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PRINCIPAL INVESTIGATOR:	Major Cade Nylund, MC USAF
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6. AUTHOR(S): CADE NYLUND, MD (Principal Investigator)
Gregory H. Gorman (Author of Annual Report), Matthew D.
Elizabeth Hisle-Gorman, Anthony Goudie, Adam Huillet,
Matilda Eide, Stephen L. Nelson, Christine Erdie-Lalena, Luis

E-Mail: cade.nylund@usuhs.edu

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Henry M Jackson Foundation for the Advancement of Military Medicine
6720A Rockledge Dr Ste 100
Bethesda, MD 20817-1834

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14. ABSTRACT

Over 2,900 children with Autism Spectrum Disorders (ASD) were identified from Military Health System databases. Age, gender, and birth cohort matched controls were identified at a 3:1 ratio. Records from the first month of life were extracted, and conditional logistic regression was used to analyze the association between neonatal jaundice, as defined by jaundice requiring a treatment procedure, and later diagnosis of ASD. The analysis found a 38% increased odds of a child with ASD having had clinically significant jaundice as a newborn as compared to controls. The research team presented its findings at the Pediatric Academic Society Annual Meeting in Washington, DC in May 2013.

This successful first project established our procedures for data extraction, case and control identification, and analytic methods. Experience with this project has allowed refinements for future projects.

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Autism, perinatal risk factors, comorbidities

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Table of Contents

Page

INTRODUCTION:

This award funds the project entitled "Risk Factors, Comorbid Conditions, and Epidemiology of Autism in Children." The research team of pediatric specialists and researchers aims to understand contributing factors and associated condition with Autism Spectrum Disorders (ASD) using the military healthcare database. This medical system is unique in the United States in terms of the size of the population, its universal-coverage, open-access model, and its unified comprehensive electronic medical and demographic records. The researchers are examining the medical records of children diagnosed with ASDs and their mothers to determine if there are temporal associations between childhood ASD and pre-natal and post-natal conditions such as infections, pregnancy-related conditions, and perinatal conditions such as jaundice and infection. In addition, the researchers are examining records of children with ASD to determine the extent of co-morbid conditions and the use of medications.

BODY:

The following details, in a point-by-point manner, the progress and completion status of the 4 tasks outlined in the Statement of Work. For one of the research questions (association of perinatal jaundice with autism), the team nearly completed all of the tasks from the Statement of Work, from data collection to analysis to conference presentation. The manuscript draft is currently under review. The experience with this project has helped us refine our algorithms, data extraction, and analytic methods for the additional projects outlined in our plan.

Task 1: Receive IRB approval of Military Autism Research Group project protocol (months 1-5)

1a. Generate criteria for selection of control group for inclusion in submissions to IRB and Tricare Data Use Agreement (month 1)

We designed an algorithm that identifies age and gender matched controls to identified ASD cases. Each control is born within the same 3 month period to account for possible era effects.

1b. Complete IRB application and submit to USUHS IRB (month1)
The IRB application was submitted and approved after appropriate minor revisions.

1c. Complete Data Use Agreement (DUA) and submit to TriCare Management Authority (month 1)

The DUA was approved by TMA.

1d. Coordinate with IRB, provide additional materials as needed and respond to questions (months 2-4)

Necessary revisions were submitted. All were minor.

1e. Receive IRB approval for Military Autism Research Group project (month4).

See Task 1b and 1d above.

1f. Submit local USUHS IRB approval letter to Department of Defense, Health Research Protection Office (HRPO) for secondary protocol review and approval (month 4)

HRPO reviewed and approved the protocol.

1g. Finalize Data Use Agreement with TriCare Management Authority (month 5).

See Task 1c. above.

1h. Receive HRPO IRB approval (month 5)

See Task 1c. above.

Task 2: Procure hardware and software equipment, and configure components for use in data downloads, cleaning and analysis. (months 1-5)

2a. Purchase Computer Server (month 1-2)

Servers are not yet purchased. Government Information Security review of requested hardware is ongoing.

2b. Purchase Computer Software (month 1-2)

Computer software for processing large datasets more efficiently has been postponed until the hardware is procured. The research team is using software that is adequate but not as efficient.

2c. Link Computer Server with desktop computers used for data analysis and cleaning (months 2-5)

See Task 2a.

2d. Load computer software onto computers for use in data analysis (months 2-5).

See Task 2a.

Task 3: Download data from the Military Health Services (MHS) Management Analysis and Reporting Tool (M2) (month 6-9)

3a. Use established criteria to generate a list of control group members. (month 6-7)

Controls were identified for children with ASD in a 2:1 ratio. These controls and cases were used for the first project examining the link between neonatal jaundice and later diagnosis of ASD. We are refining our identification and matching algorithm with incidence-density matching methods.(*1*)

3b. Identify electronic data interchange patient number (EDIPN), a unique identifier common to Department of Defense databases for experimental and control groups. (month 6-7)

Completed.

3c. Identify mothers of experimental and control group identified children, of appropriate age to accurately identify prenatal & perinatal risk factors. (month 6-7)

The first project did not involve maternal records. These have been identified.

3d. Download all health care visit and medication data for identified experimental and control group members and subjects (month 7-9)

Specific types of health care visits for controls and cases have been identified, and the subset of sleep disorders has been downloaded. Medication data has not yet been downloaded.

3e. Download all health care visit and medication data for perinatal period for experimental and control group mothers. (month 7-9)

Maternal health claim and pharmaceutical data has not yet been downloaded.

Task 4: Cleaning & Organization of Data, and Data Analysis (months 10-17)

4a. Convert downloaded data to format for use by Stata Statistical Software (month 10-11)

Completed

4b. Use established criteria to identify mothers with research indicated prenatal or perinatal risk factors, and create database flags (month 11-12)

Not yet completed.

4c. Use established criteria to identify subjects with research indicated co-morbid conditions (months 11-12)

Not yet completed.

4d. Merge Health Care utilization data with parental data provided to the research team by the Defense Manpower Data Center. Data will include: parental deployment history, rank, age, gender and other demographic characteristics. (months 11-13)

Not yet completed.

4e. Write code for analysis of data. (months 13-15)

Code for analysis of a case:control study of neonatal jaundice with children with ASD and controls was completed.

4f. Run statistical analysis, analyze results and refine analysis as appropriate (months 15-17)

The first project completed was an analysis of the association of neonatal jaundice and ASD. The following details our findings, which were presented by platform at the Pediatric Academic Society Annual meeting in Washington, DC in May 2013.

Using our identification algorithm, there were 2,917 children diagnosed with ASD by a specialist between 2000 and 2012 in the Military Health System. The median age of ASD diagnosis was 5.3 years [interquartile range 3.8-7.2 years]. Of children with ASD, 80% of cases were male, 7.7% were born premature, and 44% were first-born. April-September births accounted for 51% of cases. Characteristics of included cases are shown in Table 1. Controls included 8,751 gender, age, and birth-cohort matched subjects without an ASD diagnosis.

Table 1: Characteristics of 2,917 Children Aged 0-12 Years with an Outpatient Specialists-Diagnosis of Autistic Spectrum Disorder in the Military Health System from 2000-2012

Characteristic	
Age at 1st ASD Diagnosis (yrs)	5.3 [IQR 3.8-7.2]
Male	80 %
Premature (< 36 weeks)	7.7 %
Firstborn	44 %
April-September Birth	51 %
Jaundice Admission	22 %
Jaundice Procedure	3.7 %

ASD=Autistic Spectrum Disorder; IQR=Interquartile Range

Admissions for neonatal jaundice occurred in 19% of subjects. A procedure for treating hyperbilirubinemia was documented in 2.8%. A history of neonatal jaundice was present in 22% children with ASD compared to 18% of controls ($p<0.0001$). A procedural treatment for jaundice was documented in 3.7% of children with ASD and 2.5% of controls ($p<0.0001$).

In McNemar's Test and unadjusted conditional logistic regression, there was a 24% increased odds of developing an ASD in children who had an inpatient diagnosis of jaundice (OR 1.24; 95%confidence interval [CI], 1.12-1.38; $p<0.001$). There was a 47% increased odds of ASD in children who required phototherapy or exchange transfusion (OR, 1.47; 95%CI, 1.16-1.86; $p=0.001$). After adjustment for season of birth, birth order, multiple gestation and prematurity, there remained an increased odds of developing ASD in children with an admission for jaundice (OR 1.20; 95%CI, 1.08-1.33; $p=0.001$). Using the more rigorous definition of jaundice of need for phototherapy or exchange transfusion, the increased odds of ASD in children with a history of neonatal jaundice remained (OR 1.38; 95%CI, 1.09-1.75; $p=0.008$). Point estimates and confidence intervals determined by multivariate models are shown in Table 2.

Table 2: Adjusted Odds Ratios of the Diagnosis of Autistic Spectrum Disorders associated with Neonatal Jaundice in 11,668 Children aged 0-12 Years in Conditional Logistic Regression

	Jaundice Admission as Surrogate for Exposure		Jaundice Procedure as Surrogate for Exposure	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Jaundice	1.24 [1.12-1.38]	1.20 [1.08-1.33]	1.47 [1.16-1.86]	1.38 [1.09-1.75]
Male	--		--	
Prematurity	--		--	
Multiple Gestation	--	1.94 [1.55-2.42]	--	1.99 [1.60-2.48]
Firstborn	--	1.15 [1.04-1.26]	--	1.15 [1.04-1.26]
April-September Birth	--	1.07 [0.97-1.17]	--	1.06 [0.97-1.17]

Prematurity defined as gestation < 36 weeks.

4g. Interpret results of data analysis in the clinical context of Autism care (months 15-17)

See 4f above.

4h. As results emerge, create and submit abstracts for presentation at medical conferences (months 15-17)

See 4f above.

Task 5: Present and Write up research results (months 18-24)

5a. Create presentations and posters for presentation at medical conferences (months 18-20)

See 4f above.

5b. Present findings at medical conferences (months 18-24)

See 4f above.

5c. Draft manuscripts for publication (months 18-24)

Draft manuscript written and under internal review.

5d. Finalize papers and submit to pediatric medical journals (months 20-24)

Not yet completed.

KEY RESEARCH ACCOMPLISHMENTS:

- Successful execution of algorithm for identifying ASD cases using health claims data
- Confirmation of association between neonatal jaundice and subsequent diagnosis of ASD using a stricter definition of jaundice than previous research

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

Luis E. Lozada, Cade M. Nylund, Matthew D. Eberly, Elizabeth Hisle-Gorman, Anthony Goudie, Adam Huillet, Matilda Eide, Stephen L. Nelson, Christine Erdie-Lalena, Gregory H. Gorman, Devon Kuehn. Neonatal Hyperbilirubinemia as a Risk Factor for Autism Spectrum Disorder, a Retrospective Cohort Study. Pediatric Academic Society Annual Meeting, Washington D.C., May 6, 2013.

Society for Pediatric Research House Officer Research Award, Luis E. Lozada, M.D.

CONCLUSION:

The research team has developed an algorithm to identify ASD cases from medical claims files and to identify controls from the population. Using this algorithm, one of the largest epidemiological populations of children with ASD and with longitudinal health data has been assembled. In the first use of this database of children with ASD, the team has confirmed the association of neonatal jaundice with childhood ASD diagnosis reported in the Danish population.(*2*)

While epidemiologic associations do not indicate causality, they do help inform more detailed studies. With this large population and the methods used in the case of confirming a jaundice-autism association, more subtle associations of medical conditions in the pre-natal, peri-natal, and post-natal period, as well as the prevalence of contemporaneous conditions, with ASD can be detected. Associations potentially found in this large epidemiologic study can help researchers generate hypotheses for focused research into links and into therapies and anticipatory guidance for children diagnosed with ASD.

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1. **R. DB, An incidence density sampling program for nested casecontrol analyses. *Occup Environ Med* 61, e59 (2004).**
2. **B. B. Maimburg RD, Vaeth M, Møller-Madsen B, Olsen J., Neonatal jaundice, autism, and other disorders of psychological development. . *Pediatrics.* 126, 872 (2010).**

APPENDICES: None

SUPPORTING DATA: Tables inserted in text.