

Comment on 'Allergy and acute leukaemia in children with Down syndrome: a population study. Report from the Mexican Inter Institutional Group for the Identification of the Causes of Childhood Leukaemia (MIGICCL)' – Is increased surveillance by hypersensitive immune system a reality or myth?

Z Aryan¹ and N Rezaei^{*,1,2,3}

¹Molecular Immunology Research Center, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran; ²Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Children's Medical Center Hospital, Dr Qarib Street, Keshavarz Blvd, Tehran 14194, Iran and ³Department of Infection and Immunity, School of Medicine and Biomedical Sciences, University of Sheffield, Sheffield, UK

Sir,

We read with great interest the study by Nunez-Enriquez *et al* (2013)¹ recently published in this journal. They conducted a multi-institutional population-based case-control study on children with Down syndrome and found that asthma is a risk factor of acute leukaemia development (odds ratio: 4.18 and 95% confidence interval: 1.47–11.87). However, other allergies had no effect on acute leukaemia development or were protective, in their experience. This study has revived an old question about effect of having allergies and chance of cancer development. Previous studies in this regard unveiled that allergies usually do not increase the risk of cancers, and in contrast, might be protective from cancer development (Vojtechova and Martin, 2009; Chen *et al*, 2011; Dikalioti *et al*, 2012). In allergic subjects, there is bone marrow involvement with reprogramming of bone marrow stem cells, regarded as 'reflex nature of allergic disease' (Holt and Strickland, 2010). Allergic phenotype in an atopic child may lead to epigenetic reprogramming that in turn affects immune surveillance by increasing antigen-presenting cell activity (Holt and Strickland, 2010). In addition, recent studies have demonstrated that serum eosinophil count is inversely associated with colorectal cancer

development (Prizment *et al*, 2011). Hence, it seems that increased surveillance by hyperactive immune system of allergic patients is a reality. Here, the main question is 'why was asthma found as a risk factor of acute leukaemia development?'

The method of allergy diagnosis and definition of allergic conditions affect categorisation of patients into different allergic groups, particularly with regard to recruitment of patients from different institutions. Moreover, considerable proportion of asthmatic patients might also have rhinitis, skin allergies or food allergies. Asthma and allergic rhinitis are too close in which more than half of asthmatic patients have also allergic rhinitis and up to 40% of allergic rhinitis patients experience asthma (Bousquet *et al*, 2012; Aryan *et al*, 2013). Skin allergies and food allergies are other allergic conditions that are common in asthmatics, in such a way up to 15% of asthmatics have food allergies (Fiocchi *et al*, 2013). It is not clear in this study that how investigators categorised patients who had several allergic conditions and it might affect their results.

Another point is that wheezing in Down syndrome children is not likely to be asthma and asthma misclassification is possible to be occurred. It has been shown that Down syndrome children

*Correspondence: Dr N Rezaei; E-mail: rezaei_nima@tums.ac.ir
Published online 1 August 2013



might experience episodes of wheezing mimicking asthma phenotype. Weijerman *et al* (2011) studied recurrent wheeze in 173 Down syndrome children and found that none of Down syndrome children below 4 years of age had asthma according to international guidelines, and only 3.1% of overall Down syndrome children were actually asthmatic. Weijerman *et al* (2011) demonstrated that 46% of wheezes in Down syndrome children were due to congenital heart defects. In addition, neither of increased immunoglobulin-E level nor evidence of aeroallergen sensitisation was found in these children (Weijerman *et al*, 2011). Hence, the diagnosis of asthma should be made more carefully in Down syndrome patients and only reliance of parent's memory might probably lead to misclassification of asthma in Down syndrome children. Moreover, not all asthmatic Down syndrome children have allergy, and in contrast, asthma in Down syndrome patients seem to be non-allergic (Weijerman *et al*, 2011). Collectively, the results of this study regarding asthma might be affected by misdiagnosis and misclassification of asthma as an allergic condition.

On the other hand, Down syndrome is a primary immune deficiency characterised by lymphopenia, thrombocytopenia, and vulnerability to autoimmune and infectious diseases. Down syndrome children have increased susceptibility to respiratory syncytial virus infections, a known risk factor of asthma, thus they may experience manifestations quasi-asthma or actually develop asthma (Bloemers *et al*, 2010). Down syndrome patients have also inherited risk of acute leukaemia development. Accumulating evidences show that several genes on chromosome 21 have relevant functions in haematopoiesis and their qualitative or quantitative changes affect blood cells. Transient abnormal haematopoiesis and acute myeloid leukaemia are more likely to develop in Down syndrome children with *GATA1* mutation (Maclean *et al*, 2012; Toki *et al*, 2013). It indicates that regardless of role of environmental factors, inborn genetic defects in Down syndrome children affect haematopoietic cell biology and cause leukaemogenesis. Down syndrome might be a confounder in relation between asthma and acute leukemia. Altogether, Down syndrome may be considered as a cause of both asthma and acute leukaemia and drawing a causative link from asthma to acute leukaemia in this setting seems a raw conclusion.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Aryan Z, Comapalati E, Canonica GW, Rezaei N (2013) Allergen-specific immunotherapy in asthmatic children: from the basis to clinical applications. *Expert Rev Vaccines* **12**(6): 639–659.
- Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ, Kimpen JL, Bont L (2010) High incidence of recurrent wheeze in children with down syndrome with and without previous respiratory syncytial virus lower respiratory tract infection. *Pediatric Infect Dis J* **29**(1): 39–42.
- Bousquet J, Schunemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, Bonini S, Boulet LP, Bousquet PJ, Brozek JL, Canonica GW, Casale TB, Cruz AA, Fokkens WJ, Fonseca JA, van Wijk RG, Grouse L, Haahela T, Khaltaev N, Kuna P, Lockey RF, Lodrup Carlsen KC, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Palkonen S, Papadopoulos NG, Passalacqua G, Pawankar R, Price D, Ryan D, Simons FE, Togias A, Williams D, Yorgancioglu A, Yusuf OM, Aberer U, Adachi M, Agache I, Ait-Khaled N, Akdis CA, Andrianarisoa A, Annesi-Maesano I, Ansotegui IJ, Baiardini I, Bateman ED, Bedbrook A, Beghe B, Beji M, Bel EH, Ben Kheder A, Bennoor KS, Bergmann KC, Berrissoul F, Bieber T, Bindslev Jensen C, Blaiss MS, Boner AL, Bouchard J, Braido F, Brightling CE, Bush A, Caballero F, Calderon MA, Calvo MA, Camargos PA, Caraballo LR, Carlsen KH, Carr W, Cepeda AM, Cesario A, Chavannes NH, Chen YZ, Chiriac AM, Chivato Perez T, Chkhartishvili E, Ciprandi G, Costa DJ, Cox L, Custovic A, Dahl R, Darsow U, De Blay F, Deleanu D, Denburg JA, Devillier P, Didi T, Dokic D, Dolen WK, Douaoui H, Dubakiene R, Durham SR, Dykewicz MS, El-Gamal Y, El-Meziane A, Emuzyte R, Fiocchi A, Fletcher M, Fukuda T, Gamkrelidze A, Gereda JE, Gonzalez Diaz S, Gotua M, Guzman MA, Hellings PW, Hellquist-Dahl B, Horak F, Hourihane JO, Howarth P, Humbert M, Ivancevich JC, Jackson C, Just J, Kalayci O, Kaliner MA, Kalyoncu AF, Keil T, Keith PK, Khayat G, Kim YY, Koffi N'goran B, Koppelman GH, Kowalski ML, Kull I, Kvedariene V, Larenas-Linnemann D, Le LT, Lemiere C, Li J, Lieberman P, Lipworth B, Mahboub B, Makela MJ, Martin F, Marshall GD, Martinez FD, Masjedi MR, Maurer M, Mavale-Manuel S, Mazon A, Melen E, Meltzer EO, Mendez NH, Merk H, Mihaltan F, Mohammad Y, Morais-Almeida M, Muraro A, Nafti S, Namazova-Baranova L, Nekam K, Neou A, Niggemann B, Nizankowska-Mogilnicka E, Nyembue TD, Okamoto Y, Okubo K, Orru MP, Ouedraogo S, Ozdemir C, Panzner P, Pali-Scholl I, Park HS, Pigearias B, Pohl W, Popov TA, Postma DS, Potter P, Rabe KF, Ratomaharo J, Reitano S, Ring J, Roberts R, Rogala B, Romano A, Roman Rodriguez M, Rosado-Pinto J, Rosenwasser L, Rottem M, Sanchez-Borges M, Scadding GK, Schmid-Grendelmeier P, Sheikh A, qSisul JC, Sole D, Sooronbaev T, Spicak V, Spranger O, Stein RT, Stoloff SW, Sunyer J, Szczeklik A, Todo-Bom A, Toskala E, Tremblay Y, Valenta R, Valero AL, Valeyre D, Valiulis A, Valovirta E, Van Cauwenberge P, Vandenas O, van Weel C, Vichyanond P, Viegi G, Wang DY, Wickman M, Wohlrl S, Wright J, Yawn BP, Yiallourou PK, Zar HJ, Zernotti ME, Zhong N, Zidarn M, Zuberbier T (2012) Allergic rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* **130**(5): 1049–1062.
- Chen C, Xu T, Chen J, Zhou J, Yan Y, Lu Y, Wu S (2011) Allergy and risk of glioma: a meta-analysis. *Eur J Neurol* **18**(3): 387–395.
- Dikaloti SK, Chang ET, Dessypris N, Papadopoulou C, Skenderis N, Pourtsidis A, Moschovi M, Polychronopoulou S, Athanasiadou-Piperopoulou F, Sidi V, Kalmanti M, Petridou ET (2012) Allergy-associated symptoms in relation to childhood non-Hodgkin's as contrasted to Hodgkin's lymphomas: a case-control study in Greece and meta-analysis. *Eur J Cancer* **48**(12): 1860–1866.
- Fiocchi A, Annunziato F, Assa'ad A, Arshad H, Bahna SL, Boyle R, Brozek J, Bush A, Canonica W, Cicardi M, Compalati E, Dahdah L, Dupont C, Finegold I, Fineman SM, Grabenhenrich L, Holgate S, Kuitunen M, Lau S, Maggi E, Martelli A, Matricardi P, Moretta L, Palmer D, Parronchi P, Pawankar R, Prescott S, Restani P, Rosenwasser L, Terracciano L, Scheurer S, Tripodi S, Vieths S, Von Berg A, Vultaggio A, Weber RW (2013) The management of paediatric allergy: not everybody's cup of tea – 10–11th February 2012. *Curr Opin Allergy Clin Immunol* **13**(Suppl 1): S1–50.
- Holt PG, Strickland DH (2010) Interactions between innate and adaptive immunity in asthma pathogenesis: new perspectives from studies on acute exacerbations. *J Allergy Clin Immunol* **125**(5): 963–972; quiz 973–974.
- Maclean GA, Menne TF, Guo G, Sanchez DJ, Park IH, Daley GQ, Orkin SH (2012) Altered hematopoiesis in trisomy 21 as revealed through in vitro differentiation of isogenic human pluripotent cells. *Proc Natl Acad Sci USA* **109**(43): 17567–17572.
- Nunez-Enriquez JC, Fajardo-Gutierrez A, Buchan-Duran EP, Bernaldez-Rios R, Medina-Sanson A, Jimenez-Hernandez E, Amador-Sanchez R, Penaloza-Gonzalez JG, Paredes-Aguilera R, Alvarez-Rodriguez FJ, Bolea-Murga V, de Diego Flores-Chapa J, Flores-Lujano J, Bekker-Mendez VC, Rivera-Luna R, Del Carmen Rodriguez-Zepeda M, Rangel-Lopez A, Dorantes-Acosta EM, Nunez-Villegas N, Velazquez-Avina MM, Torres-Nava JR, Reyes-Zepeda NC, Cardenas-Cardos R, Flores-Villegas LV, Martinez-Avalos A, Salamanca-Gomez F, Gorodezky C, Arellano-Galindo J, Mejia-Arangure JM (2013) Allergy and acute leukaemia in children with Down syndrome: a population study. Report from the Mexican inter-institutional group for the identification of the causes of childhood leukaemia. *Br J Cancer* **108**(11): 2334–2338.
- Prizment AE, Anderson KE, Visvanathan K, Folsom AR (2011) Inverse association of eosinophil count with colorectal cancer incidence: atherosclerosis risk in communities study. *Cancer Epidemiol, Biomarkers Prev* **20**(9): 1861–1864.

Toki T, Kanezaki R, Kobayashi E, Kaneko H, Suzuki M, Wang R, Terui K, Kanegane H, Maeda M, Endo M, Mizuochi T, Adachi S, Hayashi Y, Yamamoto M, Shimizu R, Ito E (2013) Naturally occurring oncogenic GATA1 mutants with internal deletions in transient abnormal myelopoiesis in Down syndrome. *Blood* **121**(16): 3181–3184.

Vojtechova P, Martin RM (2009) The association of atopic diseases with breast, prostate, and colorectal cancers: a meta-analysis. *Cancer Causes Control* **20**(7): 1091–1105.

Weijerman ME, Brand PL, van Furth MA, Broers CJ, Gemke RJ (2011) Recurrent wheeze in children with Down syndrome: is it asthma? *Acta Paediatrica* **100**(11): e194–e197.



This work is licensed under the Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-sa/3.0/>

BJC

British Journal of Cancer (2013) 109, 1388–1390 | doi: 10.1038/bjc.2013.436

Reply: Comment on 'Allergy and acute leukaemia in children with Down syndrome: a population study. Report from the Mexican Inter-Institutional Group for the Identification of the Causes of Childhood Leukaemia (MIGICCL)' – A reality or myth or two viewpoints about the association between allergies and acute leukaemia in Down syndrome children

J C Núñez-Enríquez¹, A Fajardo-Gutiérrez¹, E P Buchán-Durán¹, E Jiménez-Hernández² and J M Mejía-Arangur^{*1,3}

¹Unidad de Investigación Médica en Epidemiología Clínica, Hospital de Pediatría, Centro Médico Nacional 'Siglo XXI', Instituto Mexicano del Seguro Social, Av. Cuauhtémoc 330, Delegación Cuauhtémoc, México D.F. 06720, México; ²Servicio de Hematología Pediátrica, Hospital General 'Gaudencio González Garza', Centro Médico Nacional 'La Raza', Instituto Mexicano del Seguro Social, Calzada Vallejo y Jacarandas S/N Col. La Raza, Delegación Azcapotzalco, México D.F. 02990, México and ³Coordinación de Investigación en Salud, Instituto Mexicano del Seguro Social, Torre Academia Nacional de Medicina 4to piso, Av. Cuauhtémoc 330, Delegación Cuauhtémoc, México D.F. 06720, México

Sir,

We are very grateful to Drs Aryan and Rezaei (2013b) for their interest in our manuscript; their letter is interesting as it reveals

the differences between a reductionist and a population viewpoint with regard to the relationship between allergies and the development of leukaemia in children with Down syndrome.

*Correspondence: Dr JM Mejía-Arangur; E-mail: juan.mejiaa@imss.gob.mx
Published online 1 August 2013

