Asociaciones de Cirugía Neonatal No-cardíaca con estructura del cerebro y Neurodesarrollo: Estudio prospectivo caso-control

Margaret M. Moran, Julia K. Gunn-Charlton, Jennifer M. Walsh, Jeanie L. Y. Cheong, Peter J. Anderson, Lex W. Doyle, Susan Greaves, and Rod W. Hunt

Objetivo Examinar las asociaciones de cirugía neonatal no-cardíaca con la estructura del cerebro y el neurodesarrollo a los 2 años de edad.
Diseño del estudio Los infantes que requirieron cirugía no cardíaca por hernia diafragmática congénita, atresia de esófago, o defecto de la pared abdominal fueron comparados con infantes que no requirieron cirugía, pareados por sexo, edad gestacional al nacer, y edad postmenstrual al hacer la RNM. RNM cerebral fue realizada a edad postmenstrual media de 41.6 (1.7) semanas. Las imágenes fueron evaluadas cualitativamente para maduración del cerebro e injuria y cuantitativamente para mediciones del tamaño cerebral, espacios de LCR, y anormalidad global. Luego se evaluó el neurodesarrollo a los 2 años utilizando Bayley III.
Resultados Los infantes requiriendo cirugía (n=39) tuvieron 5.9 (IC 95%, 1.9-19.5; P<.01) veces más posibilidades de presentar demora de la maduración de las circunvoluciones y 9.8 veces (IC 95%, 1.2-446; P= .01) más posibilidades de tener anormalidades en la señal de la sustancia blanca comparado con los controles (n=39). Los casos tuvieron más posibilidades de tener de tener scores globales de anormalidad más frecuentes, diámetros biparietales más pequeños, y tamaños ventriculares más grandes que los controles. Los infantes que tuvieron cirugía tuvieron media más baja de scores compuestos en las áreas de lenguaje (diferencia media,-12.5; IC 95%, -22.4 a -2.7) y motor (diferencia media, -13.4; IC 95%, -21.1 a -5.6) comparados con los controles.
Conclusiones Los infantes requiriendo cirugía neonatal no cardíaca tienen cerebros más pequeños con más anormalidades comparados con los controles pareados y tienen déficit del neurodesarrollo asociado a los dos años de edad. Estudios prospectivos con imágenes pre y postoperatoria ayudarían a determinar el momento de la injuria cerebral. (J Pediatr 2019; -:1-9).

Con las mejoras y avances en las técnicas quirúrgicas, cuidado antenatal, y neonatal en los últimos 60 años, la frecuencia de mortalidad por cirugía neonatal ha caído desde 72% en 1949 hasta <5% en 2013 (1, 2). Con el aumento de sobrevida ha existido creciente preocupación acerca de la morbilidad a largo plazo, con evidencia de que los niños están en riesgo aumentado de déficit del neurodesarrollo después de cirugía no cardíaca (3-8). Un meta-análisis de Stolwijk et al reveló scores medios de desarrollo motor y cognitivo de 0.5 DS y 0.6 DS, respectivamente, por debajo de lo esperado para la población promedio a 1-2 años de edad (3). El retraso cognitivo, incluyendo el retraso leve, fue reportado en una mediana de 23 % (rango, 3%-56%) de sobrevivientes de cirugía neonatal, con retraso motor evidente en una media de 25% (rango, 0%-77%).
La etiología del déficit del neurodesarrollo en este contexto clínico permanece poco clara y es posible que sea multifactorial. Alteraciones en el desarrollo, crecimiento y patrones de injuria del cerebro son posibles causas. La injuria cerebral es una de las más comunes e

importantes asociaciones asociadas con cirugía neonatal por enfermedad cardíaca congénita (9-12). En esta población de recién nacidos, la injuria de sustancia blanca es el más frecuente hallazgo en la RNM cerebral. Anormalidades preoperatorias, incluyendo la injuria de la sustancia blanca, infartos isquémicos, y hemorragias parenquimatosas, son observadas hasta en un tercio de los infantes con empeoramiento de las lesiones o desarrollo de lesiones nuevas en ≤70% de los infantes en el postoperatorio (9-13). El retraso de la maduración cerebral de aproximadamente un mes es común en esta población de infantes nacidos a término y puede predisponer a estos niños a injuria cerebral subsiguiente a través de similares mecanismos a los observados en infantes nacidos prematuramente (10-13). Sin embargo, poco es sabido acerca de la incidencia de injuria cerebral o madurez cerebral en neonatos que requieren cirugía no cardíaca. Stowijk et al reportaron una incidencia de anormalidades postoperatorias en la RNM cerebral de 63% en neonatos, de término o pretérmino, que requirieron cirugía no cardíaca en la primera semana de vida (14).
El objetivo del presente estudio fue comparar la estructura cerebral a la edad corregida de término y los resultados del neurodesarrollo a los 2 años de edad en infantes después de cirugía no cardíaca y un grupo control sin cirugía. La hipótesis fue que los infantes que sobrellevaban cirugía no cardíaca tendrían mayor injuria cerebral, desarrollo cerebral demorado, y peor neurodesarrollo que los controles.

Métodos

Este fue un estudio caso-control prospectivo de infantes recién nacidos que requirieron cirugía no cardíaca reclutados como parte de un estudio más amplio observando crecimiento y resultados en neurodesarrollo después de cirugía neonatal. El tamaño muestral para este estudio fue limitado por el número de casos y, como resultado, estuvo basado en la factibilidad. El reclutamiento se hizo en el Royal Children´s Hospital, Melbourne, Australia. Fueron elegibles infantes nacidos con ≥32 sem de EG con diagnóstico de atresia de esófago, HDC, o defecto de pared abdominal anterior. Los criterios de exclusión incluyeron una anomalía genética conocida como asociada a déficit del desarrollo, demora prevista de la cirugía más allá de las dos semanas de edad, o instancias en las cuales se consideró la muerte inminente. Se utilizó para medir la severidad de la enfermedad El Score de Fisiología Aguda Neonatal- Perinatal, versión II (SNAPPE II) en las 12 horas de vida en los casos quirúrgicos (15). El score provee un número desde 0 hasta un máximo de 162, con aumento del score a mayor severidad de la enfermedad. Para evaluar crecimiento, se emplearon las gráficas de OMS- Reino Unido (16, 17).
Los infantes control, nacidos con ≥32 semanas de EG, fueron pareados con los casos quirúrgicos por sexo, EG al nacer, y edad postmenstrual al nacer (EPM) al momento de la RNM ±2 semanas. Los controles fueron reclutados en forma contemporánea en un centro perinatal cercano, el Royal Women´s Hospital, y fueron parte de un estudio de cohorte prospectiva longitudinal investigando los resultados a largo plazo después de nacimiento prematuro moderado y tardío (18-21). Los participantes en este estudio fueron infantes nacidos a las 32-36 semanas completas de gestación y el grupo control de infantes sanos nacidos al término (≥37 sem de gestación) reclutados de las guardias del hospital.

Se entregó un cuestionario a todas las familias al momento de la RNM para determinar varios factores sociodemográficos. Los ítems del cuestionario fueron utilizados para calcular el score de riesgo social para cada familia. El Índice de Riesgo Social examina 6 aspectos del estado social, incluyendo la estructura de la familia, educación del cuidador primario, ocupación del principal proveedor de ingreso, estado de empleo del proveedor primario, idioma hablado en el hogar, y edad materna al parto, que se puntúan de 0 a 2 para un score total de 0-12 (22, 23). Basado en la mediana del score de riesgo general, cada familia fue categorizada como bajo (score 0-1) o mayor riesgo social (score ≥2).
Se obtuvo la aprobación ética de los comités de ética de investigación humana de ambos hospitales. Se obtuvo consentimiento informado escrito de los padres de todos los participantes. Se utilizó un intérprete si era necesario.

RNM cerebral

Los RN tuvieron una RNM a las 4 semanas postoperatorias o antes del egreso hospitalario, lo que ocurriera primero. Para aquellos nacidos prematuros, el estudio por imágenes se realizó a la edad equivalente al término. Todos los infantes fueron estudiados a una EPM entre 38 y 45 semanas completas. Los infantes no fueron específicamente anestesiados o sedados con el fin de hacer el estudio. Los infantes estaban vestidos con ropa ligera, envueltos, y ubicados en un dispositivo de fijación tipo puff (MedVac; CFI Medical Solutions, Fenton, Michigan), y luego ubicados en el scanner.
Cada infante fue escaneado con un equipo de RNM 3 Tesla (T) (3T Magnetom Trío Tim; Siemens, Erlangen, Alemania) empleando una bobina de 12 canales circular en el Royal Childen´s Hospital. Se tomaron las siguientes secuencias: imágenes 3D axiales T2 (grosor de corte 2.5 mm, tiempo de repetición de 5170 milisegundos, tiempo de eco de 145 milisegundos, ángulo flip 9º); imágenes sagitales 3d T2 (grosor de corte 1.6 mm, tiempo de repetición 6240 milisegundos, tiempo de eco de 156 milisegundos, ángulo flip de 120º) e imágenes axiales 3D T1 (grosor de corte 0.9 mm, tiempo de repetición de 2100 milisegundos, tiempo de eco 3.52 milisegundos, ángulo flip de 9º). Imágenes T1 sagital y coronal fueron reconstruidas después de ser tomadas.

Exámenes RNM

Cada scan fue evaluado por ≥1 de cuatro neonatólogos con experiencia en RNM cerebral neonatal que estaban cegados para la EPM al momento del scan. Los examinadores del los infantes control fueron cegados para la EG al nacer y el curso perinatal. Los examinadores de los pacientes quirúrgicos estuvieron cegados para el diagnóstico quirúrgico del paciente y la EG al nacer. Los scans fueron evaluados cualitativamente para evidencia de maduración cerebral e injuria, y cuantitativamente para las mediciones del tamaño del cerebro empleando un sistema de score estandarizado utilizado previamente para infante MPT y para infantes prematuros moderados a tardíos (20, 24, 25).

Mediciones del tamaño cerebral. La Biométrica es una herramienta inicialmente descripta por Nguyen et al en la población MPT y ha mostrado buena correlación con los volúmenes cerebrales (24). Las mediciones fueron obtenidas de acuerdo a métodos previamente publicados, incluyendo medidas de diámetro biparietal del cerebro y la cavidad cerebral, distancia interhemisférica, distancia superior extra-axial, anchura del ventrículo lateral, área de superficie de los núcleos grises profundos, diámetro transcerebelar, y cuerpo calloso (20, 24).

Maduración del Cerebro. Para determinar la maduración del desarrollo cerebral se empleó la mielinización del extremo posterior de la cápsula interna (PLIC) y el grado de plegamiento cortical. La mielinización del PLIC fue evaluada en imágenes axiales T2 al nivel del foramen de Monro. La mielinización fue descripta como un tercio completa, dos tercios completas, o totalmente completa. La mielinización PLIC fue considerada apropiada para la edad de término (>38 semanas de gestación) si estaba dos tercios o totalmente completa, y mielinización de un tercio o menos fue categorizada como demorada a EG de ≥ (26).
Para determinar la madurez de las circunvoluciones se empleó la presencia o ausencia de los surcos del tercio inferior temporal y del tercio inferior occipital. Ausencia de estos surcos fue considerada equivalente al grado de pliegue cortical esperado a las 36-38 sem EG. La ausencia de los surcos temporal inferior secundario y occipital secundario inferior con la ausencia de los surcos anterior y posterior orbital fue considerada equivalente a un grado de plegamiento cortical esperado a las 34-36 sem EG (25).

Medidas de Anormalidad Cerebral. Cada scan fue evaluado para la presencia de anormalidades en la intensidad de la señal, quistes dentro de la sustancia blanca, y anormalidades de intensidad de la señal específicamente dentro de la sustancia gris profunda nuclear y el cerebelo. Las anormalidades de la intensidad de señal fueron hiperintensas en la imágenes T1 e hipointensa en las imágenes T2 (25-27).

Score de anormalidad en la Imagen Global RNM. Se asignó un score global de anormalidad RNM empleando una técnica descripta por Kidokoro et al incorporando biomediciones con medidas de corte modificadas previamente publicadas de una cohorte local (20, 25). El sistema de score de anormalidad global es usado para definir la naturaleza y extensión de las anormalidades regional y global del cerebro. El cerebro es dividido en 4 áreas- sustancia blanca cerebral, sustancia gris cortical, sustancia gris de núcleos profundos, y el cerebelo. La medida del tamaño de los ventrículos laterales, diámetro biparietal, y cuerpo calloso reunidos con el grado de mielinización y la presencia de quistes o anormalidad de señal son empleados para evaluar la sustancia blanca cerebral.
La sustancia gris cortical es puntuada por mediciones de la distancia interhemisférica, maduración de circunvoluciones, y l presencia de anormalidades de señal. Los scores en cada área son categorizados como normal, o anormal leve, moderado o severo. Un score global es calculado agregando scores de cada área, que luego es categorizado en niveles de anormalidad como se describió.

Evaluación Neurosensorial

La cognición, lenguaje expresivo y receptivo, y habilidad motora gruesa y fina se evaluaron a los 2 años empleando escala Bayley- III por profesionales del área de la salud acreditados. Los investigadores no estuvieron cegados para la condición quirúrgica. Las normas estandarizadas del test tienen una media de 100 con un DS de 15. Se definió rezago del desarrollo como un score >1 DS por debajo de la media, esto es, un score <85. Todos los sobrevivientes fueron examinados también por un pediatra para signos consistentes con parálisis cerebral (PC).

Análisis estadístico

Los datos fueron analizados con Stata versión 14 (Stata- Corp LP, College Station, Texas) (28). Se aplicaron estadísticas descriptivas para describir los hallazgos generales de ambos grupos (casos y controles). Media (DS) y mediana (RIQ) se reportan para los datos paramétricos y no paramétricos de las variables continuas respectivamente. Las variables categóricas son presentadas como proporciones y OR con ICs 95%. Test t pareado de Student fue empleado para comparar diferencias en las variables continuas entre los casos y controles pareados, incluyendo mediciones de cerebro y resultados del neurodesarrollo. Test de Wilcoxon fue usado para comparar diferencias en datos no-paramétricos continuos. Los resultados se presentan como media (DS) junto con diferencia media y ICs 95%. Valos de P <.05 fue considerado estadísticamente significativo. El test X^2 o test exacto de Fisher fueron empleados para comparar variables categóricas y el test X^2 para la tendencia cuando las variables estuvieron en categorías ordenadas. ORs (ICs 95%) fueron usados para comparar resultados binarios entre los dos grupos. Se realizó regresión linear para determinar la relación entre los hallazgos de la RNM y los scores compuestos en Bayley-III, y regresión logística para evaluar la relación entre hallazgos de RNM y retraso de ND. Los resultados se ajustaron para confundidores, incluyendo EPM al momento de la imagen y riesgo social. Los resultados no fueron corregidos para múltiples tests porque los consideramos exploratorios, y debieran ser interpretados con precaución.

Resultados

Reclutamos 54 pacientes entre Abril 2011 y Julio de 2013 dentro de una cohorte más grande investigando resultados del neurodesarrollo en neonatos quirúrgicos. Se pudo parear uno-a-uno con controles 39 casos. No fue posible parear 11 casos para los cuales estaba realizada RNM, por varias razones, antes de EPM 38 semanas (2 casos) o después de EPM de 45 semanas completas (9 casos). No se realizó RNM postoperatoria en 3 casos. Los datos de 78 pacientes pareados fueron incluidos en el análisis, cuyas características se muestran en Tabla I. No hubo diferencia entre los casos quirúrgicos que no pudieron ser pareados y aquéllos que fueron pareados, aparte de la EPM al momento de RNM (Tabla II; disponible en www.jpeds.com).

Tabla 1. Características de los participantes

Variables	Casos Cirugía	Controles	Diferencia de media/OR (95% IC)	valor P
Peso al nacimiento, Kg	2.94 ± 0.69	2.95 ± 0.81	−0.02 (−0.35 to 0.32)	.93
Edad gestacional al nacer en semanas	37.8 ± 2.1 (32.0-40.7)	37.8 ± 2.5 (32.6-41.7)	0.1 (−1.0 to 1.11)	.91
EPM al tiempo de RNM en semanas	41.6 ± 1.9 (38.1-45.9)	41.5 ± 1.5 (38.9-45)	0.1 (−0.7 to 0.9)	.82
Masculino	23 (59)	23 (59)	1.0 (0.4 to 2.7)	.99
Pequeño para edad gestacional*	5 (13)	6 (15)	1.2 (0.3 to 5.6)	.74
Puntuación SNAPPE-II	5 [0-17] (0-55)			
Atresia esofágica	0 [0-5]			
HDC	25.5 [10.5-35.5]			
Defectos de pared abdominal	6 [0-17]			
Circunferencia cefálica puntuación Z†‡	0.5 (1.3)	−0.3 (1.1)	0.7 (−0.0 to 1.4)	.05
RNM Circunferencia cefálica punt z†δ	−0.1 (1.1)	0.6 (1.0)	−0.7 (−1.2 to −0.2)	.01
Edad materna en años	29.3 ± 5.6	34.1 ± 4.5	−4.8 (−7.2 to −2.5)	<.01
Educación materna terciaria ¶	20 (53)	28 (72)	0.4 (0.1 to 1.2)	.08
Riesgo social alto**	16 (44)	13 (33)	1.6 (0.6 to 4.5)	.32

Valores son media±DS, mediana(RIQ) (rangos) o numero (%) a menos que se indique lo contrario
*Pequeño para edad gestacional fue definido con peso al nacer menor de percentil 10 (puntuación z de <1.28
†La puntuación z fue calculada usando tablas de prematuros de UK-Organización Mundial de la Salud
‡30 casos de cirugía y 39 controles la circunferencia cefálica se midió al nacimiento.
δ32 casos de cirugía y 39 controles tuvieron circunferencia cefálica medida al tiempo de RNM
¶38 casos de cirugía y 39 controles tuvieron educación materna registrada
** 36 casos de cirugía y 39 controles, tuvieron datos completos para calcular riesgo social

Tabla II. Características de los participantes de todos los casos con cirugía

Variables	Casos cirugía no pareados (n =15)	Casos cirugía pareados (n= 39)	Diferencias de media/OR (IC 95%)	valor P
Peso al nacer, Kg	2.92 ± 0.63	2.94 ± 0.69	−0.01 (−0.42 to 0.40)	.94
Edad gesta. al nacer en semanas	38.2 ± 2.7 (32.9-41.7)	37.8 ± 2.1 (32.0-40.7)	0.4 (−1.0 to 1.8)	.57
EPM al tiempo de RNM, semanas	47.1 [45.1-47.6] (35.9-51.4)	41.1 [40-43] (38.1-45.9)		<.01
Masculino	10 (67%)	23 (59%)	1.4 (0.3 to 6.2)	.60
Pequeño para edad gestacional*	1 (7%)	5 (13%)	0.5 (0 to 5.0)	.52
Puntuación SNAPPE-II	19.5 [5-37] (0-59)	5 [0-17] (0-55)		.03
Atresia esofágica (n = 5)	18 (0-21)	0 (0-5)		.18
HDC (n = 8)	27.5 (7.5-51.5)	25.5 (10.5-35.5)		.60
Defectos pared abdominal (n=2)	5 (5-5)	6 (0-17)		.92
Perímetro. cefálico al nacer Punt.Z †‡	0.3 (0.8)	0.5 (1.3)	−0.2 (−1.2 to 0.9)	.75
Circunferencia cefálica RNM Punt. Z †δ	−0.1 (0.7)	−0.1 (1.1)	−0.2 (−0.9 to 0.6)	.68
Edad materna, años	30.3 ± 6.7	29.3 ± 5.6	1.0 (−2.6 to 4.6)	.58
Educación materna terciaria¶	5 (36)	20 (53)	0.5 (0.1 to 2.1)	.28
Riesgo social alto**	7 (50)	16 (44)	1.3 (0.3 to 5.2)	.92

Valores son media±DS, mediana(RIQ) (rangos) o numero (%) a menos que se indique lo contrario
*Pequeño para edad gestacional fue definido con peso al nacer menor de percentil 10 (puntuación z de <1.28
†La puntuación z fue calculada usando tablas de prematuros de UK-Organización Mundial de la Salud
‡7 no pareados y 30 pareados la circunferencia cefálica fue medida al nacimiento.
δ11 casos no pareados y 32 casos de cirugía pareados la circunferencia cefálica fue medida al tiempo de RNM.
¶ 14 no pareados y 38 casos de cirugía pareados tuvieron educación maternal registrada.
** 13 no pareados y 36 casos de cirugía pareados tuvieron datos completos para calcular riesgo social

De los 39 casos quirúrgicos, 12 tuvieron atresia de esófago, 8 tuvieron HDC, y 19 defectos de pared abdominal. La edad media al momento de la cirugía fue 17 horas (RIQ, 5.6-40 horas). Los infantes con HDC fueron operados en promedio en el ddv 4 y los otros dos grupos generalmente fueron operados en el día 1 (P<.01). La duración media de la cirugía fue 135 minutos (RIQ, 75-180 minutos). Se empleó anestesia por gas inhalado, generalmente sevoflurano, en 79% de los participantes, incluyendo 21% que también recibió propofol. Un participante recibió sólo propofol para anestesia y otro recibió anestesia local. Seis participantes tuvieron sólo relajación muscular y opiáceos para la realización de su cirugía. Para analgesia los opiáceos usados fueron morfina y/o fentanilo. Los relajantes musculares usados durante la cirugía fueron pancuronio, suxametonio, y atracurium. Dos participantes estuvieron infusión de midazolam para sedación antes de la cirugía y esta continuó durante el procedimiento. Los neonatos con diagnóstico de HDC tuvieron scores SNAPPE-II más altos que aquellos con un diagnóstico atresia de esófago o defecto de pared abdominal (P<.01) y fueron ventilados por un período más largo de tiempo (P<.01). Sin embargo, no hubo diferencia en la estadía promedio en el Hospital (P=.532).

Las madres de los participantes quirúrgicos fueron más jóvenes que las madres de los participantes controles. La frecuencia de educación terciaria en las madres fue más alta en el grupo control. El riesgo social fue similar entre grupos.

Estudio por Imagen del Cerebro

RNM cerebral en todos los niños fue realizada a una mediana de edad de 25.5 días (RIQ, 16-33). Un pequeño número de scans fueron degradados por artefactos de movimiento. Las imágenes coronales fueron posibles de puntuar en 37 de 39 pares casos-controles. Las imágenes axiales estuvieron disponibles en los 39 pares. Imágenes cerebelosas fueron descartadas en uno de los pacientes quirúrgicos y la distancia superior extra-axial no pudo ser determinada en 1 control. Consecuentemente hubo 36 pares caso-control que tuvieron los datos completos registrados y por tanto pudieron tener un score global de anormalidad asignado.

Madurez e injuria del cerebro

A la edad equivalente al término, los infantes que tuvieron cirugía tuvieron una frecuencia más alta de demora en el plegamiento cortical comparado con los controles (Tabla III). No hubo diferencia en las frecuencias de mielinización completa de PLIC entre los dos grupos. Las anormalidades de señal de la sustancia blanca (WMSAs) fueron vistas con más frecuencia en infantes que requirieron cirugía comparados con los controles. Las frecuencias de quistes y hemorragias fueron bajas en ambos grupos.

Mediciones del tamaño cerebral. Los infantes que requirieron cirugía tuvieron diámetros biparietales y mayor anchura de los ventrículos laterales comparados con los controles (Tabla III). No hubo diferencia en el tamaño del cerebelo, los núcleos grises profundos, espacios extra-axiales, o el cuerpo calloso entre los 2 grupos.

Score global de Imagen Cerebral

La Tabla III delinea la proporción de infantes con score normal, anormal leve, moderado o severo en cada una de las 4 áreas junto con su score general. Más anormalidades fueron detectadas en aquellos que tuvieron cirugía comparados con sus controles pareados (Tabla IV). Las anormalidades en la sustancia gris cortical y en la sustancia blanca cerebral dieron cuenta de la diferencia en los scores de anormalidad.

Resultados de Neurodesarrollo

De los 39 pares casos-controles, el seguimiento hasta los dos años fue completado en 35 de los participantes quirúrgicos y en 37 de los controles a una edad media de 26 meses (DS, 2). Un participante del grupo quirúrgico con atresia de esófago falleció a los 15 meses relacionado con un episodio de atragantamiento y 3 se perdieron para el seguimiento (2 con defecto de pared abdominal, 1 con atresia de esófago). Dos participantes del grupo control se perdieron al

Tabla III. Hallazgos y medidas de RNM

RNM Variables	Casos Cirugía (n = 39)	Controles (n=39)	OR (95% CI)	Diferencia de media (95% IC)	Valor P
Maduración giral retrasada No. (%)	22 (56)	7 (18)	5.92 (1.91 to 19.47)		<.01
Retraso de mielinizacion PLIC no. (%)	12 (31)	11 (28)	1.13 (0.38 to 3.36)		.80
Signos de anormalidades No. (%)					
Materia blanca	8 (21)	1 (3)			.01
Materia gris cortical	1 (3)	0 (0)	9.81 (1.18 to 446)		.31
Núcleos grises profundos	0 (0)	1 (3)			.31
Cerebelo*	1 (3)	0 (0)	–	–	.31
Quistes periventriculares No. (%)	1 (3)	0 (0)	–		.31
Hemorragia, No. (%)					
Alguna HIV	2 (5)	0 (0)	–		.16
Hemorragia cerebelar * (mm)	1 (2.5)	1 (2.5)	1 (0.01 to 80.5)		.99
DBP cerebral* (mm)Cavidad cerebral DBP(mm)	83.99 (4.73)	86.16 (4.50)		−2.17 (−4.28 to −0.06)	.04
Distancia interhemisferica (mm)	86.77 (5.32)	89.75 (4.58)		−2.98 (−5.25 to −0.71)	.01
Distancia extra axial derecha superior† (mm)	1.87 (0.96)	2.18 (0.83)		−0.31 (−0.72 to 0.10)	.13
Ancho del atrio ventricular* (mm)	2.45 (1.39)	2.68 (1.28)		−0.23 (−0.85 to 0.40)	.47
Derecho	6.26 (1.99)	5.21 (1.11)		1.05 (0.31 to 1.79)	<.01
Izquierdo	5.86 (1.82)	4.91 (1.46)		0.96 (0.20 to 1.71)	.01
Área se superficie de NGP (mm^2)					
Derecho	615.12 (61.53)	625.11 (66.83)		−9.99 (−38.96 to 18.98)	.49
Izquierdo	610.57 (63.30)	618.18 (59.70)		−7.60 (−35.36 to 20.15)	.59
Cuerpo Calloso† (mm)					
Longitud AP	44.56 (5.88)	43.26 (4.07)		1.30 (−1.04 to 3.64)	.27
Rodilla (genu)	5.34 (1.14)	5.44 (1.22)		−0.10 (−0.65 to 0.44)	.71
Medio cuerpo	2.33 (0.48)	2.53 (0.53)		−0.20 (−0.44 to 0.03)	.09
Esplenio	3.83 (0.51)	4.11 (0.90)		−0.28 (−0.62 to 0.06)	.10
Diámetro transverso cerebelar† (mm)	55.38 (3.54)	56.52 (2.62)		−1.15 (−2.59 to 0.30)	.12

DBP:Distancia biparietal; HIV: Hemorragia interventricular(todas fueron menores)
Los datos esta presentados como promedios (DS) a menos que se indique lo contrario.
+Los datos están disponibles para 38 pares igualados
† Los datos están disponibles para 37 pares igualados

seguimiento. De los 37 controles que fueron evaluados, uno no completó el componente lenguaje y otro no completó el componente motor. Consecuentemente hubo 35 pares caso-control que tuvieron evaluación cognitiva y 34 pares caso- control que tuvieron evaluación de lenguaje y habilidades motoras.

Los controles tuvieron scores compuestos más altos en todos los dominios comparados con los casos quirúrgicos (Tabla V). Ninguno de los participantes en este estudio tuvo diagnóstico de parálisis cerebral o déficit visual o auditivo a los 2 años de edad. Hubo frecuencias más altas de retraso en ≥1 área en el grupo quirúrgico (34%) comparado con los controles (17%; P=.10).

Dentro del grupo quirúrgico, los infantes con HDC tuvieron resultados más pobres en el desarrollo comparados con aquellos con AE o DPA. Pese a que no hubo evidencia fuerte de diferencias en los scores medios entre los grupos (Tabla V), comparados con AE/DPA aquellos que tuvieron HDC

Tabla V Puntaje de la escala de Bayley – III a los 24 meses

Bayley-III dominios	Casos Cirugia	Controles	Diferencia de medias (CI 95%)	valor P
Cognición (n = 35 pares)	97.7 (17.2)	104.9 (16.9)	7.1 (–0.9 to 15.2)*	.08
HDC (N = 8)	*96.3 (26.2)*			
Atresia esofágica/defecto de pared abdominal (n=27)	*98.1 (14.2)*		*–1.8 (–16.1* to *12.5)*†	*.80*
Lenguaje (n = 34 pares)	94.3 (20.0)	106.8 (20.6)	12.5 (2.7 to 22.4)*	.01
HDC (N = 8)	*84.9 (21.9)*			
Atresia esofágica/defecto de pared abdominal (n=27)	*96.6 (18.1)*		*–11.7 (–27.2* to *3.8)*†	*.14*
Motor (n = 34 pares)	94.7 (12.5)	108.1 (18.7)	13.4 (5.6 to 21.1)*	<.01
HDC (N = 8)	*91.9 (13.1)*			
Atresia esofágica/defecto de pared abdominal (n=27)	*94.7 (13.0)*		*–2.8 (–13.5* to *7.9)*†	*.60*

Datos presentados como promedios (DS) y valores de P en letra itálica esta en relación a la diferencia entre los diagnósticos quirúrgicos.
*Comparación de todos los casos quirúrgicos con todos los controles.
†Comparación entre HDC (hernia diafragmática congénita) con los de atresia esofágica/defectos de pared abdominal

fueron más propensos a tener retraso de lenguaje con un score compuesto de <85 (HDC, 63% [5/8] vs AE/DPA, 15% [4/27]; OR, 9.6 [IC 95%, 1.2-82.6; P=.02) y también más proclives a tener retraso cognitivo con un score compuesto de <85 a los 24 meses (HDC, 37% [3/8] vs AE/DPA, 4% [1/27]; OR, 15.6 [IC 95%, 0.9-848.8; P=.03]). Las frecuencias de retraso de desarrollo motor fueron similares entre los grupos (HDC, 25% [2/8] vs. AE/DPA, 19% [5/27]; OR, 1.5 [IC 95%, 0.1- 12.1; P=.69]).

Asociación entre hallazgos de RNM Neonatal y resultado de Neurodesarrollo a los 2 años en casos quirúrgicos y controles

En el análisis univariado el aumento del espacio extra-axial medido usando la distancia superior extra-axial estuvo asociado con scores compuestos cognitivo y motor más pobres y riesgo más alto de retraso motor (Tabla VI; disponible en www.jpeds.com). El aumento de dilatación del ventrículo izquierdo lateral estuvo asociado con peores scores compuestos en todas las áreas y mayor riesgo de retraso en el lenguaje, pese a que no todos los resultados fueron significativos. Los scores más altos de anormalidad en la sustancia blanca, la sustancia gris cortical, y los scores globales estuvieron relacionados con peor desempeño en todas las áreas del Bayley III. En el análisis multivariado (resultados ajustados en Tabla VI), potenciales confundidores incluyendo EPM al momento de la RNM y riesgo social elevado tuvieron poco efecto sobre la evidencia de asociación entre mediciones anormales en RNM y resultados del ND a los 2 años.

Tabla VI. Asociación entre hallazgos de RNM y resultados de neurodesarrollo a los 2 años

Predictores	Puntaje cognitivo (n = 70) β (IC 95%)	valor P	Puntaje lenguaje (n = 68) β (IC 95%)	valor P	Puntaje motor (n = 68) β (IC 95%)	valor P	Retraso cognitivo (n = 70) OR (IC 95%)	valor P	Retraso lenguaje (n = 68) OR (IC 95%)	valor P	Retraso motor (n = 70) OR (IC 95%)	valor P
RSAD												
No ajustada	−3.04 (−6.08 to −0.01)	.05	−3.44 (−7.61 to 0.73)	.10	−3.83 (−6.96 to −0.69)	.02	1.24 (0.67 to 2.30)	.49	1.17 (0.74 to 1.86)	.50	1.84 (1.10 to 3.10)	.02
Ajustada*	−3.11 (−5.91 to −0.31)	.03	−3.90 (−7.83 to 0.04)	.05	−3.38 (−6.56 to −0.20)	.04	1.52 (0.76 to 3.03)	.24	1.31 (0.79 to 2.15)	.29	1.77 (1.04 to 3.01)	.04
IHD												
No ajustada	−3.75 (−8.28 to 0.79)	.10	−3.88 (−9.69 to 1.92)	.19	−3.81 (−8.55 to 0.92)	.11	2.05 (0.82 to 5.14)	.13	1.74 (0.91 to 3.34)	.10	1.96 (0.90 to 4.24)	.09
Ajustada*	−3.95 (−8.05 to 0.16)	.06	−4.55 (−10.00 to 0.91)	.15	−3.30 (−8.05 to 1.44)	.17	2.95 (1.0 to 8.73)	.15	2.09 (1.01 to 4.32)	.05	1.85 (0.85 to 4.05)	.12
Talla ventrículo lat. Izq.												
No ajustada	−2.25 (−4.72 to 0.23)	.07	−3.10 (−6.26 to 0.07)	.06	−3.21 (−5.67 to −0.75)	.01	1.43 (0.85 to 2.41)	.18	1.65 (1.11 to 2.44)	.01	1.41 (0.91 to 2.17)	.12
Ajustada*	−1.99 (−4.23 to 0.24)	.08	−2.68 (−5.67 to 0.31)	.08	−3.14 (−5.59 to 0.70)	.01	1.49 (0.82 to 2.69)	.19	1.73 (1.13 to 2.67)	.01	1.43 (0.93 to 2.20)	.11
TCD												
No ajustada	1.03 (−0.28 to 2.34)	.12	0.04 (−1.70 to 1.78)	.96	0.92 (−0.39 to 2.24)	.17	1.07 (0.79 to 1.45)	.64	1.08 (0.88 to 1.33)	.44	0.77 (0.59 to 0.98)	.04
Ajustada*	0.90 (−0.95 to 2.76)	.34	0.17 (−2.44 to 2.47)	.99	0.96 (−1.07 to 2.99)	.35	1.18 (0.70 to 1.99)	.53	1.02 (0.74 to 1.40)	.91	0.72 (0.50 to 1.04)	.08
Puntuación global												
No ajustada	−2.67 (−5.07 to −0.27)	.03	−4.22 (−7.16 to −1.28)	.01	−4.24 (−6.49 to −1.99)	<.01	1.32 (0.85 to 2.03)	.22	1.34 (0.97 to 1.85)	.08	1.53 (1.05 to 2.22)	.03
Ajustadada*	−2.29 (−4.60 to 0.01)	.05	−4.22 (−7.11 to −1.33)	.01	−4.06 (−6.45 to −1.68)	<.01	1.43 (0.88 to 2.33)	.14	1.45 (1.01 to 2.10)	.04	1.50 (1.01 to 2.23)	.04
Materia blanca												
No ajustada	−4.29 (−8.22 to −0.36)	.03	−4.29 (−8.22 to −0.36)	.03	−6.70 (−10.47 to −2.93)	<.01	1.31 (0.63 to 2.70)	.47	1.67 (0.98 to 2.83)	.06	1.71 (0.91 to 3.22)	.10
Ajustadada*	−3.57 (−7.33 to 0.18)	.06	−7.29 (−11.90, −2.67)	<.01	−6.03 (−10.04 to −2.03)	<.01	1.44 (0.66 to 3.13)	.36	1.86 (1.02 to 3.39)	.04	1.63 (0.83 to 3.21)	.16
CGM												
No ajustada	−6.38 (−12.4 to 0.65)	.08	−9.72 (−18.49 to −0.95)	.03	−12.18 (−18.89 to −5.47)	<.01	2.70 (0.66 to 11.04)	.17	1.49 (0.55 to 4.04)	.4		.14
Ajustadada*	−6.72 (−13.24 to −0.20)	.04	−11.29 (−19.60 to −2.97)	.01	−11.82 (−18.72 to −4.92)	<.01	4.31 (0.89 to 20.85)	.07	1.93 (0.66 to 5.65)	.23	2.16 (0.64 to 7.35)	.22
DGM												
No ajustada	1.64 (−10.98 to 14.26)	.80	−4.33 (−19.82 to 11.16)	.58	−3.89 (−17.00 to 9.22)	.56	1.83 (0.27 to 12.37)	.54	3.05 (0.66 to 14.02)	.15	2.93 (0.60 to 14.33)	.19
Ajustadada*	−0.07 (−11.94 to 11.81)	.99	−3.48 (−18.74 to 11.78)	.65	−2.31 (−14.95 to 10.32)	.72	2.11 (0.28 to 16.22)	.47	2.58 (0.47 to 14.17)	.28	5.18 (0.75 to 35.71)	.10
Cerebelar												
No ajustada	−4.92 (−14.79 to 4.95)	.32	−3.14 (−15.63 to 9.34)	.62	−6.39 (−16.58 to 3.80)	.22	1.56 (0.35 to 6.94)	.56	0.88 (0.18 to 4.30)	.87	3.27 (0.72 to 14.88)	.13
Ajustadada*	−0.24 (−9.68 to 9.21)	.96	1.02 (−11.29 to 13.33)	.87	−7.04 (−17.18 to 3.12)	.17	–	–		–	3.21 (0.61 to 16.73)	.17
Maduración giros normal												
No ajustada	5.71 (−2.66 to 14.08)	.18	10.75 (0.41 to 21.09)	.04	13.72 (5.84 to 21.59)	<.01	0.60 (0.11 to 3.21)	.56	0.72 (0.22 to 2.40)	.60	0.35 (0.08 to 1.60)	.17
Ajustadada*	5.05 (−3.10 to 13.20)	.22	12.63 (2.38 to 22.88)	.02	13.89 (5.46 to 22.33)	<.01	0.37 (0.05 to 2.66)	.33	0.47 (0.12 to 1.80)	.27	0.41 (0.08 to 2.11)	.29
Mielinizacion NL PLIC												
No ajustada	3.53 (−5.22 to 12.28)	.42	8.59 (−2.34 to 19.53)	.12	6.49 (−2.22 to 15.20)	.14	2.62 (0.29 to 23.83)	.39	1.15 (0.31 to 4.19)	.83	0.83 (0.18 to 3.84)	.82
Ajustada*	1.91 (−7.51 to 11.32)	.69	12.85 (1.00 to 24.70)	.03	5.81 (−4.51 to 16.13)	.27	2.74 (0.22 to 33.83)	.43	0.62 (0.13 to 2.96)	.55	1.40 (0.23 to 8.48)	.71

β, coeficiente de regresión; CGM, materia gris cortical; DGM, materia gris profunda; IHD, distancia inter hemisférica; RSAD, distancia extra-axial superior derecha; TCD, diámetro transcerebelar; PLIC, brazo posterior de capsula interna.

*Ajustada para edad postmenstrual al tiempo de la RNM y riesgo social

NL, normal

Discusión

Los resultados de este estudio agregan más peso a la creciente evidencia de que los niños están en riesgo aumentado de retraso del neurodesarrollo después de cirugía no-cardíaca (3, 5). Es posible que la injuria cerebral y el crecimiento alterado tengan que ver. Este estudio demuestra asociaciones de la cirugía no-cardíaca con WMSA, diámetros biparietales más pequeños, y tamaños ventriculares más grandes (sugestivos de pérdida de volumen de sustancia blanca), peores scores de anormalidad cerebral, mayor retraso de maduración, demora en el plegamiento cortical, y score del desarrollo más bajo a los 2 años de edad comparados con controles.

Stolwijk et al describieron una elevada incidencia de anormalidades del cerebro leves a moderadas en la RNM realizada precoz después de la cirugía no-cardíaca, particularmente lesiones del parénquima, vistas en 63% de la muestra de 101 infantes (14). Treinta y seis infantes con lesiones punctata de sustancia blanca tuvieron RNM dentro de los 10 días postquirúrgicos. La difusión restringida en la imagen sopesada por difusión, sugestiva de isquemia, fue observada en 61% de esos infantes. Esto sugiere que la injuria ocurrió en el período peri-operatorio. Nuestro estudio sólo mostró frecuencias aumentadas de WMSA luego de cirugía no-cardíaca; sin embargo, dado que el tiempo medio en que la RNM fue realizada fue de 21 días (RIQ, 16-31 días), el momento de la injuria no puedo ser definitivamente relacionada al período peri-operatorio.

La injuria del cerebro es uno de las complicaciones más comunes y significativas asociadas a la cirugía neonatal por enfermedad cardíaca congénita. La injuria de sustancia blanca es la anormalidad más común observada preoperatoria y postoperatoria en esa población de alto riesgo, seguido por injuria isquémica y hemorrágica (9-13). El hallazgo común de retraso maduracional puede predisponer a estos infantes a subsiguiente injuria cerebral a través de mecanismos similares a aquellos vistos en niños nacidos prematuros (10, 13). La inmadurez del cerebro ha sido asociada con injuria cerebral preoperatoria y postoperatoria y también se ha asociado con injuria cerebral postoperatoria más severa (9, 10). Beca et al mostraron que la inmadurez del cerebro más que la injuria, está asociada con déficit del neurodesarrollo a los dos años de edad después de cirugía cardíaca neonatal (9). Los resultados de nuestro estudio mostraron similares hallazgos con la maduración demorada de circunvoluciones asociada con retraso motor y del lenguaje a los 2 años tanto en los casos quirúrgicos como en los controles.

La mayoría de la literatura que reporta acerca de neuroimagen en infantes después de cirugía no-cardíaca se relaciona con infantes post-cirugía de HDC. Hunt et al mostraron anormalidades en RNM en una pequeña cohorte de sobrevivientes de HDC, ninguno de los cuales había requerido ECMO (29). Hubo un predominio de injuria de sustancia blanca y sustancia gris profunda; fluido extra-axial aumentado y ventriculomegalia también fueron comunes. Reportes más recientes de neuroimagen en el período neonatal y en los subsiguientes 2 años de sobrevivientes a reparación de HDC han continuado mostrando anormalidades en ≤90% de los casos (30-36). Atrofia cerebral, como sugiere la ventriculomegalia y los espacios aumentados del fluido cerebro-espinal, continúa siendo el hallazgo más común observado en la imagen hecha postoperatoriamente antes del alta hospitalaria. Hemorragia intraventricular es detectada en alrededor de 20% de los casos.

Similar a los neonatos que requieren cirugía cardíaca, los neonatos con HDC han mostrado tener maduración cerebral demorada (37). Danzer et al encontraron maduración cerebral demorada en 37.5% de los infantes con imagen al término, con rango entre 2 a 4 semanas. Otras anormalidades incluyeron LPV, subdesarrollo del opérculo, HIC, y espacios de líquido extra-axial prominentes. Una proporción de estos infantes tuvo seguimiento del neurodesarrollo a una edad media de 14 meses (DS, 7 meses) usando Bayley-III. Los scores compuestos se encontraban en bajo promedio a levemente demorados con scores medios de 91.2 (DS, 14.4) para cognición, 87.1 (DS 17.2) para lenguaje, y 82.3 (DS, 18.7) para motor. Los espacios de fluido extra-axial agrandados estuvieron asociados con scores cognitivos más bajos y la HIC estuvo asociada con scores motores más bajos.

Similarmente, este estudio explora las asociaciones de cirugía neonatal no cardíaca con tamaño cerebral, maduración, y resultado del neurodesarrollo a los 2 años. Los espacios de líquido extra-axial aumentados con aumento del tamaño del ventrículo lateral izquierdo en la imagen RNM en el período neonatal están asociados con déficit del ND a los 2 años de edad con scores compuestos más bajos en todos los dominios y un riesgo aumentado de retraso madurativo. Los scores de anormalidad de la sustancia blanca y sustancia gris cortical en aumento están asociados con peor desempeño en la prueba de ND a los 2 años de edad. La demora en la maduración de circunvoluciones cortical está asociada con scores compuestos de lenguaje y motor más bajos.

Las fortalezas de este estudio incluyen su naturaleza prospectiva y el uso de una sistema de puntuación sistemático estructurado que aumenta la confiabilidad y reproducibilidad de los resultados. El uso de controles pareados para comparar el tamaño cerebral y la estructura limita los factores de confusión, tales como la EG al nacer y al momento de la imagen. Nos permitió examinar infantes con atresia de esófago y DPA que con frecuencia nacen en el período de PT tardío. Dados los muchos cuestionamientos acerca de la subestimación del retraso ND por el Bayley-III, una de las mayores fortalezas de este estudio es el uso de un grupo de control local reclutado contemporáneamente (38-40). Al tener un grupo control pareado, hemos mostrado el significativo impacto de la cirugía no-cardíaca en la maduración cerebral, el tamaño cerebral, y los resultados del ND a los 2 años de edad.

Varias limitaciones deben ser consideradas al interpretar los resultados. El pequeño tamaño muestral disminuyó el poder del estudio para encontrar asociaciones clínicamente importantes de la cirugía no-cardíaca con los variados resultados. Pese a que los niños en el grupo quirúrgico presentaron diámetros biparietales del cerebro más pequeños, ventrículos laterales más grandes, demora en la maduración de circunvoluciones, y frecuencia mayor de WMSA, con scores compuestos más bajos a los 2 años de edad en Bayley-III, la frecuencia de retraso leve del ND a los 2 años de edad no alcanzó significancia estadística. Sin embargo, sabemos por otros grupos de alto riesgo, incluyendo aquellos nacidos prematuros y los que requieren cirugía cardíaca, que la inmadurez cerebral, la injuria de la sustancia blanca, y el volumen cerebral disminuido están asociados con subsiguiente déficit del ND a los 2 años y en la edad escolar temprana (9, 25, 27, 41-45). Pese a que las mediciones del cerebro han mostrado correlacionar bien con los volúmenes del cerebro y LCR, es posible que si se hubiera empleado un análisis formal volumétrico cuantitativo podríamos haber encontrado asociación más fuerte entre los

cambios RNM y resultados del ND (24). El examen de los resultados del ND a los 2 años de edad para la cohorte quirúrgica fue realizado como parte de un programa de seguimiento neonatal. Los examinadores no estuvieron cegados para el diagnóstico y el curso clínico de los participantes quirúrgicos, lo cual puede haber generado algún sesgo, pese a que los examinadores no estaban al tanto de que los datos del seguimiento serían utilizados en el análisis con hallazgos de RNM en el período postoperatorio.

Pese a que se hicieron intentos para reclutar un grupo relativamente homogéneo de pacientes, la rara naturaleza de estas condiciones significó 3 cohortes simultáneas reclutadas para 1 estudio para mejorar el tamaño muestral de manera que, finalmente, el grupo quirúrgico fue heterogéneo con niveles variables de severidad de enfermedad, lo cual aumenta el potencial de confusión. Una mayor limitación del presente estudio es que ninguno de los infantes fue escaneado antes de la cirugía, así que las anormalidades del cerebro identificadas postcirugía no pueden ser directamente atribuibles a la cirugía o anestesia per se, porque otras variables asociadas con el problema quirúrgico subyacente pueden haber conducido a las anormalidades cerebrales encontradas.

Los niños después de cirugía neonatal no- cardíaca, cuando se examinan con Bayley-III a los 2 años, tienen scores compuestos con DS 0.5-0.9 inferior a los controles pareados en las áreas de cognición, lenguaje y motor. Este estudio ha mostrado que las anormalidades vistas en la RNM neonatal, particularmente de sustancia blanca y sustancia gris cortical, son posiblemente significativos contribuyentes al peor desempeño en ND a los 2 años. Cuando se comparó con controles pareados, los infantes que requirieron cirugía no-cardíaca fueron más susceptibles de tener cerebros más pequeños, más inmaduros con más anormalidades en la RNM al término. Los cambios en la RNM en el período neonatal son predictivos de subsiguiente déficit del ND (9, 37, 44-47). Se requieren más estudios con mayor muestra para confirmar si la demora en la maduración del cerebro y las alteraciones en el crecimiento y estructura del cerebro están asociadas con subsiguiente déficit del ND después de cirugía no-cardíaca. Dada la baja incidencia de estas condiciones quirúrgicas, se requerirían estudios multicéntricos para evaluar cada entidad por separado. Estudios de RNM prospectivos ayudarían a dilucidar el momento de la injuria cerebral con la perspectiva de explorar potenciales intervenciones.

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Associations of Neonatal Noncardiac Surgery with Brain Structure and Neurodevelopment: A Prospective Case-Control Study

Margaret M. Moran, DMedSci[1,2,3], Julia K. Gunn-Charlton, PhD[3,4,5], Jennifer M. Walsh, MD[5,6], Jeanie L. Y. Cheong, MD[5,6,7], Peter J. Anderson, PhD[5,8], Lex W. Doyle, MD[3,5,6,7], Susan Greaves, PhD[9], and Rod W. Hunt, PhD[3,4,7]

Objective To examine the associations of neonatal noncardiac surgery with newborn brain structure and neurodevelopment at 2 years of age.

Study design Infants requiring neonatal noncardiac surgery for congenital diaphragmatic hernia, esophageal atresia, or anterior abdominal wall defect were compared with infants who did not require surgery, matched for sex, gestation at birth, and postmenstrual age at magnetic resonance imaging. Cerebral magnetic resonance imaging was performed at a mean (SD) postmenstrual age of 41.6 (1.7) weeks. Images were assessed qualitatively for brain maturation and injury and quantitatively for measures of brain size, cerebrospinal fluid spaces, and global abnormality. Neurodevelopment was then assessed at 2 years using the Bayley Scales of Infant and Toddler Development, 3rd edition.

Results Infants requiring surgery (n = 39) were 5.9 times (95% CI, 1.9-19.5; $P < .01$) more likely to have delayed gyral maturation and 9.8 times (95% CI, 1.2-446; $P = .01$) more likely to have white matter signal abnormalities compared with controls (n = 39). Cases were more likely to have higher global abnormality scores, smaller biparietal diameters, and larger ventricular sizes than controls. Infants who had surgery had lower mean composite scores in the language (mean difference, −12.5; 95% CI, −22.4 to −2.7) and motor domains (mean difference, −13.4; 95% CI, −21.1 to −5.6) compared with controls.

Conclusions Infants requiring neonatal noncardiac surgery have smaller brains with more abnormalities compared with matched controls and have associated neurodevelopmental impairment at 2 years of age. Prospective studies with preoperative and postoperative imaging would assist in determining the timing of brain injury. *(J Pediatr 2019;■:1-9)*.

With improvements and advances in surgical techniques, antenatal care, and neonatal care over the last 60 years, the mortality rate from neonatal surgery has declined from 72% in 1949 to <5% in 2013.[1,2] With improving survival there has been increasing concern about long-term morbidity, with evidence that children are at increased risk of neurodevelopmental impairment after noncardiac surgery.[3-8] A meta-analysis from Stolwijk et al revealed mean cognitive and motor development scores of 0.5 SD and 0.6 SD, respectively, below the expected population average at 1-2 years of age.[3] Cognitive delay, including mild delay, was reported in a median of 23% (range, 3%-56%) of survivors of neonatal surgery, with motor delay evident in a median of 25% (range, 0%-77%).

The etiology of neurodevelopmental impairment in this clinical context remains unclear and is likely to be multifactorial. Alterations in brain development, growth, and injury patterns are possible causes. Brain injury is one of the most common and important complications associated with neonatal surgery for congenital heart disease.[9-12] In this population of neonates, white matter injury is the most frequent finding on cerebral magnetic resonance imaging (MRI). Preoperative abnormalities, including white matter injury, ischemic strokes, and parenchymal hemorrhages, are seen in up to one-third of infants with worsening

3D	3-dimensional
MRI	Magnetic resonance imaging
Bayley-III	Bayley Scales of Infant and Toddler Development, 3rd Edition
CDH	Congenital diaphragmatic hernia
SNAPPE-II	Score for Neonatal Acute Physiology – Perinatal Extension, Version II
PMA	Postmenstrual age
PLIC	Posterior limb of the internal capsule
WMSA	White matter signal abnormality

From the [1]Department of Neonatology, Children's University Hospital, and [2]Department of Neonatology, The Rotunda Hospital, Dublin, Ireland; [3]Department of Pediatrics, University of Melbourne; [4]Neonatal Medicine, The Royal Children's Hospital; [5]Clinical Sciences, Murdoch Children's Research Institute; [6]Newborn Services, The Royal Women's Hospital; [7]Department of Obstetrics and Gynecology, The University of Melbourne; [8]Turner Institute of Brain and Mental Health, Monash University; and [9]Department of Occupational Therapy, The Royal Children's Hospital, Melbourne, Australia

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of lesions or development of new lesions in ≤70% of infants postoperatively.[9-13] Brain maturation delay of approximately 1 month is common in this population of term-born infants and may predispose these children to subsequent brain injury through similar mechanisms to those seen in infants born prematurely.[10,13] Conversely, very little is known about the incidence of brain injury or brain maturity in neonates requiring noncardiac surgery. Stolwijk et al reported an incidence of cerebral MRI abnormalities postoperatively of 63% in neonates, both term and preterm, requiring noncardiac surgery in the first week of life.[14]

The aim of the current study was to compare brain structure at term corrected age and neurodevelopmental outcomes at 2 years of age in infants after noncardiac surgery with a nonsurgical control group. It was hypothesized that the infants who underwent noncardiac surgery would have more brain injury, delayed brain development, and worse neurodevelopment than controls.

Methods

This was a prospective case-control study of newborn infants requiring noncardiac surgery recruited as part of a larger study looking at growth and neurodevelopmental outcomes after neonatal surgery. The sample size for this study was limited by the number of cases and, as a result, was based on feasibility. Recruitment occurred at the Royal Children's Hospital, Melbourne, Australia. Infants born at ≥32 weeks of gestation with a diagnosis of esophageal atresia, congenital diaphragmatic hernia (CDH), or anterior abdominal wall defect were eligible. Exclusion criteria included a known genetic anomaly associated with developmental impairment, anticipated delay of surgery beyond 2 weeks of age, or instances when death was thought to be imminent. The Score for Neonatal Acute Physiology – Perinatal Extension, version II (SNAPPE-II) was used as a measure of illness severity over the first 12 hours of life in the surgical cases.[15] The score provides a number from 0 to a maximum of 162, with the score increasing with worsening illness severity. The UK-World Health Organization preterm growth charts were used to assess growth.[16,17]

Control infants, born at ≥32 weeks of gestation, were matched to surgical cases by sex, gestational age at birth, and postmenstrual age (PMA) at the time of MRI ±2 weeks. Controls were recruited contemporaneously from a nearby perinatal center, the Royal Women's Hospital, and were part of a prospective longitudinal cohort study investigating the long-term outcomes after moderate and late preterm birth.[18-21] Participants for that study were infants born at 32-36 completed weeks of gestation and a control group of healthy infants born at term (≥37 weeks of gestation) recruited from the postnatal wards.

A questionnaire was given to all families at the time of the MRI to assess various sociodemographic factors. Items from the questionnaire were used to calculate a social risk score for each family. The Social Risk Index assesses 6 aspects of social status, including family structure, education of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home, and maternal age at birth, which are scored from 0 to 2 for a total score of 0-12.[22,23] Based on the median for the overall risk score, each family were categorized as either lower (score 0-1) or higher social risk (score ≥2).

Ethics approval was obtained from the human research ethics committees in both hospitals. Written informed consent was obtained from the parents of all participants. An interpreter was used if required.

Cerebral MRI

Neonates underwent MRI at 4 weeks' postoperative age or before discharge, whichever happened first. For those born preterm, imaging was carried out at term-equivalent age. All the infants were imaged at a PMA of between 38 and 45 completed weeks. Infants were not specifically anesthetized or sedated for the purpose of the scan. Infants were lightly clothed, swaddled, and placed in a beanbag vacuum fixation device (MedVac; CFI Medical Solutions, Fenton, Michigan), and then placed in the scanner.

Each infant was scanned with a 3 Tesla (T) MRI scan (3T Magnetom Trio Tim; Siemens, Erlangen, Germany) using a 12-channel circular polarized volume extremity coil at Royal Children's Hospital. The following sequences were taken: 3-dimensional (3D) T2-weighted axial images (slice thickness 2.5 mm, repetition time of 5170 milliseconds, echo time of 145 milliseconds, flip angle 9°); 3D T2-weighted sagittal images (slice thickness of 1.6 mm, repetition time of 6240 milliseconds, echo time of 156 milliseconds, flip angle of 120°), and 3D T1-weighted axial images (slice thickness of 0.9 mm, repetition time of 2100 milliseconds, echo time of 3.52 milliseconds, flip angle of 9°). Coronal and sagittal T1-weighted images were reconstructed after acquisition.

MRI Assessments

Each scan was assessed by ≥1 of 4 neonatologists with expertise in neonatal cerebral MRIs who were blinded to PMA at the time of the scan. Assessors of the control infants were blinded to gestational age at birth and perinatal course. Assessors for the surgical patients were blinded to the surgical diagnosis of the patient and the gestational age at birth. Scans were assessed qualitatively for evidence of brain maturation and injury, and quantitatively for measures of brain size using a standardized scoring system previously used for very preterm infants and for moderate to late preterm infants.[20,24,25]

Measures of Brain Size. Biometrics is a tool initially described by Nguyen et al in the very preterm population and has shown good correlation with brain volumes.[24] The metrics were obtained according to methods previously published, including biparietal diameter of the brain and cerebral

cavity, interhemispheric distance, superior extra-axial distance, lateral ventricular width, surface area of the deep gray nuclei, transcerebellar diameter, and corpus callosum measures.[20,24]

Maturation of the Brain. Myelination within the posterior limb of the internal capsule (PLIC) and the degree of cortical folding were used to assess the maturation of brain development. Myelination of the PLIC was assessed on T2-weighted axial images at the level of the foramen of Monro. Myelination was described as one-third complete, two-thirds complete, or fully complete. Myelination of the PLIC was felt to be appropriate for term-corrected (>38 weeks of gestation) if it was two-thirds to fully complete, and myelination of one-third or less was categorized as delayed at ≥38 weeks of gestation.[26]

The presence or absence of the tertiary inferior temporal and tertiary inferior occipital sulci were used to assess gyral maturation. Absence of these gyri was considered to be equivalent to the degree of cortical folding expected at 36-38 weeks of gestation. The absence of secondary inferior temporal and secondary inferior occipital sulci together with the absence of anterior and posterior orbital sulci was considered to be equivalent to the degree of cortical folding expected at 34-36 weeks of gestation.[25]

Measures of Brain Abnormality. Each scan was assessed for the presence of abnormalities in signal intensity, cysts within the white matter, and abnormalities of signal intensity specifically within the deep nuclear gray matter and cerebellum. Signal intensity abnormalities were hyperintense on T1-weighted images and hypointense on T2-weighted images.[25-27]

Global MR Imaging Abnormality Score. A global MR abnormality score was assigned using a technique described by Kidokoro et al incorporating biometrics with modified cutoff measurements previously published from a local cohort.[20,25] The global abnormality scoring system is used to define the nature and extent of regional and global brain abnormalities. The brain is divided into 4 areas—cerebral white matter, cortical gray matter, deep nuclear gray matter, and the cerebellum. Measurement of the size of the lateral ventricles, biparietal diameter, and corpus callosum together with the degree of myelination and presence of cysts or signal abnormality are used to assess the cerebral white matter.

Cortical gray matter is scored by measures of interhemispheric distance, gyral maturation, and the presence of signal abnormalities. Both the deep nuclear gray matter and the cerebellum are assessed using measures of size and the presence of signal abnormalities. The scores in each area are categorized as normal, mild, moderate, or severely abnormal. A global score is calculated by adding the scores from each area, which is then categorized into levels of abnormality as described.

Neurodevelopmental Assessment

Cognition, expressive and receptive language, and gross and fine motor skills were assessed at 2 years of age using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III) by accredited allied health care professionals. Assessors were not blinded to the surgical conditions. The standardized test norms have a mean of 100 with a SD of 15. Developmental delay was defined as a score of >1 SD below the mean, that is, a score of <85. All survivors were also examined by a pediatrician for signs consistent with cerebral palsy.

Statistical Analyses

Data were analyzed using Stata software version 14 (StataCorp LP, College Station, Texas).[28] Descriptive statistics were applied to describe the overall findings of both groups (cases and controls). Mean (SD) and median (IQR) are reported for the parametric and nonparametric data of continuous variables respectively. Categorical variables are presented as proportions and ORs with 95% CIs. The Student paired *t* test was used to compare differences in continuous variables between matched cases and controls, including brain metrics and neurodevelopmental outcomes. The Wilcoxon rank-sum test was used to compare differences in continuous nonparametric data. Results are presented as mean (SD) along with mean difference and 95% CIs. A *P* value of <.05 was considered statistically significant. The χ^2 test or Fisher exact test were used to compare categorical variables and the χ^2 test for trend when the variables were in ordered categories. ORs (95% CIs) were used to compare binary outcomes between the 2 groups. Linear regression was used to determine the relationship between MRI findings and the composite scores on the Bayley-III, and logistic regression was used to evaluate the relationship between MRI findings and developmental delay. The results were adjusted for confounders, including PMA at the time of imaging and social risk. Results were not corrected for multiple testing because we considered them to be exploratory, and they should be interpreted with caution.

Results

We recruited 54 patients between April 2011 and July 2013 into a larger cohort study investigating neurodevelopmental outcomes in surgical neonates. One-to-one matching with controls was possible in 39 cases. Matching was not possible in 11 cases for whom the cerebral MRI was performed, for various reasons, before a PMA of 38 weeks (2 cases) or after a PMA of 45 completed weeks (9 cases). There was no postoperative MRI performed in 3 cases. Data from the 78 matched patients only were included in the analysis, the characteristics of whom are shown in **Table I**. There was no difference between the surgical cases which could not be matched and those that were matched, apart from PMA at time of MRI (**Table II**; available at www.jpeds.com).

Table I. Participant characteristics

Variables	Surgical cases	Controls	Mean difference/OR (95% CI)	*P* value
Birth weight, kg	2.94 ± 0.69	2.95 ± 0.81	−0.02 (−0.35 to 0.32)	.93
Gestational age at birth in weeks	37.8 ± 2.1 (32.0-40.7)	37.8 ± 2.5 (32.6-41.7)	0.1 (−1.0 to 1.11)	.91
PMA at time of MRI in weeks	41.6 ± 1.9 (38.1-45.9)	41.5 ± 1.5 (38.9-45)	0.1 (−0.7 to 0.9)	.82
Male	23 (59)	23 (59)	1.0 (0.4 to 2.7)	.99
Small for gestational age*	5 (13)	6 (15)	1.2 (0.3 to 5.6)	.74
SNAPPE-II score	5 [0-17] (0-55)			
Esophageal atresia	0 [0-5]			
CDH	25.5 [10.5-35.5]			
Abdominal wall defect	6 [0-17]			
Birth head circumference z-score†,‡	0.5 (1.3)	−0.3 (1.1)	0.7 (−0.0 to 1.4)	.05
MRI head circumference z-score†,§	−0.1 (1.1)	0.6 (1.0)	−0.7 (−1.2 to −0.2)	.01
Maternal age in years	29.3 ± 5.6	34.1 ± 4.5	−4.8 (−7.2 to −2.5)	<.01
Maternal tertiary education¶	20 (53)	28 (72)	0.4 (0.1 to 1.2)	.08
Higher social risk**	16 (44)	13 (33)	1.6 (0.6 to 4.5)	.32

Values are mean ± SD, median [IQR] (range), or number (%) unless otherwise indicated.
*Small for gestational age was defined as a birth weight of less than the 10th percentile (z-score of <−1.28).
†The z-scores were calculated using UK-World Health Organization preterm charts.
‡Thirty surgical cases and 20 controls had head circumference measured at birth.
§Thirty-two surgical cases and 39 controls had head circumference measured at time of MRI.
¶Thirty-eight surgical cases and 39 controls had maternal education recorded.
**Thirty-six surgical cases and 39 controls had complete data to calculate social risk.

Of the 39 surgical cases, 12 had esophageal atresia, 8 had a CDH, and 19 had an abdominal wall defect. The median age at time of surgery was 17 hours (IQR, 5.6-40.0 hours). Infants with CDH were operated on average on day 4 of life and the other 2 groups were generally repaired day 1 of life ($P < .01$). The median duration of surgery was 135 minutes (IQR, 75-180 minutes). Inhalational gas, generally sevoflurane, was used for anesthesia in 79% of participants, including 21% who also received propofol. One participant received propofol alone for anesthesia and another received local anesthesia. Six participants had surgery performed using muscle relaxation and opiates alone. Morphine and/or fentanyl were the opiates used for analgesia. Pancuronium, suxamethonium, and atracurium were the muscle relaxant agents used during surgery. Two participants were on a midazolam infusion for sedation before surgery and this was continued throughout the procedure. Neonates with a diagnosis of CDH had higher SNAPPE-II scores than those with a diagnosis of esophageal atresia or abdominal wall defect ($P < .01$) and were ventilated for a longer period of time ($P < .01$). However, there was no difference in the average length of hospital stay ($P = .532$).

Mothers of the surgical participants were younger than the mothers of the control participants. Rates of maternal tertiary education were higher in the control group. Social risk was similar between groups.

Brain Imaging

MRI brain for all infants was performed at a median age of 25.5 days (IQR, 16-33) days. A small number of scans were degraded by motion artefact. Coronal images were suitable for scoring in 38 of 39 case-control pairs, and sagittal images were suitable for scoring in 37 of 39 case-control pairs. Axial images were available in all 39 pairs. Cerebellar images were degraded in one of the surgical participants and the superior extra-axial distance could not be assessed in 1 control participant. Consequently there were 36 case-control pairs that had a complete dataset recorded and therefore could have a global abnormality score assigned.

Brain Maturity and Injury

At term-equivalent age, infants who had surgery had a higher rate of delay in cortical folding compared with controls (Table III). There was no difference in the rates of complete myelination of the PLIC between the 2 groups. White matter signal abnormalities (WMSAs) were seen more frequently in infants who required surgery compared with the controls. Rates of cysts and hemorrhage were low in both groups.

Measures of Brain Size. Infants who required surgery had smaller biparietal diameters and larger lateral ventricular widths compared with controls (Table III). There was no difference in the size of the cerebellum, deep gray nuclei area, extra-axial spaces, or corpus callosum between the 2 groups.

Global MR Imaging Score

Table III outlines the proportion of infants with normal, mild, moderate, or severely abnormal scores in each of the 4 brain areas together with their overall score. More abnormalities were detected in those who had surgery compared with their matched controls (Table IV). Abnormalities in the cortical gray matter and cerebral white matter accounted for the difference in abnormality scores.

Neurodevelopmental Outcomes

Of the 39 case-control pairs, 2-year follow-up was completed in 35 of the surgical participants and in 37 of the controls at a mean age of 26 months (SD, 2). One participant from the surgical group with esophageal atresia died at 15 months related to a choking episode and 3 were lost to follow-up

Table III. MRI findings and brain measurements

MRI variables	Surgical cases (n = 39)	Controls (n = 39)	OR (95% CI)	Mean difference (95% CI)	*P* value
Delayed gyral maturation, no. (%)	22 (56)	7 (18)	5.92 (1.91 to 19.47)		<.01
Delayed PLIC myelination, no. (%)	12 (31)	11 (28)	1.13 (0.38 to 3.36)		.80
Signal abnormalities, no. (%)					
White matter	8 (21)	1 (3)			.01
Cortical gray matter	1 (3)	0 (0)	9.81 (1.18 to 446)		.31
Deep gray nuclei	0 (0)	1 (3)			.31
Cerebellum*	1 (3)	0 (0)	–	–	.31
Periventricular cysts, no. (%)	1 (3)	0 (0)	–		.31
Hemorrhage, no. (%)					
Any IVH	2 (5)	0 (0)	–		.16
Cerebellar hemorrhage*	1 (2.5)	1 (2.5)	1 (0.01 to 80.5)		.99
Brain BPD* (mm)	83.99 (4.73)	86.16 (4.50)		−2.17 (−4.28 to −0.06)	.04
Cerebral cavity BPD* (mm)	86.77 (5.32)	89.75 (4.58)		−2.98 (−5.25 to −0.71)	.01
Interhemispheric distance* (mm)	1.87 (0.96)	2.18 (0.83)		−0.31 (−0.72 to 0.10)	.13
Right superior extra-axial distance† (mm)	2.45 (1.39)	2.68 (1.28)		−0.23 (−0.85 to 0.40)	.47
Ventricular atrial width* (mm)					
Right	6.26 (1.99)	5.21 (1.11)		1.05 (0.31 to 1.79)	<.01
Left	5.86 (1.82)	4.91 (1.46)		0.96 (0.20 to 1.71)	.01
DGN surface area (mm^2)					
Right	615.12 (61.53)	625.11 (66.83)		−9.99 (−38.96 to 18.98)	.49
Left	610.57 (63.30)	618.18 (59.70)		−7.60 (−35.36 to 20.15)	.59
Corpus callosum† (mm)					
AP length	44.56 (5.88)	43.26 (4.07)		1.30 (−1.04 to 3.64)	.27
Genu	5.34 (1.14)	5.44 (1.22)		−0.10 (−0.65 to 0.44)	.71
Midbody	2.33 (0.48)	2.53 (0.53)		−0.20 (−0.44 to 0.03)	.09
Splenium	3.83 (0.51)	4.11 (0.90)		−0.28 (−0.62 to 0.06)	.10
Transverse cerebellar diameter† (mm)	55.38 (3.54)	56.52 (2.62)		−1.15 (−2.59 to 0.30)	.12

BPD, biparietal diameter; *DGN*, deep gray nuclei; *IVH*, intraventricular hemorrhage (all were minor).
Data are presented as mean (SD) unless otherwise stated.
*Data were available for 38 matched pairs.
†Data were available for 37 matched pairs.

(2 with abdominal wall defect, 1 with esophageal atresia). Two control participants were lost to follow-up. Of the 37 controls who were assessed, one did not complete the language component and another did not complete the motor component. Consequently there were 35 case-control pairs who had cognition assessed and 34 case-control pairs who had language and motor skills assessed.

Controls had higher composite scores in all domains compared with surgical cases (Table V). None of the participants in this study had a diagnosis of cerebral palsy or visual or hearing impairment at 2 years of age. There were higher rates of delay in ≥1 domain in the surgical group (34%) compared with the controls (17%; $P = .10$).

Within the surgical group, infants with CDH had poorer developmental outcomes compared with those with esophageal atresia or abdominal wall defect. Although there was no strong evidence for differences in mean scores between the groups (Table V), compared with the esophageal atresia/

Table IV. Global abnormality score

Variables	Normal	Mild	Moderate	Severe	*P* value*
Global abnormality score (n = 36 pairs)	(Total 0-3)	(Total 4-7)	(Total 8-11)	(Total >12)	
Surgical cases	29 (81)	7 (19)	0	0	<.01
Controls	36 (100)	0	0	0	
White matter abnormality score (n = 37 pairs)	(Total 0-2)	(Total 3-4)	(Total 5-6)	(Total ≥7)	
Surgical cases	31 (84)	6 (16)	0	0	.01
Controls	37 (100)	0 (0)	0	0	
Cortical gray matter abnormality score (n = 38 pairs)	(Total 0)	(Total 1)	(Total 2)	(Total ≥3)	
Surgical cases	17 (45)	18 (47)	2 (5)	1 (3)	<.01
Controls	30 (79)	7 (18)	1 (3)	0	
Deep gray nuclei abnormality score (n = 39 pairs)	(Total 0)	(Total 1)	(Total 2)	(Total ≥3)	
Surgical cases	36 (92)	2 (5)	1 (3)	0	.47
Controls	37 (95)	2 (5)	0	0	
Cerebellar abnormality score (n = 37 pairs)	(Total 0)	(Total 1)	(Total 2)	(Total ≥3)	
Surgical cases	33 (89)	3 (8)	0	1 (3)	.16
Controls	36 (97)	1 (3)	0	0	

Values are number (%).
**P* value from χ^2 for linear trend.

Table V. Bayley-III scores at 24 months

Bayley-III domains	Surgical cases	Controls	Mean difference (95% CI)	*P* value
Cognition (n = 35 pairs)	97.7 (17.2)	104.9 (16.9)	7.1 (–0.9 to 15.2)*	.08
CDH (n = 8)	*96.3 (26.2)*			
Esophageal atresia/abdominal wall defect (n = 27)	*98.1 (14.2)*		*–1.8 (–16.1* to *12.5)*†	*.80*
Language (n = 34 pairs)	94.3 (20.0)	106.8 (20.6)	12.5 (2.7 to 22.4)*	.01
CDH (n = 8)	*84.9 (21.9)*			
Esophageal atresia/abdominal wall defect (n = 27)	*96.6 (18.1)*		*–11.7 (–27.2* to *3.8)*†	*.14*
Motor (n = 34 pairs)	94.7 (12.5)	108.1 (18.7)	13.4 (5.6 to 21.1)*	<.01
CDH (n = 8)	*91.9 (13.1)*			
Esophageal atresia/abdominal wall defect (n = 27)	*94.7 (13.0)*		*–2.8 (–13.5* to *7.9)*†	*.60*

Data presented as mean (SD); the mean difference and *P* values in italics relate to difference between surgical diagnoses.
*Comparing all surgical cases with controls.
†Comparing CDH with esophageal atresia/abdominal wall defect, within the surgical group.

abdominal wall defect group those who had CDH were more likely to have language delay with a composite score of <85 (CDH, 63% [5/8] vs esophageal atresia/abdominal wall defect, 15% [4/27]; OR, 9.6 [95% CI, 1.2-82.6; $P = .02$) and more likely to have cognitive delay with a composite score of <85 at 24 months (CDH, 37% [3/8] vs esophageal atresia/abdominal wall defect, 4% [1/27]; OR, 15.6 [95% CI, 0.9-848.8; $P = .03$]). Rates of motor delay were similar between the groups (CDH, 25% [2/8] vs esophageal atresia/abdominal wall defect, 19% [5/27]; OR, 1.5 [95% CI, 0.1-12.1; $P = .69$]).

Association between Neonatal MRI Findings and Neurodevelopmental Outcome at 2 Years in Surgical Cases and Controls

On univariable analysis increasing extra-axial space measured using the superior extra-axial distance was associated with poorer cognitive and motor composite scores and higher risk of motor delay (**Table VI**; available at www.jpeds.com). Increasing dilatation of the left lateral ventricle was associated with poorer composite scores in all domains and a higher risk of language delay, although the results did not all reach significance. Higher abnormality scores for white matter, cortical gray matter, and global scores were related to poorer performance in all domains of the Bayley-III. On multivariable analysis (adjusted results in **Table VI**), potential confounders including PMA at time of MRI and higher social risk had little effect on the evidence for association between MRI abnormality measures and neurodevelopmental outcomes at 2 years.

Discussion

The results of this study add further weight to the growing evidence that children are at increased risk of developmental delay after neonatal noncardiac surgery.[3,5] Brain injury and altered growth is likely to play a role. This study demonstrates associations of neonatal noncardiac surgery with WMSA, smaller biparietal diameters, and larger lateral ventricular sizes (suggestive of white matter volume loss), worse brain abnormality scores, more maturational delay, delayed cortical folding, and lower developmental score at 2 years of age compared with controls.

Stolwijk et al described a high incidence of mild to moderate brain abnormalities on MRI performed soon after neonatal noncardiac surgery, particularly parenchymal lesions, seen in 63% of a sample of 101 infants.[14] Thirty-six infants with punctate white matter lesions had MRI performed within 10 days of their surgery. Restricted diffusion on diffusion weighted imaging, suggestive of ischemia, was seen in 61% of those infants. This suggests that the injury occurred in the perioperative period. Our study also showed increased rates of WMSA following neonatal noncardiac surgery; however, because the median time the MRI was performed was 21 days (IQR, 16-31 days), the timing of the injury could not be definitively related to the perioperative period.

Brain injury is one of the most common and significant complications associated with neonatal surgery for congenital heart disease. White matter injury is the most common abnormality seen both preoperatively and postoperatively in that high-risk population, followed by ischemic and hemorrhagic injury.[9-13] The common finding of brain maturation delay may predispose these infants to subsequent brain injury through similar mechanisms as those seen in infants born preterm.[10,13] Brain immaturity has been associated with brain injury preoperatively and postoperatively and has also been associated with more severe postoperative brain injury.[9,10] Beca et al showed that brain immaturity rather than brain injury is associated with neurodevelopmental impairment at 2 years of age after neonatal cardiac surgery.[9] The results of our study showed similar findings with delayed gyral maturation associated with language and motor delay at 2 years in both the surgical cases and the controls.

Most of the literature reporting on neuroimaging in infants after noncardiac surgery relates to infants post CDH repair. Hunt et al showed abnormalities on MRI in a small cohort of CDH survivors, none of whom had required extracorporeal membrane oxygenation.[29] There was a predominance of white matter and deep gray matter injury; increased extra-axial fluid and ventriculomegaly were also common. More recent reports of neuroimaging in the newborn period and in the subsequent 2 years from survivors of CDH repair have continued to show abnormalities in ≤90% of cases.[30-36] Cerebral atrophy, as suggested by ventriculomegaly and increased cerebrospinal fluid spaces,

continues to be the most common finding noted on imaging done postoperatively before hospital discharge. Intraventricular hemorrhage is detected in about 20% of cases.

Similar to neonates requiring cardiac surgery, neonates with CDH have been shown to have brain maturational delay.[37] Danzer et al found delayed brain maturation in 37.5% of infants imaged at term, ranging from 2 to 4 weeks. Other abnormalities included periventricular leukomalacia, underdevelopment of the opercula, intracranial hemorrhage, and prominent extra-axial fluid spaces. A proportion of these infants had neurodevelopmental follow-up at a mean age of 14 months (SD, 7 months) using Bayley-III. Composite scores were in the low average to mildly delayed range with mean scores of 91.2 (SD, 14.4) for cognition, 87.1 (SD, 17.2) for language, and 82.3 (SD, 18.7) for motor. Larger extra-axial fluid spaces were associated with lower cognitive scores, whereas brain immaturity correlated with lower language scores and intracranial hemorrhage was associated with lower motor scores.

Similarly, this study explores the associations of neonatal noncardiac surgery with brain size, maturation, and neurodevelopmental outcome at 2 years. Increased extra-axial fluid spaces with increasing left lateral ventricular size on MR imaging in the neonatal period are associated with neurodevelopmental impairment at 2 years of age with lower composite scores in all domains and an increasing risk of developmental delay. An increasing global abnormality score is associated with lower composite scores in the cognitive, language, and motor domains with a trend toward increased cognitive delay. Increasing white matter abnormality scores and cortical gray matter abnormality scores are associated with poorer performance on neurodevelopmental assessment at 2 years of age. Delay in cortical gyral maturation is associated with lower language and motor composite scores.

The strengths of this study include its prospective nature and the use of a structured systematic scoring system to assess brain size and abnormality on MRI, which increases the reliability and reproducibility of the results. The use of matched controls to compare brain size and structure limits confounding factors, such as gestational age at birth and at the time of imaging. It allowed us to assess infants with esophageal atresia and abdominal wall defects who are often born in the late preterm period. Given the many concerns about the underestimation of developmental delay by the Bayley-III, one of the major strengths of this study is the use of a local contemporaneously recruited control group.[38-40] By having a matched control group, we have shown the significant impact noncardiac surgery has on brain maturation, brain size, and neurodevelopmental outcomes at 2 years of age.

Several limitations need to be addressed when interpreting the results. The small sample size decreased the power of the study to find clinically important associations of noncardiac surgery with the various outcomes. Although children in the surgical group had smaller brain biparietal diameters, larger lateral ventricles, delayed gyral maturation, and higher rates of WMSA, with lower composite scores at 2 years of age on Bayley-III, the rates of mild developmental delay did not reach statistical significance. However, we know from other high-risk groups, including those born preterm and those requiring neonatal cardiac surgery, that brain immaturity, white matter injury, and decreased brain volume are associated with subsequent neurodevelopmental impairment both at 2 years and early school age.[9,25,27,41-45] Although brain metrics have been shown to correlate well with brain and cerebrospinal fluid volumes, it is possible that if formal quantitative volumetric analysis had been used we may have found a stronger association between MRI changes and neurodevelopmental outcomes.[24] Assessment of neurodevelopmental outcomes at 2 years of age for the surgical cohort was performed as part of a dedicated neonatal follow-up program. The assessors were not blinded to the diagnosis and clinical course of the surgical participants, which may have introduced some bias, although the assessors were not aware that the follow-up data collected would be used in analysis with MR findings in the postoperative period.

Although attempts were made to recruit a relatively homogeneous group of patients, the rare nature of these conditions meant that 3 simultaneous cohorts were recruited for 1 study to improve the sample size such that, ultimately, the surgical group was heterogeneous with varying levels of illness severity, which increases the potential for confounding. A further limitation of the current study is that none of the infants was scanned before surgery, so any brain abnormalities identified postsurgery cannot be directly attributed to the surgery or anesthesia per se, because other variables associated with the underlying surgical problem may have led to the observed brain abnormalities.

Children after neonatal noncardiac surgery, when assessed using the Bayley-III at 2 years, have composite scores 0.5-0.9 SD lower than matched controls in the domains of cognition, language, and motor. This study has shown that abnormalities seen on neonatal MRI, particularly of white matter and cortical gray matter, are likely to be significant contributors to poorer neurodevelopmental performance at 2 years. When compared with matched controls, infants requiring noncardiac surgery were more likely to have smaller, more immature brains with more abnormalities on MRI imaging at term. Changes on brain MRIs in the newborn period are predictive of subsequent neurodevelopmental impairment.[9,37,44-47] Further larger studies are required to confirm if delayed brain maturation and alterations in brain growth and structure are associated with subsequent neurodevelopmental impairment after noncardiac surgery. Given the low incidence of these surgical conditions, multicenter studies would be required to evaluate single disease entities. Prospective MRI studies using both preoperative and postoperative imaging would assist with

elucidating the timing of brain injury with a view to exploring potential interventions. ■

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Reprint requests: Professor Rod Hunt, Neonatal Medicine, The Royal Children's Hospital, 50 Flemington Rd, Parkville, Victoria 3052, Australia. E-mail: rod.hunt@rch.org.au

Data Statement

Data sharing statement available at www.jpeds.com.

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Table II. Patient characteristics of all surgical cases

Variables	Unmatched surgical cases (n = 15)	Matched surgical cases (n = 39)	Mean difference/OR (95% CI)	*P* value
Birth weight, kg	2.92 ± 0.63	2.94 ± 0.69	–0.01 (–0.42 to 0.40)	.94
Gestational age at birth in weeks	38.2 ± 2.7 (32.9-41.7)	37.8 ± 2.1 (32.0-40.7)	0.4 (–1.0 to 1.8)	.57
PMA at time of MRI, weeks	47.1 [45.1-47.6] (35.9-51.4)	41.1 [40-43] (38.1-45.9)		<.01
Male	10 (67%)	23 (59%)	1.4 (0.3 to 6.2)	.60
Small for gestational age*	1 (7%)	5 (13%)	0.5 (0 to 5.0)	.52
SNAPPE-II score	19.5 [5-37] (0-59)	5 [0-17] (0-55)		.03
Esophageal atresia (n = 5)	18 (0-21)	0 (0-5)		.18
CDH (n = 8)	27.5 (7.5-51.5)	25.5 (10.5-35.5)		.60
Abdominal wall defect (n = 2)	5 (5-5)	6 (0-17)		.92
Birth head circumference z-score†,‡	0.3 (0.8)	0.5 (1.3)	–0.2 (–1.2 to 0.9)	.75
MRI head circumference z-score†,§	–0.1 (0.7)	–0.1 (1.1)	–0.2 (–0.9 to 0.6)	.68
Maternal age, years	30.3 ± 6.7	29.3 ± 5.6	1.0 (–2.6 to 4.6)	.58
Maternal tertiary education¶	5 (36)	20 (53)	0.5 (0.1 to 2.1)	.28
Higher social risk**	7 (50)	16 (44)	1.3 (0.3 to 5.2)	.92

Values are mean ± SD, median [IQR] (range), or number (%) unless otherwise indicated.
*Small for gestational age was defined as a birth weight less than the 10th percentile (z-score of <–1.28).
†The z-scores were calculated using UK-World Health Organization preterm charts.
‡Seven unmatched and 30 matched had head circumference measured at birth.
§Eleven unmatched and 32 matched surgical cases had head circumference measured at time of MRI.
¶Fourteen unmatched and 38 matched surgical cases had maternal education recorded.
**Thirteen unmatched and 36 matched surgical cases had complete data to calculate social risk.

Table VI. Association between neonatal MRI findings and neurodevelopmental outcome at 2 years

	Cognition score (n = 70)		Language score (n = 68)		Motor score (n = 68)		Cognition delay (n = 70)		Language delay (n = 68)		Motor delay (n = 68)	
Predictors	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
RSAD												
Unadjusted	−3.04 (−6.08 to −0.01)	.05	−3.44 (−7.61 to 0.73)	.10	−3.83 (−6.96 to −0.69)	.02	1.24 (0.67 to 2.30)	.49	1.17 (0.74 to 1.86)	.50	1.84 (1.10 to 3.10)	.02
Adjusted*	−3.11 (−5.91 to −0.31)	.03	−3.90 (−7.83 to 0.04)	.05	−3.38 (−6.56 to −0.20)	.04	1.52 (0.76 to 3.03)	.24	1.31 (0.79 to 2.15)	.29	1.77 (1.04 to 3.01)	.04
IHD												
Unadjusted	−3.75 (−8.28 to 0.79)	.10	−3.88 (−9.69 to 1.92)	.19	−3.81 (−8.55 to 0.92)	.11	2.05 (0.82 to 5.14)	.13	1.74 (0.91 to 3.34)	.10	1.96 (0.90 to 4.24)	.09
Adjusted*	−3.95 (−8.05 to 0.16)	.06	−4.55 (−10.00 to 0.91)	.15	−3.30 (−8.05 to 1.44)	.17	2.95 (1.0 to 8.73)	.15	2.09 (1.01 to 4.32)	.05	1.85 (0.85 to 4.05)	.12
Left lateral ventricle size												
Unadjusted	−2.25 (−4.72 to 0.23)	.07	−3.10 (−6.26 to 0.07)	.06	−3.21 (−5.67 to −0.75)	.01	1.43 (0.85 to 2.41)	.18	1.65 (1.11 to 2.44)	.01	1.41 (0.91 to 2.17)	.12
Adjusted*	−1.99 (−4.23 to 0.24)	.08	−2.68 (−5.67 to 0.31)	.08	−3.14 (−5.59 to 0.70)	.01	1.49 (0.82 to 2.69)	.19	1.73 (1.13 to 2.67)	.01	1.43 (0.93 to 2.20)	.11
TCD												
Unadjusted	1.03 (−0.28 to 2.34)	.12	0.04 (−1.70 to 1.78)	.96	0.92 (−0.39 to 2.24)	.17	1.07 (0.79 to 1.45)	.64	1.08 (0.88 to 1.33)	.44	0.77 (0.59 to 0.98)	.04
Adjusted*	0.90 (−0.95 to 2.76)	.34	0.17 (−2.44 to 2.47)	.99	0.96 (−1.07 to 2.99)	.35	1.18 (0.70 to 1.99)	.53	1.02 (0.74 to 1.40)	.91	0.72 (0.50 to 1.04)	.08
Global score												
Unadjusted	−2.67 (−5.07 to −0.27)	.03	−4.22 (−7.16 to −1.28)	.01	−4.24 (−6.49 to −1.99)	<.01	1.32 (0.85 to 2.03)	.22	1.34 (0.97 to 1.85)	.08	1.53 (1.05 to 2.22)	.03
Adjusted*	−2.29 (−4.60 to 0.01)	.05	−4.22 (−7.11 to −1.33)	.01	−4.06 (−6.45 to −1.68)	<.01	1.43 (0.88 to 2.33)	.14	1.45 (1.01 to 2.10)	.04	1.50 (1.01 to 2.23)	.04
White matter												
Unadjusted	−4.29 (−8.22 to −0.36)	.03	−4.29 (−8.22 to −0.36)	.03	−6.70 (−10.47 to −2.93)	<.01	1.31 (0.63 to 2.70)	.47	1.67 (0.98 to 2.83)	.06	1.71 (0.91 to 3.22)	.10
Adjusted*	−3.57 (−7.33 to 0.18)	.06	−7.29 (−11.90, −2.67)	<.01	−6.03 (−10.04 to −2.03)	<.01	1.44 (0.66 to 3.13)	.36	1.86 (1.02 to 3.39)	.04	1.63 (0.83 to 3.21)	.16
CGM												
Unadjusted	−6.38 (−12.4 to 0.65)	.08	−9.72 (−18.49 to −0.95)	.03	−12.18 (−18.89 to −5.47)	<.01	2.70 (0.66 to 11.04)	.17	1.49 (0.55 to 4.04)	.4		.14
Adjusted*	−6.72 (−13.24 to −0.20)	.04	−11.29 (−19.60 to −2.97)	.01	−11.82 (−18.72 to −4.92)	<.01	4.31 (0.89 to 20.85)	.07	1.93 (0.66 to 5.65)	.23	2.16 (0.64 to 7.35)	.22
DGM												
Unadjusted	1.64 (−10.98 to 14.26)	.80	−4.33 (−19.82 to 11.16)	.58	−3.89 (−17.00 to 9.22)	.56	1.83 (0.27 to 12.37)	.54	3.05 (0.66 to 14.02)	.15	2.93 (0.60 to 14.33)	.19
Adjusted*	−0.07 (−11.94 to 11.81)	.99	−3.48 (−18.74 to 11.78)	.65	−2.31 (−14.95 to 10.32)	.72	2.11 (0.28 to 16.22)	.47	2.58 (0.47 to 14.17)	.28	5.18 (0.75 to 35.71)	.10
Cerebellar												
Unadjusted	−4.92 (−14.79 to 4.95)	.32	−3.14 (−15.63 to 9.34)	.62	−6.39 (−16.58 to 3.80)	.22	1.56 (0.35 to 6.94)	.56	0.88 (0.18 to 4.30)	.87	3.27 (0.72 to 14.88)	.13
Adjusted*	−0.24 (−9.68 to 9.21)	.96	1.02 (−11.29 to 13.33)	.87	−7.04 (−17.18 to 3.12)	.17	–	–		–	3.21 (0.61 to 16.73)	.17
Normal gyral maturation												
Unadjusted	5.71 (−2.66 to 14.08)	.18	10.75 (0.41 to 21.09)	.04	13.72 (5.84 to 21.59)	<.01	0.60 (0.11 to 3.21)	.56	0.72 (0.22 to 2.40)	.60	0.35 (0.08 to 1.60)	.17
Adjusted*	5.05 (−3.10 to 13.20)	.22	12.63 (2.38 to 22.88)	.02	13.89 (5.46 to 22.33)	<.01	0.37 (0.05 to 2.66)	.33	0.47 (0.12 to 1.80)	.27	0.41 (0.08 to 2.11)	.29
Normal PLIC myelination												
Unadjusted	3.53 (−5.22 to 12.28)	.42	8.59 (−2.34 to 19.53)	.12	6.49 (−2.22 to 15.20)	.14	2.62 (0.29 to 23.83)	.39	1.15 (0.31 to 4.19)	.83	0.83 (0.18 to 3.84)	.82
Adjusted*	1.91 (−7.51 to 11.32)	.69	12.85 (1.00 to 24.70)	.03	5.81 (−4.51 to 16.13)	.27	2.74 (0.22 to 33.83)	.43	0.62 (0.13 to 2.96)	.55	1.40 (0.23 to 8.48)	.71

B, regression coefficient; *CGM*, cortical gray matter; *DGM*, deep gray matter; *IHD*, interhemispheric distance; *RSAD*, right superior extra-axial distance; *TCD*, transcerebellar diameter.
*Adjusted for PMA at time of MRI and social risk.