MILD EXTERNAL EAR MALFORMATIONS AND RENAL TRACT ABNORMALITIES: A META-ANALYSIS

MALFORMACIONES LEVES DEL OIDO EXTERNO Y ANORMALIDADES DEL TRACTO RENAL: UN META-ANALISIS

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ABSTRACT

Background: The association between isolated mild external ear malformations and urinary tract anomalies has not been sufficiently researched, and prevalence of renal abnormalities reported in different studies is controversial, which is the subject of considerable debate, currently causing confusion over which specific ear anomalies do and do not require imaging. Therefore, we examined this controversial issue by conducting a meta-analysis to asses the association of renal tract abnormalities in infants with isolated mild external ear malformations.

Methodology: A meta-analysis of all published case-controlled studies, published in all languages. 65 articles were found, but only 4 were relevant. Main outcome measure was prevalence of urinary tract abnormalities detected by ultrasonography. Four studies involving 32983 evaluable infants were identified. The combined results indicated that the risk, in a fixed effects model, of renal tract anomalies in infants with isolated mild external ear malformations was O.R 1.56 (95%CI 1.25-1.94)

Conclusions: This meta-analysis confirms a significant association between renal tract abnormalities and isolated mild external ear malformations.

Key words: Infants. Ear malformations. Renal tract abnormalities. Ultrasonography.

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RESUMEN

Antecedentes: La asociación entre anomalías del tracto urinario y malformaciones moderadas del oído externo no ha sido suficientemente investigad. La prevalencia de anomalías del tracto urinario informadas en diferentes estudios, presentan resultados controversiales, lo cuál es materia de considerable debate, causando considerable confusión sobre cuales anomalías específicas del oído externo deberían o no ser estudiadas mediante imágenes para descartar asociación con malformaciones del tracto urinario. Por esto revisamos este punto controversial de la literatura, realizando un meta-análisis para evaluar el grado de asociación entre anomalías moderadas del oído externo y malformaciones del tracto urinario.

Metodología: Se realizó un meta-análisis de todos los estudios de casos y controles publicados en todos los idiomas. De 65 artículos publicados, sólo 4 se consideraron relevantes. El resultado a medir fue la prevalencia de anomalías del

tracto urinario detectadas por ultrasonido. Los cuatro estudios evaluados involucraban 32983 niños. Los resultados combinados indican que el riesgo de presentar anomalías del tracto urinario en niños con malformaciones moderadas del oído externo, en un modelo de efectos fijos, fue de un OR 1.56 (IC95% 1.25-1.94)

Conclusiones: Éste meta-análisis confirma una asociación significativa entre malformaciones moderadas del oído externo y anomalías del tracto urinario.

Palabras clave: Niños. Tubérculos pre-auriculares. Anomalías del tracto urinario. Ecografía.

The association between external ear abnormalities and renal tract abnormalities was recognized originally in 1957 by Hilson et.al. (1), and with the description of the Braquio-oto-renal dysplasia syndrome by Melnick et al. (2) in 1976, and by Fraser (3) in 1978.

Pre-auricular tags, pits, sinuses and other mild external ear malformations are relatively uncommon isolated anomalies with a prevalence of 5 to 10 per 1000 live births (4). In pediatric populations structural renal anomalies occur in 1 to 3 per 100 live births (5).

It has been classical teaching that infants with external ear abnormalities should be studied for renal anomalies (6). A potential association between isolated mild external ear abnormalities and renal abnormalities is an important public health concern to prevent renal scars and end stage renal disease during adult life.

The mechanism of this potential association is believed to be due in part to genes which expressed in developing ear and kidney structures at different times during morphogenesis (7).

However, the association between isolated mild external ear malformations and urinary tract anomalies has not been sufficiently researched, and prevalence of renal abnormalities reported in different studies is controversial (8,9), which is the subject of considerable debate (10), currently causing confusion over which specific ear anomalies do and do not require imaging.

Therefore, we examined this controversial issue by conducting a meta-analysis to asses the association of renal tract abnormalities in infants with isolated mild external ear malformations.

METHODS

Inclusion criteria. We included Case Control Studies, level 3b of evidence, which evaluated patients with isolated pre-auricular tags, pits, sinuses or other mild isolated external ear anomalies and urinary tract abnormalities, and included outcome data on prevalence of urinary tract malformations. The study subjects were newborns (livebirths, stillbirths or aborted) infants and children with renal tract abnormalities diagnosed by ultrasonography but without any other major structural anomalies or underlying syndromes.

Exclusion criteria. Case series and reviews with only historical or anecdotal population based controls were excluded.

Outcomes were collected according to predefined criteria, and included prevalence of renal abnormalities and presence of pre-auricular tags, pits, sinuses and other mild external ear malformations.

Literature search. Medline, Lilacs, Science Citation Index and the Cochrane Collaboration were searched independently by two reviewers without language restriction. The optimally sensitive search strategy (11) was combined with medical subject headings and textwords specific for renal tract abnormalities and isolated mild external ear malformations: (("Kidney / abnormalities" [MeSH] OR "Kidney / ultrasonography" [MeSH]) OR ("Urinary Tract / abnormalities" [MeSH] OR "Urinary Tract / ultrasonography [MeSH])) AND "Ear / abnormalities" [MeSH]). Reference lists of retrieved articles were searched and those known to have conducted relevant studies were contacted (One author was contacted).

Data extraction and analysis. Relevant abstracts were reviewed independently by two authors to determine suitability of

inclusion. Any disagreements were resolved by discussion with a third author.

Where the results of studies were published more than once, the most complete data were sought from all sources and included only once for each analysis.

We include studies if they have used clear criteria for association between isolated mild external ear malformations and renal tract abnormalities, and provide data to calculate the risk of renal tract abnormalities as O.R with 95% confidence intervals.

Assessment of quality. The assessment of quality included the analysis allocation, perfomance bias, analysis of looses and analysis of outcome assessment (12).

Summary statistics were calculated using Epidat v3 (13), using a fixed effects model, as O.R. with 95% CI, taking into account between-study variability as well as within-study variability, with the respective coefficients. The test for heterogeneity was Q statistic with Galbraith graphic. The publication biases were evaluated with tests of Begg and Egger. Sensibility analysis was made. A level of significance was set at $p< 0.05$ (14).

RESULTS

Full paper assessment identified 65 studies. In total we included four case-control studies (8,9,15,16) (Table 1). We excluded 61 studies for the followings reasons: review articles, described gross or multiple ear anomalies or specific

Table 1. Studies included in the meta-analysis

Author	Patients	Study type	Outcome	Results	Comments
Kohelet Pediatrics 2000;105:E61	Study group: 70 patients with isolated preauricular tags underwent renal ultrasonogram on 3-4 day of life. Control group; 69 infants without tag underwent urinary tract ultrasonogram after day 5 as part of research associated with cyanotic spells	Case-control (level 3b of evidence)	Urinary tract anomalies detected on ultrasonogram which were further researched by voiding cystouretrography and radionuclectide scintigraphy.	6/70 (8.6 95%CI 2.2-12.4). None in control group.	The study included only preauricular tags. There were no cases of renal malformations in the control group which is less than normal population.
Kugelman J Pediatrics 2002;141:388-91	Study group: 92 patients with isolated preauricular tags and pits underwent renal ultrasonogram on 1-3 months of life. Control group; 95 infants without tag or pits underwent urinary tract ultrasonogram on day 2nd.	Case-control (level 3b of evidence)	Urinary tract anomalies detected on ultrasonogram.	2/92 (2.2 95%CI 0.2-7) of study group had renal anomalies. 4/95 (4.2 95%CI 1.1-10) of control group has anomalies.	Age disparity at time of examination between cases and controls.
Mishra Indian Pediatrics 2003;40:796-7	Study group: 34 patients with isolated preauricular tags underwent renal ultrasonogram Control group, 34 infants without tag underwent urinary tract ultrasonogram for non renal problems.	Case-control (level 3b of evidence)	Urinary tract anomalies detected on ultrasonogram.	3/34 (9 95%CI 0.6-8) of study group had renal anomalies. None anomalies in control group.	The study included only preauricular tags. There were no cases of renal malformations in the control group which is of less than normal population. The study includes children up to 10 years of age.
Queisser-Luft XXI DW Smith Worshop. San Diego.CA 2000:60.	Study group: 6192 patients with isolated external ear anomalies . Control group; 26397 infants without ear anomalies. Examination was made in the 1st week after birth.	Case-control (level 3b of evidence)	Urinary tract anomalies detected on ultrasonogram.	105/6192 (1.7 95%CI 1.4-2) of study group had renal anomalies. 290/26397 (1.1 95%CI 1-1.3) had anomalies in control group	The study include Inewborns (ivebirth, stillbirths or abortions). The study includes isolated mild external ear anomalies: pits , tags,lowest ears, cupears and other mild auricular errors of morphogenesis.

genetic syndromes with ear and renal abnormalities. One study was included from the reference list of another study, which has been published in conference proceedings only (16) (The results have been published partially in a peer reviewed journal by de same authors (17).

The four studies enrolled 32983 subjects, the age of participants in included studies ranged from newborns to ten-year-old children. All studies report outcomes as renal anomalies detected on ultrasonography. Only one study reports posterior investigation with voiding cystography and another with additional scintigraphy (both of which were necessary). The report of results was the absolute number of patients, a relative number as a percentage of prevalence with 95%CI. Three studies report only pre-auricular tags, and the remainder report tags, pits, microtia and other mild structural abnormalities. The time of the first examination varied from 2nd day of life to 1-3 months, and the second examination up to 23 months.

Our meta-analysis shows a pooled prevalence of renal tract anomalies of 116/6338 (1.8 95%CI 1.5-2.2) in the cases group, and 294/26595 (1.1 95%CI 1.-1.2) in the controls group, the pooled positive predictive value of ear abnormalities to detect renal malformations by ultrasonography was 1.79 (1,78 a 1.80) with a negative predictive value of 98.85 (98.84-98.86), with a positive likehood ratio of 1.4 (95%CI 1.2-1.6) and a negative likehood ratio of 90.2 (95%CI 85-95.6)

The heterogeneity Q test was equal 3.67, with d.f. 3, p 0.2995. The studies were therefore homogeneous. The variability between-studies was 0.1204, and within-studies 0.0508, the coefficient of variation was 0,7830. The Queisser-Luft (16) study has a precision of nearly 8, the most precise.

The meta-analysis showed that the risk of urinary tract anomalies is higher in infants with isolated external ear malformations. The pooled O.R for renal tract abnormalities in case-control studies was 1.55 (95%CI 1.25-1.94) in a fixed model, see Table 2, Figure 1. The cumulated number of patients included in the meta-analysis shows a tendency for a positive association between isolated mild external ear malformations and renal tract abnormalities (Figure 2).

The Begg test was p of 0.7341 and Egger test was p of 0.9732, whereas the present meta-analysis has no publication bias.

Table 2. Pooled risk of renal malformations in infants with pre-auricular tags or pits.

Study	Year	n	O.R.	95%CI	Weight (%)
Queisser-Luft (Germany)	2000	32589	1.55	1.24-1.94	96.38
Kohelet (Israel)	2000	139	6.37	0.75-54.42	1.06
Mishra (India)	2003	68	3.19	0.31-32.35	0.91
Kugelman (Israel)	2002	187	0.50	0.09-2.83	1.64
Fixed global effect		32983	1.55	1.25-1.94	

Figure 1. Individual and pooled odds ratios with 95% confidence interval for renal tract abnormalities.

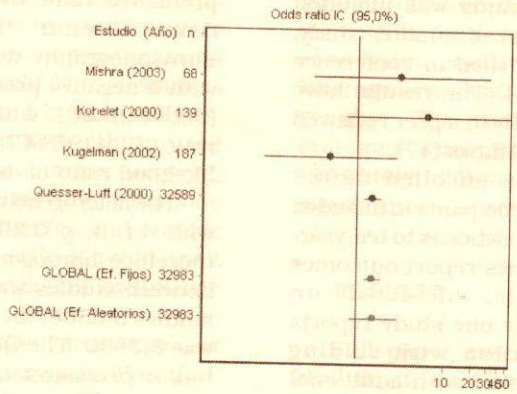
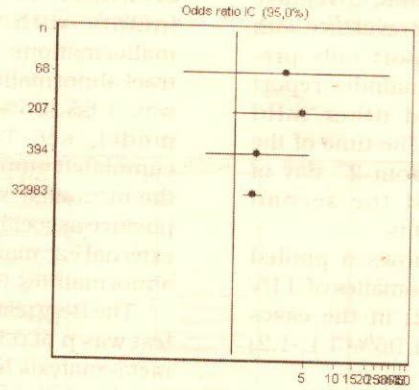


Figure 2. Meta-analysis with cumulated effect.



DISCUSSION

The results of our study, confirm a significant association between isolated mild external ear malformations and renal tract abnormalities. The analysis of all case-control studies, shows a clear tendency of pooled O.R with the superior 95%CI of 1.94, which means a near possible double risk of renal tract anomalies in infants with isolated mild abnormal external ears. If we consider the fact that the incidence of isolated mild external ear malformations ranged between 5 and 10 per 1000 live births, and the reported postnatal renal malformations prevalence around 2.2-8.6%, to achieve a significant sample size in a individual study would demand a considerable period of time (18). This would explain the scarce number of individual studies on this issue and the existence of only one with sufficient statistical power.

All studies in this meta-analysis use ultrasonography as a diagnostic tool, and define the prevalence of renal tract abnormalities mainly as hydronefrosis; however, ultrasonography is not the most indicated tool for diagnosing vescicoureteric reflux in newborn infants: We may assume that even more infants have had reflux if voiding cystography had been performed (8).

Considerable discrepancy exists between the different studies, and several factors may account for this. Two of four control series reported zero prevalence of urinary tract abnormalities, which could reflect very small sample sizes (type II error) and selection bias for different timing of imaging may have occurred; however, the wide confidence intervals in both studies show upper limits of over 10,

and this suggests a great possibility of under estimation of real prevalence, and the other series are limited by small size and, in all of them, the lower 95% confidence interval limit goes beyond number one, except in the case of the study with most wieght (16).

Three studies were underpowered by small size, and also rose in risk of type II error. Two articles which are from the same country give paradoxically opposite results (8,9); the authors explain dissimilarities between the two populations in general prevalence of malformations, the age of subjects, and argue that imaging timing in case and control groups was widely different, because the incidence of renal tract abnormalities decreases with time, as well as between pre and postnatal ultrasonography (19).

The mechanism of this association is believed to be due in part to genes which expressed in developing ear and kidney structures at different times during morphogenesis (7). As Kohelet and coworkers (9) cited, the association between ear malformations and renal abnormalities is difficult to explain, which is why certain authors have proposed linking several conditions including fascio-auriculo-vertebral syndrome, hemifacial micrognatia, oto-mandibular dysostosis, 1st and 2nd branquial arch anomalies, Goldenhar syndrome, how oculo-oto-vertebral spectrum, where the common denominator is unknown etiology (20). Temporally and spacially asynchronous gene expression is providing to be recurring theme in embriogenesis. One example is the nested expression of Hox genes, PAX2 expression, EYA1 and SALL1 in ear, kidney and other organ malformations (21), this fact is consistent with biological plausibility in the association between ear and renal abnormalities.

Because the number of articles in medical literature is scanty regarding specific isolated mild ear malformations, such tags, pits, sinuses, earlobe crease, Darwinian tubercle, attached earlobe and the rest of mild malformations, it is necessary to conduct large studies on association between each of these ear malformations and renal abnormalities. Therefore the policy implications of ultrasound screening should be considered and discussed critically, in the different contexts, until the degree, natural history and types of specific associated renal anomalies will be established.

Even the presence of a pre-auricular tag or pit should lead to a thorough search for other malformations and dysmorphies (21).

Our meta-analysis is limited by: a) The biological heterogeneity between the included studies, due to different age inclusions, ear malformation inclusions and ethnically heterogeneous groups b) The great weight of Queisser-Luft study affects the pooled estimates. Obviously exclusion of the Queisser-Luft study ruins the meta-analysis, this fact in itself is highly important, and thus the interpretation of the summary statistic should be see with caution c) Our limited availability of resources to identify all literature is subject to selection bias due to publication bias, language bias and citation bias d) All included studies are case-controlled. Case-controlled studies are notoriously subject to bias, and unless designed, executed and selected carefully, results thereof should be interpreted with care e) Ultrasound is operator dependent. Only in two cases the included studies refers a gold standard for assessment renal abnormalities. External ear malformations is based on clinical judgment: there may be miscategorisation causing dilution bias.

The predictive values of mild auricular error of morphogenesis are not sufficient to serve as a reason for renal screening by itself . This study suggests that there is a significant association of urinary tract abnormalities in infants and children with isolated mild external ear malformations. Until evidence may provide more definitive information to derive a firm conclusion on the need for renal ultrasonogram, we think that children with isolated mild ear abnormalities should undergo an ultrasographic evaluation for urinary tract anomalies.

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