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Rare metabolic diseases among the Irish Travellers: results from the All Ireland Traveller Health Study census and birth cohort (2007-2011)

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ABSTRACT

Irish Travellers are a minority population group on the island of Ireland, in whom it has been documented previously that some rare inborn metabolic diseases are more prevalent. However, these were mostly based on population estimates, rather than accurate denominator data. This study aimed to document the prevalence of these rare metabolic diseases, employing data from the All Ireland Health Study census and subsequent birth cohort study (2007-2011). The prevalences for Hurler disease, Phenyketonuria, Galactosaemia and Brittle Bone Disease were 1.3, 1.3, 2.6 and 1.9 per 1,000 Traveller children respectively. Other recorded diseases were Mucolipidosis type II, Marfan's syndrome, Charcot-Marie-Tooth, Phenyketonuria and Byler's Disease. These, however, may be an under-estimated numbers and also highlights the limitations in rare diseases epidemiology. There is a limited newborn screening service in the Republic of Ireland; given the higher prevalence of these metabolic diseases among the Travellers, a Traveller-specific prevention strategy should be considered. Services should also be sensitive to the needs of the population. (160 words)

KEYWORDS

rare disease epidemiology, metabolic diseases, Irish travellers

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INTRODUCTION

Rare diseases pose many challenges not just for clinical medicine [1] but also for public health practice [2]. For clinicians, these challenges range from recognition, diagnostic to treatment strategies. From a public health perspective, these include conducting effective population-based research, providing epidemiological evidence and policy formulation for these diseases. There is also a social issue, as most of these diseases are debilitating, affect quality of life, social functions and life expectancy [3]. This 'health orphan' status also poses a problem for classification [4] and therapeutic development. There is often a lack of concrete epidemiological data on the incidence and prevalence for most rare diseases; these are reported in the literature based on narrowly defined hospital or specialist clinic populations which made reporting of incidence and prevalence of the disease in a large population inconclusive [5]. Due to this inconsistency and lack of consensus, initiatives to create global rare diseases infrastructure projects such as RD-Connect (http://rd-connect.eu/about/) [6] and Global Rare Disease Patient Registry And Data Repository (GRDR, http://rarediseases.info.nih.gov/research/pages/43/global-rare-disease-patient-registry-and-data-repository) [7] have been commenced.

The Irish Travellers are a nomadic minority on the Island of Ireland. They have a set of cultures, values system and distinct Shelta language which set them apart from the general Irish population [8]. The Equal Status Act [8] defined the Traveller Community as '*the community of people who are commonly called Travellers and who are identified (both by themselves and others) as people with a shared history, culture and traditions, including historically, a nomadic way of life on the island of Ireland*'. An updated population health status and socioeconomic disparity of this population has been reported elsewhere in a comprehensive series of reports [9]. There are approximately 40, 129 Travellers on the Island of Ireland, majority of whom (estimated 36, 224) reside in the Republic of Ireland and a smaller population of 3,905 in Northern Ireland. Life expectancy of a Traveller man is 61.7 years compared to 76.8 years of the general Irish population, while for woman this is 70.1 years and 81.6 years respectively. In terms of lifestyle, approximately 78.5% of Travellers in Republic of Ireland and 62.6% of those in Northern Ireland are no longer nomadic. Traditionally, Traveller men are the sole bread-winner in the family. The All Ireland Traveller Health Study showed that less than 14% of Traveller men are in some form of employment [9]. In terms of child health, our own study showed that Traveller infant mortality rate is more than three times that of the general population rate and causes of death from autosomal recessive disorders are higher compared to the general population [10].

Establishing the true incidence and prevalence of rare diseases suffers from the common problem of poor epidemiological data on disease events and population demography [11] and this is also true for reporting of rare diseases associated with Irish Travellers. For example, Murphy, *et al.* [12,13], in reporting on the annual incidence of mucopolysaccharidosis type I and galactosaemia in the general population of the Republic of Ireland and in Traveller births, had to estimate the number of Traveller births based on a 1987 study of the Irish Travellers [14]. This difficulty has also been highlighted recently by Coss, *et al.* [15].

To overcome this problem, an updated disease-specific count providing population data is essential. The aim of this paper was to report on the prevalence of a selected group of recorded metabolic diseases among 5-, 9- and 14-year old Traveller children on the island of Ireland using the latest Irish Traveller census and the birth incidence of rare diseases detected from the birth cohort study. The use of prevalence rates has been advocated by Paz [11] as the preferred system of rare disease reporting due to its advantages in managing rarity and health service planning.

METHODOLOGY

The All Ireland Traveller Health Study (AITHS) was a comprehensive study of Irish Travellers on the island of Ireland. It consisted of a complete census and a number of sub-studies, including the establishment of a birth cohort followed over three years [9]. Briefly, the Traveller census surveyed all Traveller families on the Island of Ireland in October 2009 in the Republic of Ireland and in February 2010 in Northern Ireland. The census survey was conducted by trained Traveller peer researchers using a novel audio-visual computer assisted data collection tool. The primary respondent was usually the mother and thereafter at random a further sub-study interview took place. If a child aged exactly 5,9 or 14-year old resided in the household, the mother gave a proxy health status interview on that child's behalf including questioning on a pro forma list of inherited metabolic diseases which have been previously documented among the Travellers. Only one child was selected per family unit. This procedure was adopted to ensure a complete sample of these specific age-groups for the purpose of calculating prevalence rates. If there was no child of this age group in the household then an adult respondent was selected for the adult health survey.

The general child health questionnaire specifically asked if the index child had any chronic diseases and, if he/she did, the parents selected an answer from a specific list of conditions from the next leading questions. These included asthma, cerebral palsy, cystic fibrosis, diabetes, epilepsy, Hunter syndrome (mucopolysaccharidosis type II),

Hurler syndrome (mucopolysaccharidosis type I), phenylketonuria (PKU), galactosaemia and brittle bone disease (osteogenesis imperfect). No other diseases were recorded during the census.

In the birth cohort study, Traveller mothers who delivered their babies between 14th October 2008 to 13th October 2009 were invited to participate, further methodology of the birth cohort study can be obtained elsewhere [10,16]. The cohort was followed up for twelve months post-partum and a General Registry Office search was made for mortality of cohort members. The participating mothers carried with them specially-designed parent-held child records which were presented during each contact with the medical services. In most cases, the Public Health Nurse assisted the mothers in completing the records. The All Ireland Traveller Health Study received ethical approval from University College Dublin Human Research Ethics Committee.

Prevalence of a disease is defined as 'the number of positive cases detected per 1,000 population' in this study. The denominator for the prevalence calculation of this study is the number of children enumerated from the AITHS census.

RESULTS

A list of rare diseases (and disease mode of inheritance) recorded by the All Ireland Traveller Health Study census and birth cohort is given in *(Table 1)*. There were 10,618 families identified with an 80% response rate in the AITHS census, including a total subsample of 1,541 families with children aged 5, 9 and 14 years on the island of Ireland [9]. There were 1,390 and 185 from Republic of Ireland and Northern Ireland respectively responded to the children questionnaires (Total n=1, 575). Out of the n=1,390 in the Republic of Ireland, n=522, n=400 and n=468 were from the 5-, 9- and 14-years old questionnaires respectively while n=61, n=66 and n=58 were from Northern Ireland respectively. However, 97.9% (n=1,541) answered the target questions, with a small number of missing variables. *Table 2* shows the breakdown of cases by disease type, age group, and prevalence/ birth incidence of the diseases. There were two cases each for Hurler syndrome and PKU, four for galactosaemia, three for brittle bone disease and no cases reported for Hunter syndrome. The prevalence rates per 1,000 Traveller children age 5, 9 and 14 on the island of Ireland were 1.3 for Hurler syndrome, 1.3 for PKU, 2.3 for galactosaemia and 1.9 for brittle bone disease.

Table 1: diseases recorded in the all ireland traveller health study census and birth cohort and their mode of inheritance

Study	Disease (OMIM code)	Mode of inheritance
All Ireland Traveller Health Study census	Hunter syndrome (OMIM 309900)	X-linked recessive
	Hurler syndrome (OMIM 607014)	Autosomal recessive
	Phenyketonuria (OMIM 261600)	Autosomal recessive
	Galactosaemia (OMIM 230400)	Autosomal recessive
	Brittle Bone disease (OMIM 166200)	Autosomal dominant/ recessive
Traveller birth cohort	Byler's disease (OMIM 211600)	Autosomal recessive
	Charcot-Marie Tooth disease (OMIM 604563)	Autosomal dominant/ recessive/ X-linked
	Marfan syndrome (OMIM 154700)	Autosomal dominant
	Mucolipidosis type II (OMIM 252500)	Autosomal recessive

The birth cohort study detected 986 Traveller births for the period of 14th October 2008 to 13th October 2009. Of these, 508 (51.2%) mothers consented to the study. The parent-held child records were successfully retrieved for 383 (75.4%) of participating mothers. The birth incidence rates for rare diseases recorded in the parent-held child record are given in *(Table 2)*.

Table 2: Number of cases by cohort, age group, type of diseases and the calculated incidence and prevalence (for island of Ireland)

	Birth cohort study (N=383)		AITHS Census (N=1,541)					
	Under 1 year old	Birth incidence per 1,000 births (95% CI)	5 years old (n=570)	9 years old (n=454)	14 years old (n=517)	Total	Prevalence (per 1,000)* (95% CI)	Estimated prevalence **
Hunter syndrome	0	-	0	0	0	0	0	0.6
Hurler syndrome	0	-	1	0	1	2	1.3 (0.2-5.2)	0.6
Phenyketonuria	1	2.6 (0.1-16.7)	0	1	1	2	1.3 (0.2-5.2)	7.0
Galactosaemia	0	-	1	2	1	4	2.6 (0.8-7.1)	6.6
Brittle Bone Disease	0	-	1	0	2	3	1.9 (0.5-6.2)	6.5
Byler's Disease	1	2.6 (0.1-16.7)	-	-	-	-	-	-
Charcot-Marie Tooth disease	1	2.6 (0.1-16.7)	-	-	-	-	-	-
Marfan's Syndrome	1	2.6 (0.1-16.7)	-	-	-	-	-	-
Mucolipidosis type II	2	5.2 (0.9-20.8)	-	-	-	-	-	-
Total	6	-	3	3	5	11		

**per 1,000 Traveller children age 5, 9 and 14 on island of Ireland, ** Estimated rate per 100,000 by Orphanet [17] converted to per 1,000 for comparison*

DISCUSSION

The aim of this study was to investigate the prevalence of a selection of rare diseases among Traveller children and incidence of rare diseases from a Traveller birth cohort. In total 17 cases were detected across the four age groups of a variety of heritable conditions. Whilst still rare in incidence and prevalence, these rates greatly exceed the expected rates in all four age groups. In this study, the prevalence of Hurler syndrome was higher than the estimated prevalence reported by Orphanet [17] and Moore [18]. Other publications have concentrated on reporting of incidence [19-20]. Similar situation exists for other recorded diseases in this study.

The differences in reporting systems and lack of accurate population estimate made it difficult to make comparisons across populations as demonstrated by Badawi, *et al.* [21], using data from the newborn screening programme in the Republic of Ireland, reported the frequency of galactosaemia as 1 in 23,000 births over the period 1971 to 1992, with a frequency of 1 in 700 births among Travellers in the Republic of Ireland. Murphy *et al.* [13] re-analysed this data from 1972 to 1996 and re-estimated the incidence rate to be 1 in 480 and 1 in 30,000 in the Traveller and Irish general population respectively. However, both studies used estimated Traveller birth counts from the 1987 Traveller Health Status Study [22] thus this may have over-estimated the incidence rates. Both studies used estimated births from an outdated study but could not calculate an estimated prevalence rate due to the lack of population data. There was also a lack of reported prevalence rate of galactosaemia in the literature.

Osteogenesis imperfecta or brittle bone disease has a worldwide prevalence of 2.3 per 10,000 births [23]. The prevalence from our study was 1.9 per 1,000 Traveller children. This is much higher, an equivalent of 190 per 100,000, when compared to the point prevalence of 21.8 per 100,000 in Denmark as reported by Andersen and Hauge [24]. The database of the Latin-America Collaborative Study of Congenital Malformations reported a prevalence rate of 0.4 per 10,000 live births for the years 1978 to 1983 [23]. Martin and Shapiro [25] reported a prevalence of 1 per 10,000 live births in the United States (this is 0.04 and 0.1 per

1,000 births respectively).

There were other previously less reported diseases among the Traveller population. For example, mucolipidosis type II has only been acknowledged to occur among Travellers but has not been described or studied in detail from an epidemiological perspective. McElligot, *et al.* [26] reported an estimated incidence of 114 per 100,000 live births for the Travellers in the Republic of Ireland. In addition, Coutinho [27] demonstrated the existence of a specific mutation that was detected among Israeli and Palestinian Arab-Muslim, Turkish, Canadian, Italian, Portuguese, Irish Traveller and United States American populations. The team also hypothesised that it is an ancient disease (around 2063 years old) that originated from the peri-Mediterranean region. Case studies for mucolipidosis type II have also been reported from around the world. Orphanet [17] estimated a birth prevalence of 0.15 per 100,000 population which confirms that the incidence of mucolipidosis type II is much higher among the Travellers although there are limitations in both studies.

The higher rates of these rare diseases among the Travellers were believed to be due to the founder effect [19] and consanguinity practices in the population [28]. Although Travellers are not legally defined as an ethnic group in the Republic of Ireland, they are an ethnic group by social definition thus practices marriage arrangements within their ethnic group [8]. In addition, it is not necessarily due to relatedness as the Traveller population itself is a small population on the Island of Ireland which has been estimated to be 40,129 and 42% of whom are under 14 years old [9]. Recent laws have prohibited illegal halting, which hinders Travellers' mobility [29] which not only has economic value but also social value such as identifying potential partners [30]. Thus, prohibition of movement may have also resulted in Travellers isolation to pockets within certain areas of island of Ireland. This may have consequences on the chances of autosomal recessive disorders.

Being able to identify and calculate the incidence and/or prevalence of rare diseases facilitates interventions being put in place, especially when the disease occurrence is higher in an identifiable group like the Irish Travellers. The New York Ashkenazi Jews for instance have an anonymised screening register so that intending couples can, if a test is available, check carrier status in the run up to marriage [31]. It might not be economical to plan for newborn screening for some of these rare conditions at a general population level. However, with the advancement of genetic screening and the ability to identify this specific group, services could be provided to cater specifically for the Travellers and with particular sensitivity [19,26]. Furthermore, Murphy [13,19] have suggested that genetic testing can be performed for most of these conditions thereby allowing a family pedigree to be recorded. Specific population-based carrier screening for heterozygote detection has been shown to have an important impact on at-risk groups [4]. Bittles [32] argued that with improvements in socioeconomic conditions, the incidence of primarily environmental diseases will decline. Instead, the incidence of genetic disorders will account for an increasing proportion of mortality and morbidity. There is, therefore, a need for the health services to tackle this transition and, in an identifiable population like the Travellers, family screening should be considered. Genetic registry and counselling have been demonstrated in other ethnic groups with successful results [33-36].

Policy-making for such services should be congruous and culturally appropriate. Currently, screening is available for some of these diseases and, in addition, Ireland has a well-established newborn screening programme. However, there are issues with the coherence of current policies in relation to other health policies. As an example, McGorrian [37] showed that one of the reasons for the low breastfeeding uptake among Republic of Ireland Travellers was due to the withholding of breastfeeding until the results of screening tests for galactosaemia became available. Thus stopping breastfeeding prior to the availability of screening results became a blanket policy for all Traveller births as recommended by the Review of National Screening Programme for Inherited Metabolic Diseases [38].

The strength of this study lies in its updated and population-based data. The study received much support from the Traveller community who self-identified during the AITHS census, and therefore reflects a true count of the community, which was previously under-estimated. There was a difference in the diseases recorded due to the employment of two different methods. The census used a pro-forma closed list approach while the birth cohort used an open recording via a parent-held child record. Both of these methods have their own strengths for example, some diseases common from birth may only be compatible with a short lifespan thus not seen in older children unless recorded through elsewhere. It should be noted that this study sampled a specific population of those who reached at least the age of 5-, 9- and 14-year old Traveller children and that some of the children with these conditions may have died at an earlier interval age, thus under-estimating the true number. Furthermore as the study chose to survey on specific ages of children within one family, by definition the study would not have recorded children of other age groups within the same family who may have the diseases. This may have affected the result as these autosomal recessive conditions tend to occur within the same family. Parents who were surveyed may also choose not to report these conditions due to stigmatisation. Currently, there is no formal ethnic identifier for Travellers in all the health system records in the Republic of Ireland thus these diseases may have been recorded in the general Irish population data. This illustrates the difficulties with population-based epidemiological studies as its rarity hinders capturing it in a population survey [11].

Despite the high response rate to the census survey, there were some who declined to participate in the birth cohort study. This group was likely to contain the most marginalised and most vulnerable among the Travellers. They may also be those with poor health outcomes which were not captured by the study. This speculatively may be true in the birth cohort study where there were no reported cases of the more common diseases associated with Travellers, for example galactosaemia and Hurler syndrome

but were captured in the infant mortality component [10]. We could not access hospital records of women who did not provide informed consent. Some of those who refused to participate in the birth cohort cited their reason as being stressed because their infants were still hospitalised when approached by the Public Health Nurses (usually in the first week post maternal discharge). This was further supported by the mortality rate of Traveller children under one year as found in the birth cohort study [10]. Therefore, low participation rate in the birth cohort and compounded further by a non-retrieval of the parent-held child record may have affected the true number of cases which should have been detected. However this could affect in two ways, under-ascertainment because mothers did not participate if though might be at risk of abnormality, or over-ascertainment because mothers with a family history or concerns may have been more likely to participate. A registry-based calculation may be more accurate but as cited before, Travellers are not identified in all health records in Ireland.

CONCLUSION

This study confirms the high prevalence of rare diseases in Travellers, necessitating appropriate intervention strategies. It also demonstrates the importance of having an updated and accurate population data especially in hard to reach minorities.

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