENCE (Table 5).

See next page for Table 5.

The patient number from 1 to 15 were with identified or strongly suspected etiology (in the first page).

The patient number from 16 to 30 were without a known etiology (in the second page)

Table 5. *Information from the clinical records of the 30 children assessed for ESSENCE*

Patient No.	Gender	Gestational age (months)	Age at first visit (months)	Motor delay /motor related problem causing referral	Motor disorders at age (months)	Neurological abnormalities at first examination	Brain imaging findings	Final etiological diagnosis	Other ESSENCE diagnosis/es at age (months)
1	Boy	37	7	Raising the head	No	Hypotonus	Not done	21trisomy	IDD (33)
2	Girl	40	9	Crawling	No	Hypotonus	Not done	21trisomy	IDD (16)
3	Boy	38	14	Crawling	No	Hypotonus	Not done	21trisomy	IDD (23)
4	Boy	37	10	Sitting	No	Hypotonus	Not done	21trisomy	IDD (26)
5	Boy	38	17	Standing with support	No	No	Delayed myelination, ventricular distension (MRI)	9p partial trisomy	IDD (17) ASD (57) ADHD (57)
6	Boy	39	19	Walking	No	No	No abnormal finding (MRI)	Congenital myopathy with type 1 fiber predominance	No
7	Boy	38	16	Standing with support	No	Hypotonus	No information*	Hydrocephalus, Spina bifida	ASD (98) ADHD (98)
8	Boy	31	12	Sitting	Cerebral palsy (43)	Hypotonus	Periventlicular leukomalacia (MRI)	Periventricular leukomalacia	No
9	Boy	29	5	Cerebral Palsy was suspected because of an abnormality in brain MRI	Cerebral palsy (5)	Hypertonus	Periventricular leukomalacia (MRI)	Periventricular leukomalacia	IDD (19)
10	Girl	30	5	Cerebral Palsy was suspected because of an abnormality in brain MRI	Cerebral palsy (45)	Spasticity	Periventricular leukomalacia (MRI)	Periventricular leukomalacia	IDD (66)
11	Girl	25	7	Raising the head	Cerebral palsy (7)	Spasticity	Low density area (CT)	Cerebral abnormality	IDD (21)
12	Girl	27	9	Raising the head	Cerebral palsy (9)	Hypotonus	Low density area (CT)	Cerebral abnormality	IDD (9)
13	Boy	27	13	Cerebral Palsy was suspected because of an abnormality in brain CT	No	Spasticity in the legs	Ventricular distension (CT)	Strongly suspected etiology	No**

14	Girl	25	12	Rolling over	No	No	Small low density area, periventricular lucency and delayed myelination (MRI)	Strongly suspected etiology	IDD (34)
15	Boy	37	7	Raising the head	No	No	Periventricular lucency (MRI) (neonatal respiratory distress syndrome and intracranial bleeding at birth)	Strongly suspected etiology	IDD (24)
16	Boy	37	1	Floppy infant (Cerebral palsy suspected)	DCD (32)	Hypotonus	No abnormal findings (MRI)	No	ASD (27) ADHD (89)
17	Boy	40	13	Sitting	DCD (88)	Hypotonus	Not done	No	ASD (36) ID (50)
18	Girl	39	13	Standing with support	DCD (37)	Spasticity in the left leg	Not done	No	ASD (24)
19	Boy	40	10	Rolling over	No	No	No abnormal findings (MRI)	No	IDD (18) ASD (18)
20	Boy	37	5	Stiffness in both knees (Cerebral palsy suspected)	No	Hypertonus	Not done	No	SLD (47)
21	Boy	39	13	Crawling	No	No	No abnormal findings (CT)	No	ASD (28) IDD (59)
22	Boy	40	11	Sitting	No	Spasticity	No abnormal findings (MRI)	No	IDD (27) ASD (27)
23	Girl	39	12	Standing with support	No	Hypotonus	Not done	No	ASD (41) IDD (41) Epilepsy (54)
24	Boy	40	18	Walking	No	Hypotonus	Not done	No	IDD (25)
25	Girl	39	20	Walking	No	Hypertonus	No abnormal findings (MRI)	No	IDD (34) ASD (85)
26	Girl	39	1	Floppy infant (Cerebral palsy suspected)	No	Hypotonus	Not done	No	ASD (74)
27	Girl	38	20	Standing with support	No	Hypotonus	Not done	No	IDD (40) ASD (40)
28	Boy	38	7	Rolling over	No	No	No abnormal findings (CT, MRI)	No	IDD (48) ASD (48)
29	Boy	28	17	Standing with support	Cerebral palsy (20)	Spasticity in the legs	No abnormal findings (MRI)	No	No***
30	Boy	38	10	Sitting	Cerebral palsy (53)	Hypotonus	No abnormal findings (CT)	No	IDD (54)

*The child was initially treated by the neurosurgeon, no information in available records, **Developmental test was planned but parents did not come for the assessment of the child, ***Mother telephoned to the centre with concern regarding the child's communication development when the child was 9 years, but the child never came for an assessment. **Abbreviations:** ADHD, Attention deficit/hyperactivity disorder; ASD, Autism spectrum disorder; CT, Computed tomography; ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations; IDD, Intellectual developmental disorder; MRI, Magnetic resonance imaging; SLD, Speech language disorder

4.3 Study III

A total of 130 children, 109 boys (84%) and 21 girls (16%), were evaluated using the ESSENCE-Q and a full clinical assessment. The informants included 124 mothers (95%), five fathers (4%), and one other caregiver (1%). Of the 130 children, 113 (96 boys and 17 girls) (87%) were given ESSENCE diagnoses, and 17 (13 boys and four girls) (13%) were not. The age at first visit varied from 21 to 72 months (mean 41.6, SD 13.7). In the "diagnosis positive group", the age of the first visit had occurred between 22 and 72 months (mean 41.7, SD 13.7). In the "diagnosis negative group", the age of the first visit had occurred between 21 and 64 months (mean 40.5, SD 13.5). Table 6 shows the diagnoses and other demographic information.

Table 6. *Diagnosis and other information of 130 children*

Diagnosis	Boys	Girls	Total	Mean age (months) (SD) at first visit and ESSENCE-Q screening	Mean age (months) (SD) at diagnosis	Mean period between first visit and diagnosis (months) (SD)
SD	32	10	42	37.6 (12.7)	41.5 (13.4)	3.9 (6.9)
ADHD	14	0	14	49.1 (15.5)	60.7 (13.5)	11.6 (13.0)
IDD	11	1	12	43.9 (13.3)	46.6 (16.6)	2.7 (8.6)
BIF	1	1	2	46,5	46,5	0
LD	2	1	3	49.7 (11.4)	62.3 (11.4)	12.7 (11.4)
ASD+IDD	17	3	20	35.4 (12.5)	36.4 (12.5)	1.0 (2.5)
ASD+ADHD	8	1	9	48.6 (9.6)	57.3 (9.3)	8.8 (9.7)
ASD+DCD	3	0	3	61.3 (5.9)	64.3 (3.2)	3.0 (3.0)
ADHD+IDD	4	0	4	42.5 (13.5)	49.8 (13.0)	7.3 (10.4)
ADHD+DCD	1	0	1	46	70	24
LD+DCD	1	0	1	47	67	20
ASD+ADHD+DCD	2	0	2	44	69	25
Diagnosis (+)	96	17	113	41.7 (13.7)	47.3 (16.0)	5.5 (9.1)
Diagnosis (-)	13	4	17	40.5 (13.5)	54.8 (12.1)	13.5 (12.0)
All	109	21	130	41.6 (13.7)	48.1 (157)	6.6 (9.8)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BIF, borderline intellectual functioning; DCD, developmental coordination disorder; ESSENCE-Q, ESSENCE-Questionnaire; IDD, intellectual developmental disorder; LD, learning difficulties; SD, standard deviation

The Cronbach's alpha across all 11 items was 0.815.

The sensitivity and the specificity at the cut-off levels according to the author of the ESSENCE-Q was 0.94 and 0.53, respectively. At all possible cut-off levels, three had the sensitivity and the specificity in the 0.7-0.8 ranges, and sensitivity>specificity. These were Y≥2 or M/AL≥3, and Y≥3 or M/AL≥3. Among the cut-off levels with the three highest Youden Index, Y≥2 or M/AL≥3 fitted with the condition that the sensitivity and the specificity both in 0.7-0.8 ranges, and also sensitivity>specificity (Table 7).

Table 7. *Combination of cut-off levels with three highest Youden Index*

Cut-off levels	Sensitivity 95%CI	Specificity 95%CI	Youden index 95%CI
Y≥2or M/AL≥5	0,76	0,88	0,64
	(0.67, 0.84)	(0.64, 0.99)	(0.31, 0.82)
Y≥2or M/AL≥3	**0,87**	**0,77**	**0,63**
	(0.79, 0.92)	**(0.50, 0.93)**	**(0.29, 0.86)**
Y≥2or M/AL≥4	0,79	0,82	0,61
	(0.70, 0.86)	(0.57, 0.96)	(0.27, 0.82)

Note: Youden Index=sensitivity+specificity-1. Bold combination best fit with rule of thumb sensitivity>specificity, sensitivity and specificity both in 0.70-0.80 ranges, and Youden Index high.
Abbreviations: CI, confidence interval; M/AL, Maybe/A Little; Y, Yes.

4.4 Study IV

18-month check-ups

During the study period, all 152 children (79 boys and 73 girls) were invited to the routine 18-month check-up and 143 children (75 boys and 68 girls, mean age 18.7 (SD 0.9)) participated. The attendance rate was 94%. Of the 143 children, 50 (27 boys and 23 girls) (35%) were invited to come to the secondary check-up due to developmental concerns. However, 8 (3 boys and 5 girls) did not come to the secondary check-up. Of the remaining 42 children, 21 (10 boys and 11 girls) were regarded to have normal

development and 21 (14 boys and 7 girls) were referred to the neurodevelopmental clinic. One boy´s family moved out from the city and, as a result, 20 (13 boys and 7 girls) came to the clinic.

Of the 20 children who came to the clinic, 5 (3 boys and 2 girls) were considered to have a normal developmental trajectory and 15 children (10 boys and 5 girls) were diagnosed with neurodevelopmental disorders (10% of all participants). One third had intellectual problems (IDD, BIF), and one third had ADHD. Two had ASD (Table 8).

Table 8. *Diagnosis and background information of the 21 children referred to the clinic from 18-month check-ups*

No.	Gender	Age at the first check-up (month)	Age at the first visit (month)	ESSENCE diagnoses/conditions at age (month)
1	M	19	21	Normal developmental trajectory (44)
2	M	18	21	Normal developmental trajectory (33)
3	M	18	19	ASD (33)
4	M	18	26	ADHD (41), IDD (41)
5	M	18	20	ADHD (39), DCD (39)
6	M	19	38	BIF (39)
7	M	19	20	ASD (36)
8	M	18	21	Normal developmental trajectory (30)
9	M	21	22	IDD (30)
10	M	19	22	IDD (33)
11	M	19	25	ADHD (32)
12	M	18	29	SLD (30)
13	M	18	20	IDD (30)
14*	M	18	N/A	N/A
15	F	18	21	ADHD (42), SLD (43)
16	F	19	23	Normal developmental trajectory (38)
17	F	18	22	SLD (37)
18	F	19	28	Normal developmental trajectory (30)
19	F	18	20	SLD (42)
20	F	18	21	ADHD (36)
21	F	18	19	IDD (30)

Notes: *Lost of follow-up due to address change.

Three of the 143 children (three boys without a diagnosis) were excluded because of missing data. The 8 children who did not come for the second assessment and the child who moved from the area were excluded (because it could not be ascertained whether or not they actually had an ESSENCE diagnosis leaving 131 (63 boys and 68 girls, mean age 18.7, SD 0.8, 92% of all the participants) for statistical analyses.

The overall ESSENCE-Q-M, ESSENCE-Q-N and ESSENCE-Q-P scores produced AUC values (95% CI) of 0.69 (0.52-0.86), 0.92 (0.86-0.97) and 0.85 (0.74-0.96) respectively (Figure 2). For ESSENCE-Q-M, we did not find an optimal cut-off value that fulfilled the conditions mentioned above. For ESSENCE-Q-N, we set an optimal cut-off value of 3, that showed sensitivity 0.93 (95% CI: 0.66-1.00), and specificity 0.74 (95% CI: 0.66-0.82), PPV 0.30 (95% CI: 0.17-0.46), and NPV 0.99 (0.94-1.00). For ESSENCE-Q-P, we set an optimal cut-off value of 3, that showed a sensitivity of 0.86 (95% CI: 0.57-0.98), a specificity 0.75 (95% CI: 0.66-0.83), a PPV of 0.29 (95% CI: 0.16-0.46), and a NPV of 0.98 (95% CI: 0.92-1.00).

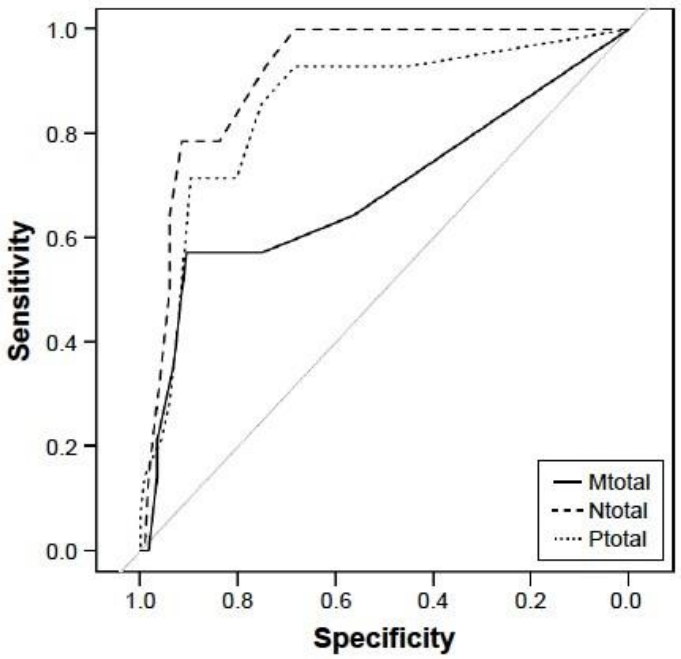

Figure 2. *ROC curves for predicting ESSENCE diagnoses at 18-month check-ups based on overall ESSENCE-Q score in ESSENCE-Q-M (Mtotal), ESSENCE-Q-N (Ntotal), and ESSENCE-Q-P (Ptotal).*

36-month check-ups

During the study period, 158 children (77 boys and 81 girls) were invited to the 36-month check-ups (which in reality occurred at 42 months in the majority of cases) and 149 children (73 boys and 76 girls, mean age 42.0 months (SD 1.0)) participated. The attendance rate was 94%. Of the 149 children, 38 (19 boys and 19 girls) (26%) were invited to come to the secondary check-up due to developmental concerns . However, 5 (5 boys) did not come to the secondary check-up. In the remaining 33 children, 17 were regarded to have a normal development (6 boys and 11 girls) and 16 (8 boys and 8 girls) were referred to the neurodevelopmental clinic. A family of a boy and another family of a girl moved from the area and, as a result, 14 (7 boys and 7 girls) came to the clinic.

All children who came to the clinic were diagnosed as having neurodevelopmental disorders (9% of all participants), 12 had AD/HD and two had ASD. Ten children had two or more diagnoses (Table 9).

Table 9. *Diagnosis and background information of the 16 children referred to the clinic from 36-month check-ups*

No.	Gender	Age at the first check-up (month)	Age at the first visit (month)	ESSENCE diagnoses/conditions at age (month)
1	Boy	41	46	ASD (48), DCD (48), Tics (48)
2	Boy	42	47	BIF (49), ADHD (56)
3	Boy	42	43	ASD (45), ADHD (58)
4	Boy	42	43	DCD (44), ADHD (51)
5	Boy	41	45	ADHD (51), SLD (51)
6	Boy	41	44	ADHD (57), SLD (57)
7*	Boy	43	N/A	N/A
8**	Boy	42	44	ADHD (52), BIF (52)
9	Girl	43	51	ADHD (59)
10	Girl	43	45	DCD (45), Tics (45), SAD (45), Congenital tremor (45)
11	Girl	41	46	ADHD (56)
12	Girl	43	44	ADHD (59), BIF (59)
13	Girl	42	45	ADHD (59)
14	Girl	42	45	ADHD (59)
15*	Girl	43	N/A	N/A
16	Girl	41	47	ADHD (53), RAD (53)

Notes: *Lost of follow-up due to address change. **Excluded from ROC analysis because of missing data.
Abbreviations: RAD, reactive attachment disorder; SAD, social anxiety disorder.

Three of the 149 children (three boys, one of whom had a diagnosis) were excluded because of missing data. Five children who did not come to the secondary assessment and 2 children who did not come for full clinical assessment were also excluded leaving 139 (64 boys and 75 girls, mean age 42.0, SD 1.0, 93% of all the participants) for statistical analyses.

Overall ESSENCE-Q-M, ESSENCE-Q-N and ESSENCE-Q-P scores produced AUC values (95% CI) of 0.63 (0.46-0.81), 0.84 (0.73-0.95) and 0.82 (0.69-0.94) respectively (Figure 3). For ESSENCE-Q-M, we did not find an optimal cut-off value that fulfilled the conditions above mentioned.

For ESSENCE-Q-N, we set an optimal cut-off value of 2, that showed a sensitivity of 0.86 (95% CI: 0.57-0.98), and a specificity of 0.70 (95% CI: 0.61-0.76), a PPV of 0.24 (95% CI: 0.13-0.38), and a NPV of 0.98 (95% CI: 0.92-1.00). For ESSENCE-Q-P, we set an optimal cut-off value of 2, that showed a sensitivity of 0.86 (95% CI: 0.57-0.98), a specificity 0.66 (95% CI: 0.57-0.75), A PPV of 0.22 (95% CI: 0.12-0.36), and a NPV of 0.98 (95% CI: 0.92-1.00).

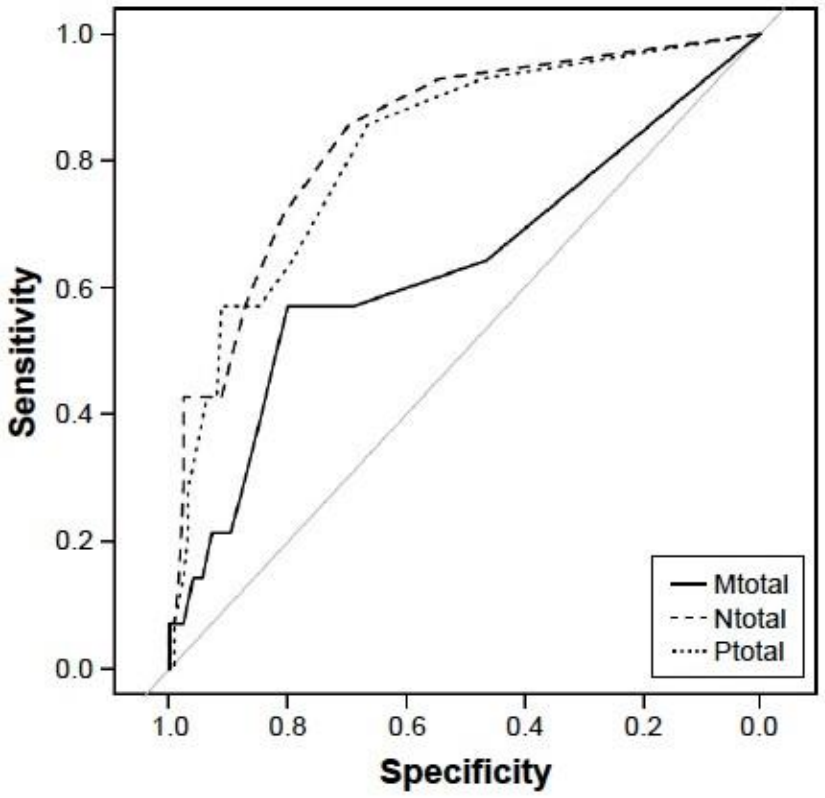

Figure 3. *ROC curves for predicting ESSENCE diagnoses at 36-month check-ups based on overall ESSENCE-Q score in ESSENCE-Q-M (Mtotal), ESSENCE-Q-N (Ntotal), and ESSENCE-Q-P (Ptotal).*

5 DISCUSSION

5.1 Main findings

This thesis regarding the early detection of ESSENCE in young children in Japan, comprises four substudies focusing on different aspects of early developmental screening of children. These aspects include the qualifications and self-appraisal of the professionals involved in the screening process, the usefulness of a new instrument used to detect a broad spectrum of developmental problems, and the psychometrics of this screening instrument for developmental deviations of clinical relevance both in a clinic and a general population sample. Study I (the Seminar study) is concerned with the individual "screener persons", their education and training of specialists (PHNs, psychologists, and others). Study II (the Motor Delay study) is focused on one type of a presenting ESSENCE symptom. Study III and IV (the ESSENCE-Q Clinic and ESSENCE-Q Public Health studies) are concerned with the actual screening tool, the questionnaire, ESSENCE-Q, including 12 short items designed to cover relevant aspects of concern about child development.

In the seminar study, it was shown that the participants appreciated the seminars that were held with the newly developed materials, focused on social communication development in children aged one to two years. Before the seminar, PHNs in municipalities, unlike other practitioners, tended to choose negatively worded response to the item about self-confidence in the surveillance of ASD. After the seminar, there was no statistically significant difference across occupations as regards professional self-esteem in this respect.

In the motor delay study, both those children who had, and those who did not have a verified etiology underlying their motor developmental problems, had a very high prevalence of ESSENCE (87% and 100 %, respectively). The study clearly demonstrated the importance of including a multi-professional approach in children referred for gross motor delay or other motor abnormalities to ensure that their needs of treatment and habilitation are met adequately.

In the ESSENCE-Q Clinic study, it was put forward that one of the major strengths of the questionnaire is that the included questions are about "concern" covering the different developmental domains within ESSENCE, and not about specific symptoms or behaviors. "Yes", "No", and "Maybe/A

Little" are the response alternatives. The internal consistency of the ESSENCE-Q was found to be acceptable as good. The cut-off levels originally suggested by the author of the ESSENCE-Q (Y≥1 or M/AL≥3) seemed reasonable. However, Y≥2 or M/AL≥3 would be alternative cut-off levels, with even better values for combined sensitivity (0.87) and specificity (0.77).

In the ESSENCE-Q Public Health study, aiming at evaluating psychometric properties of the ESSENCE-Q, data from mothers, PHNs, and psychologists, collected at two health check-ups, were compared. Results were validated against clinical ESSENCE diagnoses. AUCs for ESSENCE-Q-N (PHN) and ESSENCE-Q-P (Psychologist) were 0.8-0.9 both at the 18 and 36 months check-ups with almost 1.0 NPVs. The ESSENCE-Q used by PHNs and specialized psychologists seemed to hold promise as a general population screening tool for neurodevelopmental disorders in young children.

5.2 Limitations and Strengths

In the seminar study, two major limitations should be mentioned. One is that the result obtained from the questionnaire is subjective, and so that the objectivity of the questionnaire is "questionable". The other one is that the effect of the seminars "in practice" (i.e. overlooking of ASD in the municipalities became lesser compared with before having the seminars) was not evaluated.

In the Motor Delay study, the major limitation was the small size of the study group, which hampers generalizability. There were also nine children (19% of whole group) for whom no follow-up data with regard to ESSENCE problems could be obtained. However, the group is considered representative of the very young child population being referred for assessment of motor problems. Another strength is that the center where the study was carried out has been the only service for child developmental problems for over 20 years, and a network and referral system, comprising also health check-ups for all children in the prefecture, has been built up over time so that the vast majority of young children with developmental problems in the prefecture had been referred to the center.

In the ESSENCE-Q Clinic study, one limitation was that analyses were based only on a clinical sample, and that the number of cases in the "diagnosis negative group" was very small. Thus, the result could not be generalized for the usefulness of the ESSENCE-Q in the general population of children.

In the ESSENCE-Q Public Health study, a limitation was that the pediatrician, who made the decision whether to refer or not for secondary check-up, knew the result of the ESSENCE-Q by mothers, PHNs and specialized psychologist. However, since the study was performed in a routine clinical environment that already included some kind of explicit screening for neurodevelopmental disorders, it would have been ethically problematic to recruit a representative population if parent-reported or observed problems would not have influenced the decision of refer for in-depth assessment.

5.3 Discussion of the results obtained in each of the four substudies

Study I - The Seminar study

The result of Q1 suggests that the participants felt that, after the seminar, they understood more about the meaning of early detection of ASD and of importance of their own role for as a professional engaging in the check-ups. A similar study showing similar result has been done in preschool settings in Japan to evaluate the effect of teaching practices using a similar questionnaire to Q1 (Miki & Sakurai, 1998). The interesting thing was that PHNs of municipalities tended to choose negatively worded response compared with other professionals before the seminar. This tendency was particularly evident in Q1-2 that is "I have enough knowledge and skills for early detection of ASD suspected children". The pre-seminar responses indicated that they have low self-confidence to identify themselves as a practitioner for the surveillance of the children with suspected ASD, despite the fact that they were the practitioners who had the most critical role in it. According to a document of Japanese Nursing Association (2011) (Japanese Nursing Association, 2011.), PHNs of municipalities are working at the front line of the public health system, and their work volume is increasing continuously. As a result, they have to find the time for self-improvement of their knowledge and skill in ASD screening. Because of this, their confidence would be lower than other "specialists". After the seminar, there was no statistical significant difference between different professionals. It could be taken to mean that the seminar provided the PHNs with an opportunity to strengthen their self-confidence, and it could lead that more children with ASD would be identified in the 18 month check-up.

The most strongly emphasized topic throughout the seminars was social interaction and aspects concerning absence or delay of "neurotypical" social communication behaviors in children. It was also emphasized that aberrant

behaviors that tend to be common in ASD may not be the most useful predictors in this young age group. Not all children with ASD exhibit aberrant behaviors and, usually, these behaviors emerge after 2 to 3 years of age (Stenberg et al., 2014; Young & Brewer, 2002). The result of Q2 indicated a positive effect of the seminars on this crucial point. The result of Q3 could be taken to indicate that the materials and the procedure employed are appropriate for the purpose to provide an opportunity to get knowledge of early signs of ASD through learning about social communication development during the first two years of life.

The main target group for participation in the seminar was the PHNs in municipalities, because they are the persons who, optimally, would be "the front-line specialists" of child development surveillance. The PHNs see children at key stages in their development. There are several infant and toddler check-ups arranged by municipalities, for example, 4-month, 10-months, 18-months and 36-month. The PHNs also do "Newborn Baby Visit", i.e. they visit the house/home of the newborn baby to give some advice about baby care. Therefore, they are not only the best placed to monitor abnormal development, but also most experienced and expert to do so, given their extensive knowledge and training on developmental milestones. With a firm knowledge of "normal" early child development, the PHNs can identify potential problems via observation of the child's responses, interactions, and play through routine check-ups (Barbaro et al., 2011; Curry & Duby, 1994; Nadel & Poss, 2007).

Study II - Motor delay study

In the Motor Delay study, the cohort of 30 very young children had presented early gross motor delay or motor abnormalities and had been subjected to a comprehensive clinical follow-up with a view to also identifying other problems and disorders within the ESSENCE group. The group comprised all children, who during a 1-year period had been referred to a specialized center, serving one prefecture in Japan, and the cohort can be considered representative of very young children presenting at clinics with motor delay. The study group is heterogeneous with regard to severity of the motor problem and underlying etiology, reflecting the type of clinical setting in which this study was carried out.

From the etiological point of view, the sample consisted of several small subgroups. Children with Down syndrome who all present with concomitant IDD and many also with ASD and AD/HD, constituted one such subgroup. Another small subgroup comprised children who had been born extremely preterm, a group that is now well-known to have increased risks for many

ESSENCE problems. These two groups were included in the study since they had been referred to the center for developmental assessments primarily for their motor problems, including muscular hypo -and hypertonus.

A verified or highly suspected etiologic diagnosis had been identified in 15 of the 30 children. The diagnostic assessments had been performed on clinical grounds and were dependent on available methods and technique, and systematic medical investigations (e.g., comparative genomic hybridization array) had not been performed (Cetin et al., 2013).

It has been repeatedly demonstrated that so-called comorbidity (or "co-existence") is common in children with ASD, AD/HD, IDD, and SLD, but reports regarding the coexistence of developmental disorders in cohorts of children with motor disorders are fewer. A population-based study of children with cerebral palsy revealed that child psychiatric disorders were present in 57% of the children, and the most common disorder was AD/HD (Bjorgaas, Hysing, & Elgen, 2012). It was recommended that all children with cerebral palsy should have an early psychiatric evaluation. Children with myotonic dystrophy type 1 were studied by Ekström et al. who demonstrated that more than half of the group had additional neuropsychiatric or neurodevelopmental disorders, such as ASD, AD/HD, and IDD (Ekstrom, Hakenas-Plate, Samuelsson, Tulinius, & Wentz, 2008). In boys with Duchenne muscular dystrophy, co-occurring IDD, AD/HD, and ASD are common (Banihani et al., 2015).

In our cohort, including children with and without a verified etiology underlying their motor developmental problems, a high prevalence of ESSENCE, 87% and 100%, respectively, was found. The prevalence of ESSENCE was much higher in this cohort than in the general population, where it is expected to be about 5%-10% in preschool children (Gillberg, 2010). The finding suggests that clinical observation and assessment regarding ESSENCE should be performed in young children presenting with motor delay or other motor problems regardless of whether there is a known etiologic factor or not.

Almost all children with ASD also had at least one additional neurodevelopmental diagnosis and all children with AD/HD and DCD had at least one other ESSENCE diagnosis. This finding supports that coexistence of neurodevelopmental disorders and sharing of symptoms is the rule rather than exception in preschool children (Gillberg, 1983, 2010; Kadesjö & Gillberg, 2001).

The results show that several months of observation and repeated examinations were needed to arrive at an ESSENCE diagnosis in the majority of cases. This finding would suggest that if there are concerns regarding a child's motor development before age 2 years - and also in children with motor problems appearing later – there is a need of a broad follow-up, including considerations of different developmental disorders, besides the motor problem per se.

Study III – the ESSENCE-Q Clinic study

The ESSENCE-Q is not a tool for diagnosis but was developed as a tool for primary screening of ESSENCE (in populations and in clinics). In developmental screening, the aim is to identify children being at risk for neurodevelopmental disorders that need to be assessed by a developmental spe¬cialist or to be screened for possible further problems by a health visitor/nurse (Gillberg, 2012). Therefore, the emphasis of the ESSENCE-Q is on the sensitivity and not on the specificity. It is generally agreed that the ideal developmental screening test should err in the direction of false positive (Worobey, 2005). From this point of view, the cut-off scores suggested by the author of the ESSENCE-Q seemed reasonable, even though specificity was only moderate. On the other hand, a screening tool with a high false posi¬tive rate will be costly (Urkin, Bar-David, & Porter, 2015). For a developmental screening test, it has been suggested that the best sensitivity and specificity balance is one where both are around 0.70–0.80 (Glascoe, 2005; Mackrides & Ryherd, 2011). High sensitivity is crucial not to miss the children with devel¬opmental problems, whereas, to minimize over referrals, specificity should be closer to 80% (Glascoe, 2005). From the results obtained, the cut-off levels that have higher sensitivity than specificity and that have both sensitivity and specificity in 0.70–0.80 range were Y≥2 or M/AL≥3, and Y ≥3 or M/AL≥3. Among cut-off levels that had relatively high Youden indi¬ces on the basis of the ROC analysis, Y≥2 or M/AL≥3 was recommended as the optimal cut-off level in a clinical neurodevelopmental center.

On the basis of this pilot study, one fixed cut-off level cannot be decided, but it seems likely that the ESSENCE-Q can be a good instrument for use by nurses or general practitioners at child health care centers as a screening tool of neurodevelopmental disorders with a proper cut-off level (cut-off levels depend on the usage).

Screening tools should be simple, easy to use, acceptable, and cheap (Urkin, Bar-David, & Porter, 2015), also inexpensive in terms of training and brief in its administration (Worobey, 2005). The ESSENCE-Q fits with all these

conditions. In the ESSENCE-Q, the questions are about "con¬cern" for each of the ESSENCE domains, not about specific symptoms or behaviors. "Yes", "No", and "Maybe/A Little" are the response alternatives. It may appear to be somewhat unspecified and vague, but this is the unique strength of the ESSENCE-Q. Behaviors of young children are very varied, and if the focus is on a specific behavior, the behaviors that do raise some concern, but that we have difficulty pinpointing exactly, would be missed. Using the ESSENCE-Q provides an opportunity to catch non-specified but critical information of the child's development. ESSENCE-Q is not geared toward a specific neurodevelopmental diagnosis, and this could be the strength for screening across a whole range of ESSENCE problems.

The questionnaire could also be useful in a public health situation as a parent questionnaire and/or as an interview questionnaire and/or as an observation record. The cut-off scores might have to change according to the usage, and further studies are needed for this.

Study IV – the ESSENCE-Q Public Health study

In this Public Health study, the ESSENCE-Q was used in a validation research project in a public health setting. Mothers, PHNs, and psychologists completed the ESSENCE-Q. According to the results obtained, the validity of the ESSENCE-Q by PHNs and specialized psychologists seemed sufficient for a screening tool in public health check-ups. The ESSENCE-Q by mothers did not seem sufficient for a screening tool when used alone. An underlying reason for the better validity of the ESSENCE-Q rating by PHNs and specialized psychologists, compared to the mothers, might be that the professionals' experiences contributed to a more realistic assessment of the children's development.

Nurses working in maternal and child health are the key professionals for early identification of neurodevelopmental disorders in many western countries (Barbaro et al., 2011), and, in Japan, PHNs are expected to take this role, too (Ishii, Matsuda, & Takeda, 2013). If a trained PHN's identifica¬tion of children with ESSENCE at the first stage of screening can be shown to be valid when compared with the result of the ESSENCE-Q assessment by a specialized psychologist, the PHN might then even be suggested to take the role of "specialist" when it comes to referral for full neurodevel¬opmental assessment. Given that the PHNs who joined this study had enough knowledge and experiences with regard to neurodevelopmental disorders in young children, further studies are needed to determine whether or not the results of this study can be generalized to other, larger general population

samples, even when PHNs might not have the same levels of knowledge and experience.

In the 18-month check-up, a cut-off value of 3 satisfied our requirement (i.e., a sensitivity and a specificity of at least 0.7–0.8, and sensitivity>specificity) for ESSENCE-Q-N and ESSENCE-Q-P. The high NPVs (0.98 in ESSENCE-Q-N and in ESSENCE-Q-P) suggested that almost all children with score<3 in the ESSENCE-Q by a PHN (or by a psychologist) would be free of ESSENCE problems/diagnoses. On the other hand, the low PPVs (0.30 in ESSENCE-Q-N and 0.29 in ESSENCE-Q-P) suggested that the result on the ESSENCE-Q should not be taken to mean that all children over the cut-off value would have neurodevelopmental diagnoses. Nevertheless, screen-positive children in this cohort will be followed-up, and if later concerns regarding neurodevelopmental problems arise, they will be referred for a new neurodevelopment assessment. In the 36-month check-up, with a cut-off of 3, the sensitivity was 0.71–0.64 and the specificity was 0.81–0.79 for ESSENCE-Q-N and ESSENCE-Q-P. This was slightly under our required level. When the cut-off was set at 2, the sensitivity and the specificity almost satisfied our requirement for ESSENCE-Q-N and ESSENCE-Q-P. NPVs were almost 1.0 and PPVs (0.24 in ESSENCE-Q-N and 0.22 in ESSENCE-Q-P) were similar to levels at 18-month check-ups. These cut-off values (3 in 18-month check-ups and 2 in 36-month check-ups) are almost identical to those suggested by the originator of the ESSENCE-Q ("Yes" ≥1 or "Maybe/a little" ≥3).

There have been many studies that have claimed that the developmental concerns expressed by parents should be taken seriously by specialists (Richards, Mossey, & Robins, 2016; Sacrey et al., 2015), and the result of the ESSENCE-Q Clinic study (Study III) showed that the ESSENCE-Q completed by parents of children referred for neurodevelopmental assessment could be a useful screening tool for neurodevelopmental disorders in a clinical setting. However, given that the numbers were small in both the pres¬ent and the clinical study, further research is needed before generalizable conclusions can be drawn.

6 CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

Almost 50 years ago, Wilson and Jungner wrote their article “Principles and practice of screening for disease”, published in WHO Chronicle (1968). The paper starts: “The object of screening for disease is to discover those among the apparently well who are in fact suffering from disease” (page 9). The authors also gave their classical screening criteria, including: “The condition sought should be an important health problem”, “There should be an accepted treatment for patients with recognized disease”, “Facilities for diagnosis and treatment should be available”, “There should be a recognizable latent or early symptomatic stage”, “There should be a suitable test or examination”, “The test should be acceptable to the population”, “The natural history of the condition, including development from latent to declared disease, should be adequately understood”, “There should be an agreed policy on whom to treat as patients”, “The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole”, “Case-finding should be a continuing process and not a "once and for all" project” (Wilson & Junger, 1968).

However, the value of screening has been debated and it has been argued that data are not sufficient with regard to several aspects of screening, such as of instruments to be used and of the effectiveness in primary care settings.

6.1 ESSENCE-Q as a screening tool for neurodevelopmental disorders

The substudies performed here suggest that a short questionnaire, the ESSENCE-Q, covering developmental aspects of varying types, may be a valuable tool to identify children in need of further pediatric/neuropsychiatric assessments and also to identify additional problems in children being seen or referred for one specific developmental problem and in need of a more extended assessment. Taking into account the overlap of developmental disorders/problems that exists, it seems to be of significant importance that screening questionnaires, aimed for young children, include a holistic approach. A concept such as “ESSENCE problems” seems useful, implying that developmental problems should be viewed in a broad perspective, not

limited to distinctive diagnoses, such as ASD or AD/HD or ID or speech and language delay/disorder. As is the case with other screening tools of neurodevelopmental disorders, the ESSENCE-Q should be used as part of the screening with direct observation and interview, especially in public health setting.

6.2 PHNs as the first "screener" of ESSENCE

Early detection of children with ESSENCE would be one of the most critical issues for clinical, public health, and even our society. In Japanese child and maternal health services, PHNs in municipalities are expected to take the role of the first "screener" of the children with neurodevelopmental problems, and they have more opportunities to see child development in real setting compared with other specialist like psychologists and pediatricians. Nevertheless, according to our seminar study, their self-confidence for this role was lower than other specialists. It would be crucial to provide them with a chance to participate in educational and practical seminars about neurodevelopmental problems/disorders.

6.3 Gross motor delay as the first "red-flag" for ESSENCE

The motor delay study showed that gross motor delays, such as delay in raising the head, crawling, sitting and walking would be one of the earliest "red flag" for ESSENCE problems. These delays are able possible to be observed in daily life setting and PHNs could be able to recognize the delays when seeing children at home and/or public health check-ups and thereby initiate early identification of problems and make intervention possible.

6.4 Professional education for early detection of ESSENCE

For the early detection of the ESSENCE problems, regular and continuous educational and training opportunities should be provided to the specialists concerned, especially to PHNs in municipalities. Given that overlapping/comorbidity is "the rule" of neurodevelopmental disorders, the content of the material for the education/training should be from the ESSENCE viewpoint instead of one discrete disorder, for example, ASD or AD/HD or ID or speech and language delay/disorder. For this purpose, seminars along each items of the ESSENCE-Q would be effective and

practical, since it covers broader area of virtually all kinds of neurodevelopmental disorders. Motor development problem is one of the items of the ESSENCE-Q, and this would be easy to be recognized by the person who knows “typical” motor milestones and also has chances to see a very young child on a daily basis. PHNs in municipalities are the one at least in Japan. It is essential for them to know that gross motor developmental delay before age of two could be an early indication of the ESSENCE problems.

6.5 Intervention

Type of intervention need to be tailored to the child´s and the parents´ needs and should be initiated after the assessments. A basic requirement is that parents and preschool staff are given information/education about the specific child´s cognitive, behavioral and motor problems and about how to communicate and adapt the environment for the child.

6.6 Future research

Case control studies and cohort studies on the children with motor developmental problems are needed. These studies would be further strengthened with larger sample sizes, focusing on children with motor delay without a known etiology or underlying neurological insults.

The Clinic and the Public Health ESSENCE-Q studies are among the first studies about this questionnaire. The results implied that the ESSENCE-Q would be useful tool for the screening of neurodevelopmental problems in clinic and also in public health setting. In the future, studies with larger population in clinic and in public health setting are needed. To evaluate the optimal cut-off levels of the ESSENCE-Q, studies in other neurodevelopmental clinics and public health settings with the same methodologies are needed. The ESSENCE-Q Public Health study should be duplicated in other municipalities to validate the usefulness of the ESSENCE-Q by PHNs. The results from future studies might also help us to estimate the quality and the quantity of the education/training needed for the specialists.

ACKNOWLEDGMENTS

When I started my PhD studies in September 2012, I honestly half-doubted that I could come this long way while living and working in a rural area of Japan so far from Gothenburg. I would like to reflect on and recognize the people who have supported and helped me so much throughout this period.

First of all, my sincere gratitude goes to all the children, families and staff taking part in the studies.

My supervisors, I could not thank you enough.

Christopher Gillberg, my main supervisor. If I had not met you, I would not have even imagined jumping into the research field. I appreciate your encouragement, patient guidance and warm advice throughout my time as your student.

Elisabeth Fernell, my co-supervisor. I have been extremely lucky to have you as a supervisor who cared so much about my work. I deeply thank for your thoughtful, prompt responses to my many questions and queries.

Eva Billstedt, my co-supervisor. Your advice for my manuscript is always to the point. You also helped me to continue as a PhD student with warm and practical support.

Ingrid Vinsa and Anna Spyrou, without your help, I would not have been able to complete my PhD studies while concurrently working as a clinician in Japan. I thank you both so much.

Theo Gillberg, who helped me write the Swedish abstract. You have cheered me up while you were in Japan, and also in Sweden. I appreciate your friendship.

I would also like to thank my colleagues at the GNC, in Gothenburg and in Kochi. Completing this work would have been all the more difficult were it not for your support.

All these studies were done in the Kochi GNC that is a part of the Kochi Prefecture Government. I appreciate the Governor and other administrative officers who supported the studies both in practical and financial terms.

Finally, I want to express my sincere gratitude to Mariko, my wife, for continued heartening and support.

The studies were also financially supported by grants to Christopher Gillberg and Elisabeth Fernell; the Swedish Science Council and ALF (CG) and LifeWatch Award, Niclas Öberg Foundation (EF). Financial support was also given from Systrarna Greta Johansson and Brita Anderssons Foundation to Yuhei Hatakenaka (YH).

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APPENDIX

ESSENCE-Q-REV (Gillberg C 2012)

Name of child:	

Age:		Completed by:	
Sex:		Date:	

Please take a few minutes to read and check the following items.

- Y= Yes
- M/AL = Maybe/A little
- N= No

Have you (or anybody else, who?_____) been concerned for more than a few months regarding child´s

1. General development ☐
2. Motor development/ milestones ☐
3. Sensory reactions (e.g. touch, sound, light, smell, taste, heat, cold, pain) ☐
4. Communication/language/ babble ☐
5. Activity (overactivity/passivity) or impulsivity ☐
6. Attention/concentration/ "listening" ☐
7. Social interaction/interest in other children ☐
8. Behaviour (e.g. repetitive, routine insistence) ☐
9. Mood (depressed, elated/manic, extreme irritability, crying spells) ☐
10. Sleep ☐
11. Feeding ☐
12. "Funny spells"/ absences ☐

If Y or M/AL to any of the above, please elaborate briefly here:
