Syndromes and Hearing Loss – Clinical Practice Guideline for Audiology

(this is a section of a larger Practice Guideline "Cleft Palate, Craniofacial and Syndromic Guideline")

Care Paths for these syndromes are in separate PDF files in the same place as this document was found.

There are many known syndromes associated with hearing loss. Many of these have clefting and/or craniofacial anomalies, some of them don't. This list was generated by combining the BCCH Audiology Department list of syndromes and the BCEHP Late Onset Monitoring Risk Factor Syndromes. That list was then compared with those found in the *"Hereditary Hearing Loss and It's Syndromes"* and reviewed by all of the reviewers of this Guideline for completeness. This resulted in the syndromes listed below which are associated with hearing loss.

A literature review was conducted using Pub Med, PEDLYNX, and OMIM databases. Search terms were ('name of syndrome' as listed in Appendix B AND ('Audio*' OR Hear*') in title or abstract, from 1999 to 2010, all languages. Citations were screened by a two reviewers for relevance. Published, peer reviewed articles were selected based on level of evidence with recently published articles describing well-designed randomised controlled trials with comparatively large sample groups taking precedence. High quality systematic reviews and retrospective reviews of clinical data were also used. Case studies of noteworthy results were occasionally noted as a matter of interest or possible focus of higher level literature to be reviewed in the future (when published), but were not considered in determining association of a syndrome with late onset SNHL. If the results of a study were inconclusive or the literature could not clearly associate a syndrome with late onset SNHL (ie. small subject pool or insufficient baseline information) such information was noted but the syndrome was labelled as *not* associated with late onset SNHL.

Four distinct care paths were developed dependant on the level of risk assessed for late onset permanent hearing loss for syndromic children. One care path was developed specifically for Down Syndrome children. Each syndrome was assigned to one of the 4 care paths described. If age of diagnosis of the syndrome was known to be after childhood it is suggested that their care path be individualized (see Osteogenesis Imperfecta; Freidricks Ataxia; Turners, Klinefelter, Van Buchem and NF2). All of these infants will have had at least a newborn hearing screening and a 9 month Audiology assessment. The **BOLDED** syndromes are typically not seen through the CP/CF teams and therefore their 9 month assessment ought to be completed in their local Public Health Audiology Clinics.

SYNDROME /Description	Risk of late onset Permanent HL? Y= Yes evidence found N= No evidence found	Age of Diagnosis of Syndrome	Care Path **Cleft Palate** **1**-minimum f-up **2**-moderate f-up **3**-closest f-up **4**- Downs Syndrome f-up 5- Individualized
22Q11 (VCF/DiGeorge) Velocardiofacial Syndrome Cayler, Shprintzen: typical characteristics include cardiac abnormality (especially Fallot's Tetralogy), abnormal facies, thymic aplasia, can have cleft palate, hypocalcemia Zarchi et al, 2011. Digillio, 1999. Estimated prevalence: 1: 4,000. ~10% cleft palate	N: Primarily CHL related to auricular anomalies and cleft. ~11-20% congenital SNHL possibly related to vascular abnormalities. Case evidence of labrynthine anomalies.	Commonly at birth due to the congenital heart disease and abnormal facies, present in most all cases. If not heart problems can be later diagnosed.	2
DiGeorge sequence: cardiac defects, Thymus hypoplasia and/or T call-mediated immunodeficiency, and hypocalcemia and/or absence of parathyroids- (part of deletion 22q11 spectrum) Digillio, 1999. Erkki et al, 2007. Belmont et al, 2011. Estimated prevalence 1: 4,000.	Y: although primarily CHL related to auricular anomalies and cleft and ~11-20% congenital SNHL as well as some cases of LVA . Hearing loss can be unilateral and can be likely related to vascular abnormalities) as well as some case reports of labyrinthine anomalies. Not enough evidence to determine if significant risk of late onset snhl.	Commonly at birth due to the congenital heart disease and abnormal facies, present in most all cases. If no heart problems can be later diagnosed	2

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Alport syndrome: collagen synthesis disease characterized by renal disease. Alves et. al, '08 & Kashtan, '10	Y: BL/HF by late childhood/early adolescence for ~80-90% XL males & AR males & females. In some mutations (i.e. AD) SNHL may not occur until adulthood.	**Variable dependant on gene mutation and extent of kidney problems**	3
Alström syndrome: pigmentary retinopathy, diabetes mellitus, and obesity. Joy et al '07, Marshall et al '11 Estimated prevalence <1:1,000,000 in general population	Y: BL/HF progressive late childhood/early adolescence for ~80%. Some incidences of CHL & chronic OM. Symptom onset usually in infancy, but both onset and severity highly variable.	**Variable**	3
Apert Syndrome: FGFR2 craniosynostosis, syndactyly of hands and feet, mental retardation Rajenderhumar, 2005. Curch et al, 2007. Zhou et al, 2009. Robin et al, 2011. Prevalence: ~1: 100,000 to 200,000 live births (differing reports).	N: 3-6% Congenital CHL, >56% CHL ~10-20 yrs. Due to OME. Persistent to adulthood.	At birth or pre-natally	1

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Branchio-Oto-Renal syndrome: kidney, ears, and neck abnormalities Kemperman et al, 2004. Henricus et al, 2010. Kimberling et al, 2011. Huang et al, 2012. General prevalence: 1: 40,000 Onset variable, early childhood to early adulthood. Incidence in profoundly deaf children: ~2% ***Kemperman et al: 10/16 cases showed sig. SNHL progression in longitudinal anal. Including some fluctuation assoc. with enlarged endolymphatic duct/sac.***	Y: BL congenital. CHL (~50%), SNHL (~25%) & mixed HL.	Variable	2
Charcot-Marie-Tooth: inherited motor and sensory neuropathy, nephritis Postelmans, 2006. Kabzinska, 2010 Incidence: ~1: 2500 Prevalence varies between subclasses (0-15%). More common for auto-dom. Often slow progression.	Y: Late onset SNHL assoc. with demyelization of CN VIII.	Variable, especially if family history unknown, usually late childhood or early adulthood.	2

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CHARGE syndrome: acronym for the set of congenital features: Coloboma of the eye, Heart defects, Atresia of the nasal choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness. P*rogressive/LO assoc. with LVA (19% of SNHL).* SNHL Correlated with Facial palsy (P<.025 N=20) Edwards et al, 2002. Morimoto et al, 2006. . Huang et al, 2012 Prevalence: 1: 15,000	N: HL=81% of those: CHL (24%), SNHL or mixed (76%). Chronic OME & infections in CHL.	While features may be present at birth & many are diagnosed pre-natally or in the 1st few weeks, others not until other diagnoses have been ruled out.	2
Chondrodysplasias, e.g. Achondroplasia Szymko-Bennett, 2003. Collins, 2007. Pannier et al 2009. Braverman et al, 2010. Tokgoz-Yilmas et al. 2011. Incidence: 1: 15,000- 1: 40,000 live births (varies by type- Achondro. most common). Estimated prevalence of Rhizomelic Chondro. Punctata Type 1 < 1: 100,000.	N: CHL ~50%--OM & OME. Sporadic report of SNHL, insufficient data/ conflicting evidence.	At birth or prenatally	1

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Cornelia Delange Syndrome(also Long QT variant, aka Brachmann De Lange): slow growth before and after birth, severe to profound intellectual disability, skeletal abnormalities distinctive facial features, excessive body hair, microcephaly, some cleft palate 1:10,000-30,000	N: high incidence of congenital severe-profound SNHL	Typically at birth	1
Crouzon Syndrome: FGFR2 craniosynostosis, maxillary hypoplasia, shallow orbits. Church et al, 2007. Karam, 2011. Robin et al, 2011. Prevalence: 1.6: 100,000	N: CHL ~55%--OM & Stenosis or Atresia	Usually 1st year	1
Downs Syndrome aka Trisomy 21 Blaser, 2006. Shott, 2006. Park et al, 2012 **Incidence: 1: 600-800 live births**	**N: 80% CHL. 4-20% mixed or SNHL possibly associated with unresolved/untreated chronic OM, anomalies of the cochlea, internal auditory canal and LVA. Variable data.**	**Typically at birth**	4
Ehlers-Danlos syndrome: synthesis of collagen defects, characterized by hypotonia, ocular abnormalities, joint hypermobility. Miyajima, 2007. Fransiska, 2010 Baumann et al, 2012 Estimated prevalence 1: 20,000.	N: CHL primarily related to otosclerosis or TM immobility Evidence of a variant associated with bilateral high frequency SNHL unknown onset age.	Birth or early infancy	1

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Friedreich ataxia: spinocerebellar, resulting in progressive gait ataxia Delatycki, 2009 & Rance et al 2010 Prevalence: 2-4: 100,000	**Y: Progressive SNHL (~10-25%) related to axonal degeneration. Onset typically prior to age 25.**	**mean onset of gait symptoms between 10 and 15 years.**	5- Individualized
Goldenhar syndrome: incomplete development of the ear, nose, soft palate, lip, and mandible (part of the oculo-auriculo-vertebral spectrum) Bisdas et al, 2005. Martelli et al, 2009. Skarzynski, 2009. Prevalence estimated to range from 1: 3,500- 7,000 live births.	N: Cond. component (~70%) assoc. With Cleft palate. SNHL assoc. with cochlear malformation (Skarzynski: 5/14) Congenital. Possible evidence of progressive losses (maybe LVA related)	Within 1st year	2
Hemifacial microsomia: abnormal development of the lower half of the face, most commonly the ears, the mouth and the mandible (part of the oculo-auriculo-vertebral spectrum) Vrabec, 2010. Collett et al, 2011. Incidence: 1: 3,500- 4,500.	N: Primarily CHL. 6-16% prevalence SNHL related to cochlear & vestibular anomalies. Rate of progressive/late onset vs. congenital undetermined.	Usually within 1st year	2

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Hunter syndrome (mucopolysaccharidosis II): a lysosomal storage disease characterized by progressive intellectual impairment, death between 10 and 15 years. Rate of progression ~1 db/year. Often will present through ENT due to airway and neck problems. Wold, 2010. Keilmann, 2011. Prevalence ~1:100,000 live births (affects mainly males).	**Y: Progressive SNHL as early as age 2 and more commonly age 4. CHL also common.**	**Variable age of onset**	3

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Hurler syndrome (mucopolysaccharidosis I): lysosomal storage disease characterized by coarse facial features, skeletal malformations, recurrent OM, hepatosplenomegaly, and macroglossia, developmental delay. Often will present through ENT due to airway and neck problems. Two basic types (severe and attenuated). Shortened lifespan common (severe - <age 10 and attenuated varies from 20 to normal) Gunilla et al, 2008. Wold et al 2010. Clark et al, 2011. Prevalence: 1: 100,000 for severe form and 1: 500,000 for attenuated form.	**Y: L-O SNHL progressing to profound coinciding with developmental delay ~1-4 years of age. Involvement of CNVIII is common. Also CHL, OM & infections.**	**no clinical presentation at birth. *Severe MPS I*: feature onset ~1 year, *Attenuated MPS*: clinical onset from age 3-10 years,**	3
Jervell and Lange-Nielsen syndrome: variant of long QT syndrome (see below) Mohiddin et al, 2004. Baig 2011, Tranebjaerg, 2010 Estimated prevalence 1.6: 1,000,000 worldwide (higher in areas where consanguineous marriage is common or identified "founder mutation" is present-ie. Norway, 1: 200,000)	N: Long QT Characterized by bilateral congenital profound SNHL	Variable Half of children identified by age 3 due to cardiac issues.	1

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Klinefelter syndrome (XXY): hypogonadism, infertility Evans et al, 2000. Visootsak, 2006. Prevalence 1: 500- 1,000 males	N: CHL due to chronic OM, some reports of congenital snhl.	Later childhood	5- Individualized
Klippel-Feil Sequence: fused cervical vertebrae, webbed neck, can have cleft palate Incidence: 1: 40,000 to 50,000 live births.	N: 30% SNHL or CNHL congenital	Early infancy	1
Kabuki: postnatal growth deficiency, onset <1st yr.craniofacial abnormalities, some have cleft palate, some cardiac deficiencies. Barozzi, 2008. Matsumoto et al, 2003. Wessels, 2002. Estimated Prevalence: 1: 32,000 live births	N: 32% CNHL and ongoing OME.	Typically age 2	2
Large Vestibular Aqueduct Syndrome: enlargement of vestibular aqueduct in the inner ear Arjmand, 2004. Dewan et al, 2009. Santos et al, 2010. Gopen et al, 2011. Estimated Prevalence in clinical population 5-15%.	**Y: BL (~67%) or Uni (~33%). Prevalence of L-O SNHL ~96%. Onset of hearing loss is highly variable, ranging from birth to adolescence.**	Early infancy	3

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Long QT syndrome: prolongation of QT on ECG, syncope, and sudden death Sopontammarak, 2003. Mohiddin et al, 2004. Gritli et al, 2010. Belmont et al, 2011. Incidence 1: 2,500 Accounts for ~.21% of SNHL.	**Y: Age of onset & severity vary with type & severity of cardiac condition. Penetrance as high as 50%.**	Variable dependant on when cardiac issues arise	3
Meunke Craniosynostosis – FGFR3 mutation, coronal craniosynostosis, fifth finger clinodactyly, Ptosis, developmental delay. Agochukwu et al, 2006. Honnebier et al, 2008. Robin et al, 2011. Estimated Prevalence: 1: 30,000 live births.	N: Typically mild bilateral, symmetric, low-mid frequency, SNHL congenitally.	Usually within 1st year	2
Nager: similar to Treacher-Collins, micrognathia, low set,posteriorly rotated ears, atresia, can have cleft palate Danziger et al, 1990. Opitz, 2003. Hermann et al, 2005. Prevalence unknown, 70 published cases.	N- CHL due to middle and conductive ear pathology.	Variable dependant on severity	1

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Neurofibromatosis II (NF2): tumours of the central and peripheral nervous system, including non-malignant vestibuloschwannomas Evans, 2009 Incidence reports range from 1: 40,000 to 1:25,000; and the prevalence from 1:200,000 to 1:80,000.	**Y: Incidence of CN VIII tumours ~90%.**	**Average age of onset 18- 24 years dependant on penotype**	5- Individualized
Noonan syndrome: short stature, characteristic facial features, hypotonia, cardiac abnormalities Tartaglia, 2009. Pierpont, 2010 Estimated prevalence of 1: 1,000 -2,500 live births.	Y: SNHL ~26- 40%. Associated with temporal bone structural anomalies. Can also result in structural CHL & OM.	Most apparent in preschool years	2
Norrie syndrome: retinal detachment, often born blind, possible mental retardation Rehm et al, 2002.Halpin 2005 & 2008 Incidence/ prevalence unknown (case reports only)	**Y: X-linked. Complete penetrance of L-O progressive (mild-profound, assym. HF) SNHL in late childhood/early adolescence. Stable ~35 years.**	Early childhood	3

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Ohdo syndrome: mental retardation, congenital heart disease, blepharophimosis/ptosis, hypoplastic teeth Aizeddin et al, 1998 White et al, 2003 Verloes et al, 2006. Beckett et al, 2008 Prevalence/incidence data unavailable,literature consists of case reports.	N: Sporadic case study reports, controversy over classification. Literature indicates SNHL and CHL. Very little specific information on hearing assessment available (including degree, age of onset/diagnosis & in some cases, type)	Early childhood	1
Osteogenesis imperfecta: disorder of type I collagen metabolism characterized by bone fragility Sainz et al, 2009. Marini, 2010. Forlino et al, 2011. **Prevalence: 1: 15,000- 20,000**	**Y: SNHL or mixed hearing loss including structural CHL & otic capsule demineralization & dehiscence. Typically type III & IV. 6-7% experience loss of mild or greater by 9 years of age. SNHL in 25-60% of cases.**	**Variable**	5 -Individualized
Osteopetrosis: increased osseous density due to defects in osteoclastic resorption Dozier et al, 2005. Fattore et al , 2008. **Incidence of autosomal recessive form: 1: 250,000** **Incidence of autosomal dominant form: 5: 100,000**	**Y: Closure of bone foramina causing CN VIII compression. Can also present with otosclerosis and external auditory canal stenosis.**	**Variable onset and severity of clinical features (infancy or early childhood for autosomal recessive form and early adulthood for autosomal dominant form).**	3

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Pendred syndrome: goitre and hypothyroidism Luxon et al, 2003. Huang et al, 2012. Ito et al, 2011. **Estimated prevalence 7.5- 10: 100,000.**	**Y: congenital or L-O (devel. by age 3). Progressive & some fluctuation due to LVA and membranous labyrinth abnormalities.**	Variable	3
Pfeiffer syndrome: FGFR1/2 craniosynostosis Church et al, 2007. Desai et al, 2010. Robin et al, 2011. Incidence for all forms combined reported as 1: 100,000.	N: CHL related to ossicular fixation & stenosis ~50-70%. Congenital Mixed/SNHL ~20%	Usually in 1st year	1
Pierre Robin sequence: craniofacial abnormalities incl. cleft palate. Gruen 2005. Medard, 1999. Estimated Prevalence 1: 8500-10,000.	N*: CHL associated with middle ear pathology. Congenital SNHL with PR in isolation. *Associated with many other syndromes that may be associated with L-O SNHL. Ie. *Stickler in ~25% of PR. Case reports of LVA*	Early infancy	Cleft Palate Care Path

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Refsum syndrome: phytanic acid storage disease characterized by microcephaly, severe developmental delay, hypotonia, hepatomegaly, retinitis pigmentosa and dysmorphic facial features Bamiou et al 2003. Raine et al 2008. Wanders et al, 2010. Prevalence and incidence data is unavailable but estimated to be very low.	Y: SNHL (predominantly high frequency) related to progressive toxic effects of elevated phytanic acid on peripheral nerves. Progressive, often asymmetrical hearing loss 50-70%. Evidence of CN VIII involvement. Symptom onset, with retinitis pigmentosa usually the first symptom, ranges from 7 months of age to adulthood.	Variable	2
Saethre-Chotzen Syndrome: craniofacial anomalies including variable craniosynostosis Lee et al 2000. Robin et al 2011. 1:25,000-50,000	N: Typically CHL. Sporadic case reports of mixed or SNHL. Single cases at BCCH of presumed late onset.	Due to its variability, age is also variable	2
Stickler syndrome Type 1: flat midface, cleft palate, myopia with retinal detachment and cataracts, musculo-skeletal findings Robin et al, 2010. Francomano, 2010. Szymko-Bennett, 2001. Incidence 1:10,000 ~20% cleft palate	Progressive SNHL in 60% Y: SNHL ~40-50% more severe & *progressive* in type 2 & 3. Can be congenital or late onset. Also CHL often related to CP.	Often after 1st year as myopia not identified	2

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Stickler syndrome Type 2 &3: flat midface, cleft palate, myopia with retinal detachment and cataracts, musculo-skeletal findings Robin et al, 2010. Francomano, 2010. Szymko-Bennett, 2001. All 3 types:~20% cleft palate; 1-3:10.000	SNHL in 90% Y: SNHL ~40-50% more severe & *progressive* in type 2 & 3. Can be congenital or late onset. Also CHL often related to CP.	Often after 1st year as myopia not identified	2
Treacher Collins syndrome (mandibulofacial dysostosis): craniofacial abnormalities Pagon et al 2006 1 :50,000 births ~35% have cleft palate	N: Permanent CHL related to outer & middle ear malformation	Typically at birth (sometimes prenatally)	1
Turner syndrome: XO genotype characterized by short stature, infertility, renal abnormalities, chronic otitis media Verver et al, 2010 1:2000 live females	Y: Often mid-frequency or high frequency onset in adolescence. Differs with karyotype. **Prevalence of SNHL** varies 10- 66%.CHL ~35%.	Adolescence	5 - Individualized
Usher syndrome types I and II: retinits pigmentosa and vitiligo Friedman et al 2011. Jaijo 2004 3-5:100,000 Type 1 constitutes 90% of syndrome.	N: in type I congenital severe to profound SNHL, in type II usually stable congenital loss in low freq sloping to severe or profound in high frequencies, may also be progressive.	*Typically diagnosed as a result of the congenital hearing loss diagnosis, therefore likely <1 year*	3

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Usher Type III **Aller, 2004. Friedman et al 2011.** Prevalence 6% of all Usher cases.	Y: Type III often born with normal hearing. Onset of SNHL may be as early as 3-5 or in adolescence or late childhood. Continues to progress to severe and profound in 4-5th decade of life.	Typically diagnosed as a result of SNHL after age 3	3
Van Buchem Syndrome: skull otosclerosis facial changes over time Two types: Type I (Van Buchem's disease) progressive form for lifetime; Type II (Worth disease) the pathologic bone deposition stops at 20 years of age. The disease is incurable; surgical treatment aims to reduce the intracranial pressure and to correct bones deformity.	Onset of mixed and SNHL around age 15	Variable, often in late childhood	5 - Individualized
Waardenburg Syndrome: three types (I, II and III)white forelock, heterochromia of irises. Rehm, 2008. Toriello, 2011 Prevalence 1:42,000	N: Type I: SNHL can be BL or UL. Typically congenital hearing loss can range from normal to severe SNHL. Type II: ***Can be progressive (70%). 5% also present with CLP & associated OM. Type III: least likely to have hearing loss	Typically at or near birth	1

APPENDIX D. REFERENCES

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